Title: An investigation of granulated sugar dressing in the management of sloughy, necrotic and infected exuding wounds

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Dedication

I dedicate this thesis to my grandmother an unselfish woman, who provided me with motherly love that I never had as a child till her untimely death in 1996, to my father who knew a lot but never had any formal education, my aunt Susan Masangwi whose love and guidance has left an everlasting impact on my life and journey; to the British Isles people, who allowed me into their Island to learn and their willingness to learn from my African experience.

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Abstract

Aim: This study investigated the use of granulated sugar in the management of sloughy, necrotic and infected exuding wounds.

Method: The investigation followed the Medical Research Council (MRC, 2007) framework for investigation of complex interventions. This recommends investigating the scientific mechanisms underlying the intervention; reviewing existing evidence; then investigating effectiveness.

Pre-clinical: The study was registered with MHRA, followed by development and design of the mode of sugar delivery to patient use. The amount of sugar to be used on different sizes of wounds was determined and single use containers were designed to prevent of cross-infection

Evidence review*:* A systematic review and meta-analysis identified, assessed and synthesised the evidence for the clinical effectiveness of sugar treatment in the treatment of acute and chronic sloughy, necrotic and infected exuding wounds. The review found four randomised controlled trials, three of which reported rates of wound healing. Meta-analysis was carried out of these three and found no statistically significant difference in rates of wound healing. The identified trials were of poor quality. It was concluded that there was no existing good quality evidence to support the routine use of sugar dressings to promote wound healing in non-healing acute or chronic sloughy, necrotic and infected exuding wounds.

Phase I: Laboratory studies to determine the effects of sugars on microorganisms were carried out. These included a range of *in vitro* tests, evaluating the activities of three sugars (2 white granulated (Cane and Beet) and one Demerara/ un-refined sugar) against a range of Gram-negative and Gram-positive bacteria

These studies found that all three sugars showed relatively equal activity against all the bacteria tested although Demerara sugar was slightly less active. The sugars were only active in solution, which supports a lowering of bioavailability of water for bacterial growth as a mechanism of action. There was little variation in the concentration of sugar needed to inhibit growth of any of the strains (i.e. efflux mutants were no more susceptible) indicating the mechanism of antimicrobial action of sugar is non-specific. *Pseudomonas aeruginosa* (G1) was slightly more susceptible than other species.

Phase II: A feasibility study of 22 patients selected from an NHS vascular ward and vascular out-patient department in Birmingham UK was undertaken. All patients had acute or chronic sloughy, necrotic and infected exuding wounds. Patients with diabetes had their blood sugar level checked daily as per trust protocol until the end of the study, to investigate the effects of sugar. This study was carried out to assess the practical aspects of using sugar treatment in a modern NHS hospital. At the end of the study and following the results, a RCT working protocol was developed, including the amount of sugar required and measurement of wound outcomes.

Twenty two patients completed this study. The study found that both insulin and non-insulin treated diabetic patients can be treated with sugar dressing without affecting their blood sugar levels.

The study determined the amount of sugar required for different wound sizes and. Wounds were categorised as small- medium (5 – 19.9 cm^2) and medium to large (20 – 40 cm^2) required doses of 15 and 30 grams respectively. Although this study was not aimed at exploring debridement effect, sugar was noticed to be effective on wound debridement

Phase III: A randomised controlled trial evaluated the clinical effectiveness of granulated sugar therapy compared with standard autolytic debridement dressings.

Participants with leg ulcers, chronic surgical wounds and pressure ulcers between 5 cm^2 and 40 cm^2 in size and at least 25% slough were recruited from NHS hospital and community settings

The primary outcome was the proportion debrided at 4 weeks follow up. A number of secondary outcomes were assessed including wound area, wound pain, odour, exudate and health related quality of life.

The study failed to recruit the intended numbers and final analysis was carried out on 22 patients randomised to sugar and 19 randomised to usual care. 19 (86%) achieved debridement at 4 weeks in the sugar group compared to 6 (32%) standard care group (Fisher's exact test: $p<0.001$). There were statistically significant improvements in a number of secondary outcomes including pain, wound exudate appearance and wound area.

The data from this RCT though small in sampled patient numbers showed that granulated sugar applied topically is an effective debriding agent and well tolerated treatment option in patients with exuding necrotic or sloughy wounds.

Overall conclusion: Sugar does have an effect on micro-organisms. It is possible to use it in modern hospitals and community settings. There is now a replicable and adaptable sugar treatment protocol. There is some evidence for the effectiveness of sugar, however this study was small. There is a need for future research in this area.

1. Contents

Table of figures

Tables

1. Introduction

1.1. Why sugar? A reasoned exposition by the author

This thesis is the result of my experiences as a child in Zimbabwe, where my father used sugar to treat my wounds as well as those of others in the community. The author has seen several fascinating results from the traditional ways of treating diseases, including the use of sugar on wounds, but there was no recorded scientific backing to these treatments identified from explored literature. The author's father had recognised expertise in the use of different herbs to be used for different ailments but the dose was never consistent, although there were good results. The community around him believed in his herbs. Hence, the interest of the author lies in the science behind these traditional treatments such as treating wounds with granulated sugar, i.e. scientific epistemology (Fay, 1996; Root, 1999; Bowling, 2014). One would argue that there is often deeper truth and better new evidence that disturbs the status quo and that forces us to revise or reject some of our traditional treatments. This according to Pojman (2002), Root (1999) and Fay (1996) is the theory of knowledge, or epistemology. The author wanted to enquire into the nature of knowledge and justification of his father's belief on managing wounds (using granulated sugar) having seen many different modern wound management products. He had experienced his father's conviction that granulated sugar was effective on managing sloughy, necrotic and infected exuding wounds, but could not claim to know the truth to justify these effects. It was vital for the author to avoid the feeling that Rene Descartes pondered later in his life as cited by Pojman (2002):

> "*Several years have now passed since I first realised how many were the opinions that in my youth I took to be true and thus how doubtful were all the things that I subsequently built upon these opinions"*
>
> (Pojman, 2002 p.144).

Therefore, the thesis is written with alternative traditional remedies in mind because these methods of treating wounds are sometimes based on myths and assumptions. Because of these myths, they are sometimes discounted because of their lack of scientific basis, even though their results can be of benefit into modern medicine (Chiwenga, et al., 2009, Nakao, et al., 2006, Shi, et al. 2007). Many modern day health care professionals are not aware of this traditional remedy; however, in my opinion even if they were aware, they will be discouraged from using sugar remedy because there has not been any rigorous researched evidence to support its use. It is therefore important that rigorous research is undertaken into the effectiveness of sugar on sloughy, necrotic and infected exuding wounds.

1.2. Historical perspective of sugar as a wound care product

Methods of healing wounds using sugar have been studied for many years. Documents dating back to 1679, describe Edwin Smith Surgical Papyrus (dated around 1700 BC) treating battle wounds in Egypt with molasses and honey (Breasted, 1930) and Zorin in 1714, reported on the value of sugar in promoting the healing of wounds and ulcers. Furthermore, Sculteus (1679) reported using finely powdered sugar for cleansing and promoting wound and ulcer healing (Dawson, 1996; Pieper and Caliri, 2003). In the same way as Egypt, the Middle-East (Mesopotamians) now called Iraq and Iran are reported to have been using sugar as a wound dressing for about 4, 000 years ago (Majno, 1975). Documents showed the procedure involved the application of honey mixed with greases such as lard or resins (Majno, 1975) or use of sugar/molasses and honey (Selwyn and Durodie, 1985). Despite these early reports showing that sugar had been valued throughout the world (Wiseman et al., 1989; Rostenberg Jr., 1958; Duffet and Viau, 1986; Silvetti, 1981, Viau et al., 1986; Viau et al., 1985) as a

wound healing product, there has been little evidence published on trials exploring in depth this product to date.

1.3. Recently reported studies on sugar as a wound healing product

Currently, sugar as a wound healing product is reported in several studies ranging from 1981 to 2011 with prospective studies being those of (Herszage et al., 1980; Knutson et al., 1981; Chirife et al., 1982; Chirife et al., 1983; Gordon, 1985; Mphande et al., 2007; De Foe et al., 2000; De Foe et al., 2003; Murandu et al., 2011), Despite this documented evidence, the use of sugar for wound healing seems to be overlooked even though there is increasing indication of its value. In spite of this slow development some areas of Africa, Asia, Latin America, Europe and United States are becoming interested in exploring sugar as a wound healing product, as studies demonstrate (Dawson, 1996); Mphande et al., 2007; Biswas et al., 2009; Chirife et al., 1982; Chirife et al., 1983; Herszage et al., 1980; Middleton and Seal, 1985; Haddad et al., 1983; Drouet, 1983; Duffet and Viau, 1986 ; Haddad et al., 2000 ; De Feo et al., 2000; Tophan, 2000; De Foe et al., 2000; De Feo et al., 2003; Murandu et al., 2011 and Knutson et al., 1981) respectively.

1.4. The importance of undertaking the study

There have been various reported investigations into the study of wound healing using sugar as mentioned above, but despite this plethora of evidence, there has not been any conclusive agreement to the clinical significant of sugar on wound healing. From these sporadic reports and studies, there is a general agreement that, sugar assists with wound debridement of exudating wounds and facilitates wound healing (Archer et al., 1990; Tanner, 1998; Tophan, 2002; Booth, 2004). Nonetheless, there have not been large and sufficiently powered randomised controlled studies that explored granulated sugar and its effect on microorganisms and wound healing. In addition the knowledge of the effects of the different

sugars' action such as (Cane, Beet, White and Demerera/Brown sugars) on microorganisms has not been document from any of the reviewed studies. Only one study was found by Herszage and colleagues 1982 exploring the science behind the sugar and its effect on microorganisms. This study resulted in the understanding of the theory of water activity, where microorganisms are said to be competing with sucrose for water when it is applied on the wound topically. There is no reported studied exploring the difference in the effectiveness of the types of sugar on various microorganisms either in vitro or clinically.

The researcher believe that an understanding of the effectiveness of different sugars (beet, cane, brown/Demerara and white granulated sugars) on wound healing of exudating wounds will provide valuable information that will help health care professionals, make informed decisions when deciding on the choice of wound-care products. The increasing numbers of wound care products on the market presents a dilemma for nurses and doctors when making a choice of the appropriate dressing for a specific wound. For these reasons, it is necessary to carry out an investigation that contributes to an understanding of the effectiveness of sugar on wound healing in context of differing sugars, and the applicability in modern day NHS hospitals and health care settings and patient acceptability. Furthermore, my interest in the effectiveness of sugar on wound healing lies in the assumption that it is cheap and can be easily be accessible to both developed and developing countries.

Overall aim of the Research is to:

Investigate the use of granulated sugar in the management of sloughy, necrotic and infected exuding wounds.

There are several secondary aims of this project. These are to investigate:

- Existing evidence for the effectiveness of sugar dressings
- The microbiological effects of sugar in vitro

- The feasibility of a RCT of sugar dressing
- Undertake an RCT of sugar dressing

The investigation follows the Medical Research Council (MRC, 2007) framework for investigation of complex interventions. This recommends investigating the scientific mechanisms underlying the intervention; reviewing existing evidence; then investigating effectiveness (see

Table 1.1 adapted framework).

Table 1.1: Sugar trial framework adapted from MRC (2000)

Theory	***Modelling***	***Exploratory Trial***	***Definitive RCT***
Study registration with MHRA Developing and designing mode of sugar delivery to patient use. Developing methods of preventing cross-infection	Laboratory studies of effects of sugars on microorganisms	Non randomised clinical trial Testing of effects on diabetic patients Development of RCT working protocol	Randomised trial Monitor feasibility of RCT both in community and acute settings
Pre-clinical	***Phase I***	***Phase II***	***Phase III***

Primary Question

How effective is sugar dressing in reducing the time to debridement of sloughy, necrotic and infected exudating wounds compared with standard treatment?

Secondary Questions

Does the use of sugar dressing reduce the bacterial load in a wound to a greater extent than standard treatment?

Does the use of sugar dressing improve the quality of life of patients with sloughy, necrotic and/or infected wounds?

Is the use of sugar dressing feasible in a modern day NHS Hospital setting?

Is patient satisfaction improved when using sugar dressing?

Is sugar dressing cost-effective alternative to standard dressings?

Is sugar dressing acceptable to nursing staff?

1.5. Outline of the Thesis

This study will investigate the effectiveness of granulated sugar dressings on sloughy necrotic and infected exuding wounds. **Chapter 2** examines the laboratory studies on microbiological effects of sugar. The researcher will examine "*in vitro"* the effectiveness of different sugars derived from Beet and Cane as well as Demerara/Brown and White sugar formulas; to determine their effectiveness on eradicating microorganisms.

Chapter 3 presents a systematic review of the literature on the RCTs using granulated sugar on sloughy necrotic and infected exuding wounds. Specifically, it provides the literature search strategy used, and systematically reviews the randomised controlled trial papers on sugar and wound healing.

Chapter 4 presents the first clinical exploration. In this chapter, ethical and the Medicine and Health Regulatory Authority issues will be explored. In addition, the feasibility of using sugar as a dressing for necrotic sloughy, infected exudating wounds in a modern day National

Health Service Hospital (NHS) will be outlined. The attitude of both health care professionals and patients towards sugar dressing will be highlighted.

Chapter 5 outlines the second clinical study. This chapter describes a randomised controlled trial (RCT) of sugar compared to standard treatment for sloughy, necrotic and infected exuding wounds.

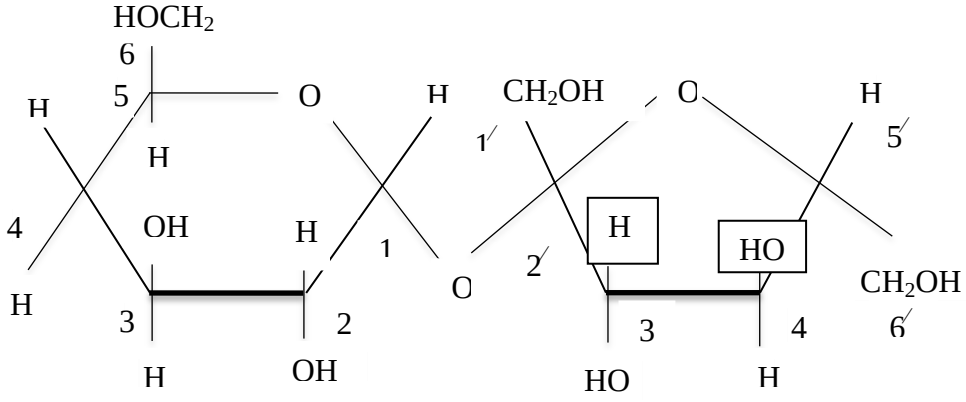
Chapter 6 presents an overview of all the studies that make up the doctoral thesis. The researcher will explore implications, recommendations, reflections and significance of these studies, and make an overall conclusion.

2. Chapter: Laboratory studies on microbiological effects of sugar

2.1. Granulated Sugar (Sucrose)

Yudkin and colleagues (1971) describe sucrose as a carbohydrate consisting of glucose and fructose. It is the predominant constituent of sugar cane and sugar beet. They go on to suggest that this substance sucrose is of great versatility and of commercial importance (Yudkin et al., 1971). It is consequently of interest to a wide range of specialists areas including the chemist, the biochemist, the animal and plant physiologist, the clinician, the historian, the sociologist, the nutritionist, the psychologist and above all the food manufacturer. Whatever the future utilisation of sucrose may be, it will always be remembered as a constituent of man's diet. According to Hough (1968) sucrose is a non-reducing disaccharide of unique structure containing eight alcoholic groups, three of which are primary hydroxyls (at carbons 6, 1', and 6), the remaining five being secondary hydroxyls. It is a white odourless, crystalline powder with a sweet taste (Yudkin et al., 1971; Lombardo et al., 1996) (see Figure 2.1).

Figure 2.1: Molecular formula of sucrose



Adapted from (Yudkin et al., 1971, page 50).

This special linkage prevents bonding with other saccharide units, hence chemically it is a non-reducing sugar. Only acidic hydrolysis can be used to convert sucrose into glucose and

fructose, but sucrose is reasonably stable in the presence of strong bases and alkalis (Yudkin et al., 1971). However, hydrolysis is so slow that solutions of sucrose can sit for years with negligible change, but if enzyme sucrase is added the reaction will proceed rapidly.

Sugar is almost ubiquitous. It is produced by all known land plants and is recovered commercially from a root (44%), several grasses (56%), and tree (<1%) (Yudkin et al., 1971).

2.2. Other uses of sucrose

Refined sugar has been a significant factor on international trade for more than 20 centuries (Yudkin et al., 1971) which seem to span the entire evolution of the organic chemicals industry. It is without doubt that there have been several attempts to harness this abundant, low priced, pure disaccharide as a raw material for chemical applications. A few of its applications are listed below; foods for human consumption; feeds for animals; fuels, though because 51% of the weight of sucrose is oxygen, this stops sugar from being realistic fuel. However, small amounts are used to make explosives as the octanitrate in nitroglycerine and mannitol hexanitrate. There are other uses such as lubricants, preservatives, surfactants, surface coatings and many others. In this study we shall ignore all other usages and focus on the sucrose's role on wound healing.

2.3. Assessment of antimicrobial activity of Cane, Beet, Demerara (unrefined) and White (refined) sugars against a range of bacteria

It is acknowledged that sugar/molasses has been known for centuries in the management of wounds (Pieper and Caliri, 2003; Breasted, 1930), but little is known of specific sugars such as that derived from beet or cane. Also of interest is knowledge of unrefined (Demerara) and (White) sugars on microorganisms. Following discussion with a microbiologist a range of *in vitro* tests were used to evaluate the activity of three sugars (2 white granulated (Cane and Beet) and one Demerara) against a range of Gram-negative and Gram-positive bacteria.

2.4. *In Vitro* Test Methods

Strains: A panel of 16 strains representing Gram-negative and Gram-positive bacteria were used in the experiments. These included representative of wild-type strains for each species. In addition a set of *Salmonella* mutants with defined disruptions in efflux genes (responsible for intrinsic resistance to numerous agents) were evaluated in order to identify whether active efflux is required for tolerance to sugar. Strains are listed in **Table 2.1** below.

Table 2.1: Strains used in the study.

Strain code	Species	Genotype/ source
I114	*E. coli*	NCTC 10538
F77	*S. aureus*	NCTC 8532 MSSA
F410	*S. aureus*	NCTC 12493 MRSA
G1	*P. aeruginosa*	NCTC 10662
H42	*K. pneumoniae*	NCTC 10896
H43	*K. pneumoniae*	NCTC 9633
L354	*S.* Typhimurium	Wild-type (SL1344)
L109	*S.* Typhimurium	SL1344Δ*tolC*
L785	*S.* Typhimurium	Wild-type ATCC 15277
L828	*S.* Typhimurium	Wild-type ATCC 14028s
L829	*S.* Typhimurium	ATCC 14028s Δ*tolC*
L830	*S.* Typhimurium	ATCC 14028s Δ*acrB*
L831	*S.* Typhimurium	ATCC 14028s Δ*acrAB*
L3	*S.* Typhimurium	Human pre-therapy clinical isolate
L10	*S.* Typhimurium	Human post-therapy clinical isolate, MDR
A1	*E. cloacae*	NCTC 10005
B14	*S. marcescens*	NCTC 2847
J29	*M. morgani*	NCTC 235

2.5. Susceptibility testing.

Antimicrobial susceptibility testing of all agents to the three sugars supplied used a variety of methods. These were:

- The agar dilution method (incorporation of sugar at doubling dilutions into a range of iso-sensitest agar plates; following the recommendations of the BSAC[1] and that described by Schillinger and Lucke, (1989).
- An agar diffusion assay (100mg of pure sugar placed onto a well bored into an iso-sensitest agar plate which was then overlaid with bacteria and incubated).

[1] BSAC – The British Society for Antimicrobial Chemotherapy

- Broth microdilution microtitre tray susceptibility assays (bacteria were inoculated into iso-sensitest broth containing doubling dilutions of sugar concentrations again following BSAC guidelines).
- Growth kinetics (Luria-bertani broth containing varying concentrations of each sugar was inoculated with bacterial cultures and incubated for 12 hours. Growth was monitored automatically in a FLUOstar OPTIMA by measuring the optical density of cultures at 600nm, similar to that described by Jacobsen et al., (1999).

2.6. Results

2.6.1. Susceptibility testing in agar

None of the sugars showed any antimicrobial activity when incorporated at a range of final concentrations (w/v) into agar plates with all strains growing on plates containing a final concentration of 25% (w/v) of sugar. Similarly in the diffusion assays, all strains were able to grow up to the wells containing sugar, there was no zone of inhibition seen for any strain.

2.6.2. Susceptibility testing in broth

In contrast to the agar experiments, all the strains were inhibited by sugar in solution. All three sugars tested were able to prevent growth of all the species at final concentrations from 6 – 25% (**Table 2.2**) below. The activity of all three sugars was similar, the granulated sugars showed some slight increased activity when compared to Demerara sugar. The pattern of inhibition of strains was similar and efflux mutants were not more susceptible to sugar than their parent strains indicating efflux is not likely to contribute to intrinsic resistance to sugar. *Pseudomonas aeruginosa* G1 was somewhat more sensitive to the granulated sugars than the other strains evaluated.

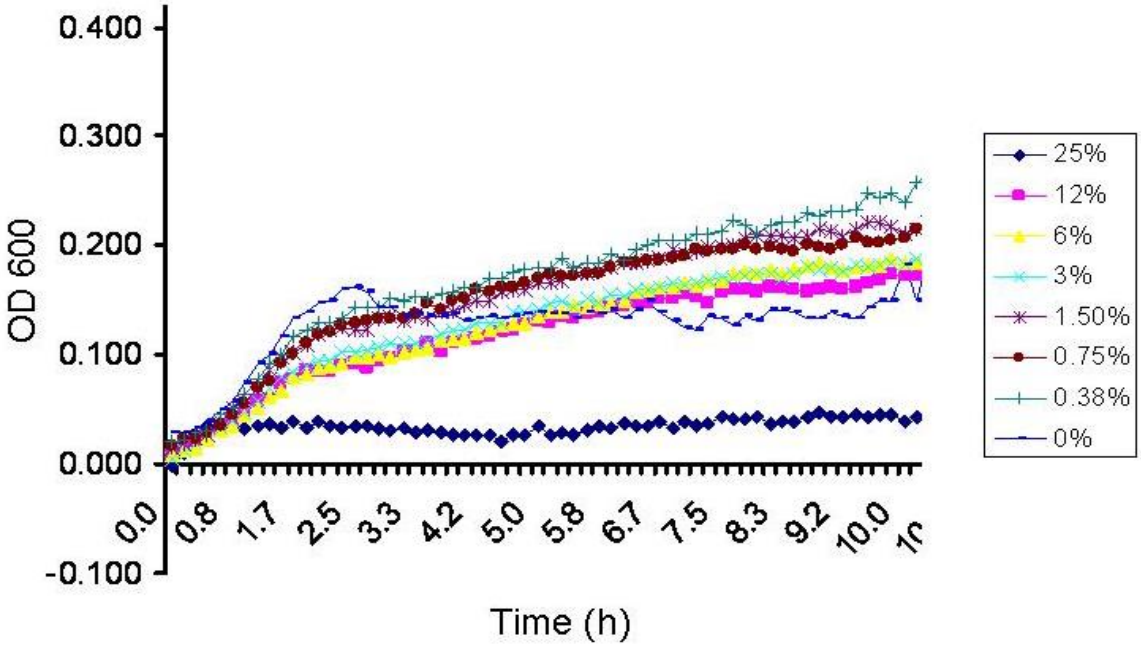
Table 2.2: Minimum inhibitory concentration of sugar against strains tested (in broth).

Strain	MIC (% sugar w/v)		
	Granulated (Tate and Lyle)	***Granulated (British Sugar)***	***Demerara***
I114	25	25	25
F77	25	25	25
F410	25	25	25
G1	12	6	25
H42	25	25	25
H43	25	25	25
L354	12	25	25
L109	25	25	25
L785	25	25	25
L828	25	25	25
L829	25	25	25
L830	25	25	25
L831	25	25	25
L3	25	25	25
L10	25	25	25
A1	25	6	25
B14	25	25	25
J29	25	25	25

2.6.3. Growth inhibition by sugar

Growth kinetics in the presence of various sugar concentrations revealed a very similar pattern to the micro broth dilution susceptibility testing. The strains were able to grow well in low concentrations of sugar. However, these strains were completely inhibited by higher concentrations which correlated well with the inhibitory concentrations seen in the MIC testing. **Figure 2.2** shows an example of one growth curve illustrating inhibition of *E. coli* I114 by Demerara sugar at 25% (w/v).

Figure 2.2: Growth inhibition of *Escherichia coli* I114 by Demerara sugar in concentrations from 0% to 25%.



[2].

2.7. Conclusions

All three sugars showed relatively equal activity against all the bacteria tested although Demerara sugar may be slightly less active. The sugars were only active in solution which supports a lowering of availability of water as a mechanism of action. There was little variation in the concentration of sugar needed to inhibit growth of any of the strains (i.e. efflux mutants were no more susceptible) indicating the mechanism of antimicrobial action of sugar is non-specific. *Pseudomonas aeruginosa* (G1) was slightly more susceptible than other species.

2.8. Theory related to sugar on microorganisms

The above study results support Engelsen and Peres' (1997) conclusion that sugar is a disaccharide of fructose and glucose which will combine with other polar substances such as water by hydrogen bonding. Micro–organisms require water to grow and reproduce and such

[2] *Optical Density 600nanometre (OD 600)-Spectrometer is used to measure the optical density at 600 nanometre of bacterial culture to monitor bacterial growth*

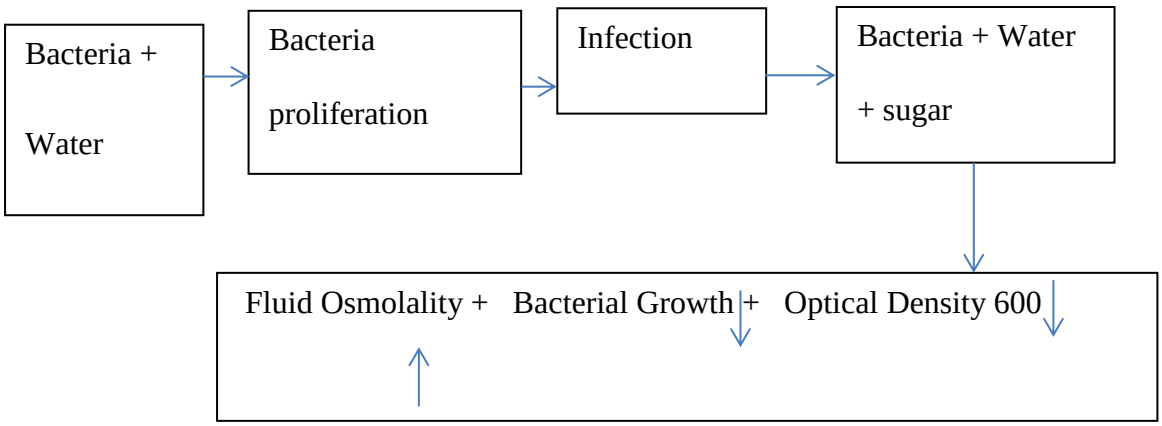
water requirements can be defined in terms of water activity (a_w) of the substrate rather than water concentration (Chirife et al., 1983, Chirife et al., 1982). The water activity of a solution is expressed according to Chirife (1983) as $a_w = p/po$ where p is the water vapour pressure of the solution and *po* is the vapour pressure of pure water at the same temperature. When a solute such as sugar is added to an aqueous solution in which a micro-organism exists, it will have the effect of lowering the $a_{w,}$ with a concomitant effect upon cell growth (see Figure 2.2). Every micro-organism has a limiting a_w below which it will not grow (Herszage et al., 1980; Chirife et al., 1983; Tophan, 2000 Biswas et al., 2010).

2.9. Water requirements for microorganisms

As briefly described earlier, the water requirements for all microorganisms and all other forms of life can be defined in terms of water activity, and every living organism has a limiting a_w below which it cannot proliferate. When the aqueous solution in the microorganisms' environment is concentrated by the addition of a solute such as sugar, the effects on microbial growth are mainly due to the change in $a_{w.}$ the minimum a_w for most bacterial pathogens (E. Coli, Pseudomonas, Klebsiela, to name a few, (see **Table 2.2**) for full range) is 0.91 or more but for Staphylococcus Aureus is 0.86 (Chirife et al., 1982). In their study Chirife and associates (1983) discovered that all bacterial growth was inhibited at an a_w of 0.858 (i.e. 195g sugar/100ml of water). They further compared a test medium of brain-heart infusion in which the a_w was 0.993 which supported rapid bacterial growth. The medium was adjusted to an a_w of 0.858 by adding sugar which caused complete inhibition of bacterial growth (Chirife et al., 1982). Therefore a concentration of 195g sugar/100g water would theoretically inhibit the proliferation of all bacteria. By following this rationale, the bacterial effect of sugar would also limit the bacterial production of ammonia, amines, and sulphur all which cause malodour (Tovey, 1991), (Nakao et al., 2006). This theory is supported by Molan and Cooper (2000) who suggest that sugar has a deodorising action,

whereby the infecting bacteria utilize the sugar instead of the amino acids, resulting in the production of lactic acid rather than malodorous compounds. In conclusion, bacteria need water to proliferate, if starved of water then there is inhibition of growth.

Figure 2.3: In vitro theory of Bacterial vs. sugar



In light of this evidence, it can be suggested that sugar may prevent microbial growth *in vivo*. Having looked at the potential of sugar as a wound dressing from the laboratory perspective, it is important to consider the clinical evidence. The next chapter presents the literature search strategy and a systematic review of randomised controlled trial papers on sugar for exuding wounds.

3. Chapter: Systematic review /Meta-analysis of sugar for exudating wounds

3.1. Introduction

There is a plethora of widespread existing evidence of non-healing wounds that has substantial cost implications to the NHS. Many interventions, new dressing products and wound care technologies are being developed and used to help to achieve optimum wound healing and eliminate infections. Many are very expensive. However, no one wound management product has been fully guaranteed to be of optimum effect. Therefore it is imperative to find out an intervention that has both therapeutic effects on the wound healing process as well as being cheap. This chapter reviews data that support the use of sugar in wound healing and its ability to manage infected wounds.

3.1.1. Description of the condition understudy

It is understood (Lammers, Christopher, and John, 2001) that the main wound care objective must be the provision of optimal conditions for the individual body to use its natural reparative processes. Chronic wounds are a major NHS Health care burden and they also affect the quality of life of those who live with them (Kilic, 2001). Lazarus (1994) suggested that acute wounds proceed through to healing in an orderly and timely reparative process. Dealey (1994) and Dealey (2005) suggests that chronic wounds are wounds where the orderly biological progression to healing has been disrupted and healing delayed. Phillips (1996) concluded that the microenvironment of a chronic wound has a negative effect on the healing of a wound resulting in prolonging the healing process. It is therefore a challenge to ensure that wounds are treated appropriately and that dressing products are easy to source and affordable.

3.1.2. Chronic wounds and microorganisms

Moist chronic skin ulcers and sinuses are believed to be ideal medium for bacterial growth and a variety of micro-organisms can be cultured from wound swabs collected from these lesions. Studies on cultured swabs have shown that over 80% of chronic leg ulcers may be contaminated with bacteria (Griffiths and Wieman, 1990; Pecoraro, 1991; Edmond, 1987). The commonest isolates are Staphylococcus aureus and Pseudomonas aeruginosa (Griffiths and Wieman, 1990; Apqelvist, Larsson and Agardh, 1993; Levin, O'Neal, 1983). Pressure ulcers are understood to have bacterial flora with aerobic organisms cultured more frequently than anaerobes, and as further reported by Boulton., et al (1995), Colagiuri et al., (1995), Pecoraro., et al (1990), that most moist chronic wounds isolates are Staphylococcus Aureus, Streptococcus species, Proteus species, Escherichia coli, Pseudomonas, Klebsiella and Citrobacter species. Apqelvist, Larsson and Agardh (1993) and Larsson (1994) believes that Pseudomonas aeruginosa and anaerobes may mainly be cultured from diabetic foot ulcers whereas anaerobes are often present in cultured exudate from chronic pilonidal sinuses (Cooppan and Habershaw, 1995).

3.2. The role of sugar in wound healing

The role of sugar in the healing of acute and chronic wounds is unclear. This lack of clarity is due in part to the different types and formulas of the sugar. Clinicians have used caster sugar in the form of sugar paste (Matthew and Binnington, 2002 Booth, 2004), povidone –iodine sugar paste (Knutson et al., 1981; Shi et al., 2007;) and granulated sugar (Chirife et al., 1982; Chirife et al., 1983; Keith & Knobel, 1988; Ambrose et al., 1991; Haughton & Young, 1995; Grauwin, Cartel & Lepers, 1999; Topham, 2000; Mathews & Binnington, 2002; Topham, 2002; De Feo et al., 2003; Hampton, 2007 and Mphande et al., 2007). While most of these studies indicate positive association between wound debridement and use of sugar, other

studies reported that alternative products were better than sugar (Mphande et al., 2007; Bajaj et al., 2009) honey and Eusol respectively.

In these studies clinicians used sugar treatment as a last resort on difficult necrotic, sloughy and infected exudating wounds. It is important to note that wound type can influence the choice of dressing product especially when the result of wound aetiology is potentially serious. For example, infectious diabetic foot ulcer that can lead to gangrene and amputation or death (Mueller et al., 1989; Wieman, Griffiths and Polk, 1992), infected pressure ulcers may lead to septicaemia or osteomyelitis (Boulton Connor and Cavanagh, 1995). Furthermore, the type and size of wound can be a deciding factor on the amount and frequency of dressing change as large necrotic, sloughy infected exuding chronic wounds require considerable amounts of sugar and frequent dressing change (Debure et al., 1987; Tophan, 2000).

3.3. The possible mechanism of sugar

It was found that solutions of high osmolality, such as sucrose and honey or sugar paste inhibit microbial growth because the sugar molecules tie up water molecules so that bacteria have insufficient water to grow (Yudkin et al., 1971; Molan, 2006). Therefore, high osmolality is valuable in the treatment of infections because it prevents the growth of bacteria and encourages healing (Archer et al., 1990). Chirife et al (1982) posit that sucrose creates a low water content (or high osmolality) when applied in a wound. This high osmolality of sugar is believed to draw lymph into a wound and dissolves nutrients within the lymph there by providing nutrition for the regeneration of tissue (Molan and Cooper, 2000).

3.4. Why it is important to do this review

There have already been two reviews of the use of sugar as a dressing. These previous reviews that were carried out by Pieper and Caliri (2003) who explored the use sugar and papaya/papain and that of Biswas and colleagues (2010) explored the use of sugar on diabetic foot ulcers only. The more recent review of Biswas and colleagues included only studies up to 2007. Therefore an updated summary of the effect of sugar on necrotic, sloughy and infected exuding wounds in all patients was warranted.

The Aim

The aim of this review was to assess systematically the evidence for the clinical effectiveness of sugar treatment in the treatment of acute and chronic wounds. Included in these wound categories are chronic leg ulcers, pressure ulcers, diabetic foot ulcers, pilonidal sinuses, chronic cavity wounds and those of non-healing surgical wounds.

3.5. Methods

3.5.1. Participants

Studies which involved humans of any age (children or adults), with an acute or chronic wound were included. For the purpose of this review an acute wound was considered to be the following; burns, lacerations, or other skin injuries resulting from minor trauma, and minor surgical wounds healing by primary or secondary intention. Chronic wounds were considered to be the following; skin ulcers of any type, pressure ulcers and infected wounds healing by secondary intention.

3.5.2. Interventions

The primary intervention was any sugar topically applied by any means, alone or in combination with other dressing components to an acute or chronic wound. Comparison interventions were dressings or other topical agents applied to the wound.

3.5.3. Outcomes considered

The primary outcome was wound healing. However, measures of wound healing can be subjective; therefore studies had to incorporate an objective assessment such as change in wound/ulcer size, rate of healing, frequency of complete healing or time to complete healing. It was also acceptable if studies reported percentage or absolute change of wound healing over a period of time. The accepted objective methods of measuring wounds/ulcers size were those of tracing the outline of wound/ulcer by counting the grids on a graph paper or measuring the longest length and width using the clinical measuring ruler; then multiplying the two in centimetres to get the total wound surface area in centimetre squared. Other methods measuring accepted were those of computerised wound image analysis. Pilonidal sinuses and cavity wounds outcomes of interests were healing rates, recurrence of disease, time to complete healing. Also included were rates of incidence of surgical complications. Studies were excluded if reporting on wound cultures, sensitivity of micro-organisms, bacterial counts and bacterial eradication because these outcomes have not shown to be accurate and reliable indicators of healing (Gotzesche et al., 1996). This review of use of sugar also focused on the rate of the number of patients reporting reduction in pain sensation using the objective visual pain analogue scale, cost and quality of life measured using validated respective assessment tools.

Comparison group

Comparisons/control group were participants who received any dressing product or usual treatment that facilitated wound debridement.

3.5.4. Types of studies

Randomised controlled trials (RCTs) and quasi- randomised controlled trials were included for meta-analysis. A quasi-randomised controlled trial was any trial that used a quasi-random allocation strategy such as alternate days, date of birth or hospital number. RCTs are considered to give the most reliable estimates of the effectiveness of interventions (Friedman, Furberg and DeMets, 1998, Jadad and Enkin (2007). This is because randomisation increases the likelihood that differences in outcomes are due to differences in the interventions received rather than to variations in other factors such as patient characteristics. Jadad and Enkin, (2007) supported by Gray, (2014) concluded that, RCTs that incorporates single or double-blind procedures help to control for the biases in health outcomes brought about by the preconceived expectations of patients and assessors.

It is also understood that useful data can be obtained from results of non-RCTs or Controlled Clinical Trials (CCTs). However, this must be considered with caution as groups may not be of homogenous nature at baseline and these studies may provide less reliable information compared to RCTs. If CCTs are to be considered, it is advisable that only prospective CCTs with concurrent control group should be accepted. Furthermore for both RCTs and CCTs, the units of allocation must be patients, limbs, or lesions. Studies of which none of these were considered were excluded because of the possibility of non-comparability of the standard care. Both published and unpublished studies were considered with no restrictions on date and language.

3.5.5. Data sources

A comprehensive and sensitive search strategy was developed and used this review. Searches of the following electronic databases were undertaken:

- Cochrane Wounds Group Specialised Register (Searched 10/3/14)
- The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Library Issue
- Ovid MEDLINE 1947 to March Week 1 2014
- Ovid EMBASE 1976 to March Week 1 2014
- Ovid CINAHL 1980 to March Week 1 2014

The following search strategy was used in the CENTRAL and adapted where appropriate for other databases: (see **Table 3.1**).

The MEDLINE search was combined with either Cochrane Highly Sensitive Search Strategy for the identifying randomised trials in MEDLINE sensitivity and precision maximizing version (2008 revision); Ovid format (Lefebvre, 2008). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN, 2008). Additionally, LILACS (1982 to March 2014), AMED (1980 to March 2014) and Google Scholar were searched using the text word “sugar”.

Table 3.1: Search strategy.

#1	MeSH descriptor Burns explode all trees
#2	MeSH descriptor Skin Ulcer explode all trees
#3	MeSH descriptor Wounds Penetrating explode all trees
#4	MeSH descriptor Pilonidal Sinus explode all trees
#5	MeSH descriptor Lacerations explode all trees
#6	MeSH descriptor Wound Infection explode all trees
#7	MeSH descriptor Surgical Wound Dehiscence explode all trees
#8	((plantar or diabetic or heel* or foot or feet or ischaemic or venous or varicose or stasis or arterial or decubitus or pressure or skin or leg or mixed or tropical Cell) NEAR/5 (wound* or ulcer*)):ti.ab.kw
#9	(bedsore* or ulcer (bed NEXT sore*):ti.ab.kw
#10	(pilonidal sinus* or pilonidal cyst*):ti.ab.kw
#11	(cavity wound* or sinus wound*):ti.ab.kw
#12	(laceration* or gunshot stab or stabbing or stabbed or bite*):ti.ab.kw
#13	(“burn” or “burns” or “burned” or scald*):ti.ab.kw
#14	(surg* NEAR/5infection*):ti.ab.kw
#15	(surg* NEAR/5wound*):ti.ab.kw
#16	(wound* NEAR/5 infection*):ti.ab.kw
#17	(malignant wound* or experimental wound* or traumatic wound*):ti.ab.kw
#18	(skin abscess* or skin abcess*):ti.ab.kw
#19	(infusion site* or donor site* or wound site* or surgical site*):ti.ab.kw

#20	(hypertrophic scar* or keloid*):ti.ab.kw
#21	(#1 OR #2 OR #3 OR#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#22	MeSH descriptor Sugar explode all trees
#23	sugar:ti.ab.kw
#24	MeSH descriptor sugar cane explode all trees
#25	sugar cane:ti.ab.kw
#26	MeSH descriptor sugar beet explode all trees
#27	sugar beet:ti.ab.kw
#28	(#22 OR #23 OR #24 OR #25 OR 26 #27)
#29	(#21 AND #28)

3.5.6. Searching other resources

There was hand search of four journals specialising in wound care (Care – Science and Practice 1981 to 1990; Decubitus 1987 -2014; Journal of Tissue viability 1991-2014; Journal of wound care 1991-2014). The bibliographies of all obtained studies and review articles were searched for potentially eligible trials. Contact was made with experts in the field and one author of the included trials. No language or date restrictions were applied to the trials and both published and unpublished trials were sought.

3.5.7. Decision on study inclusion

Decision on the inclusion of the primary studies was made independently by two reviewers; the researcher and reviewer. Disagreements were resolved by discussion.

3.5.8. Data extraction and management

Data were extracted from included trials by one reviewer (MM) and recorded on a standardised form. The extracted data were independently reviewed for accuracy by the second reviewer (CC) and disagreements resolved by discussion. If the data from the trial report were inadequate or ambiguous, additional information was attempted to be sought from the trial authors.

3.5.9. Quality assessment of selected studies

All included studies were assessed by one reviewer against a comprehensive checklist for methodological quality. The Jadad and Enkin (2007) checklist covered the following; method of randomisation for RCTs, criteria for selecting participants, use of blinding or allocation concealment, baseline comparability of groups, sample size, outcomes assessment, reporting of withdrawals and use of intention to treat (ITT) analysis. Quality assessment was then checked independently by a second reviewer and discrepancies were resolved by discussion. Use of intention to treat analysis is defined in this review as analysis that included all participants in the groups to which they were randomised regardless of whether they received the treatment, completed treatment or were found not to meet entry criteria after randomisation (Hollis and Campbell, 1999; Jadad et al., 1996).

3.6. Data analysis and synthesis

A narrative overview of the studies was conducted. The results of trials that were sufficiently alike in terms of population and comparison interventions were pooled using a meta-analysis, using the Review Manager 5 software (RevMan Version 5.0 (2008). A random effects model was used, to account for the fact that the studies being compared were based on the treatment of different types of wound, and used a variety of wound care products and protocols.

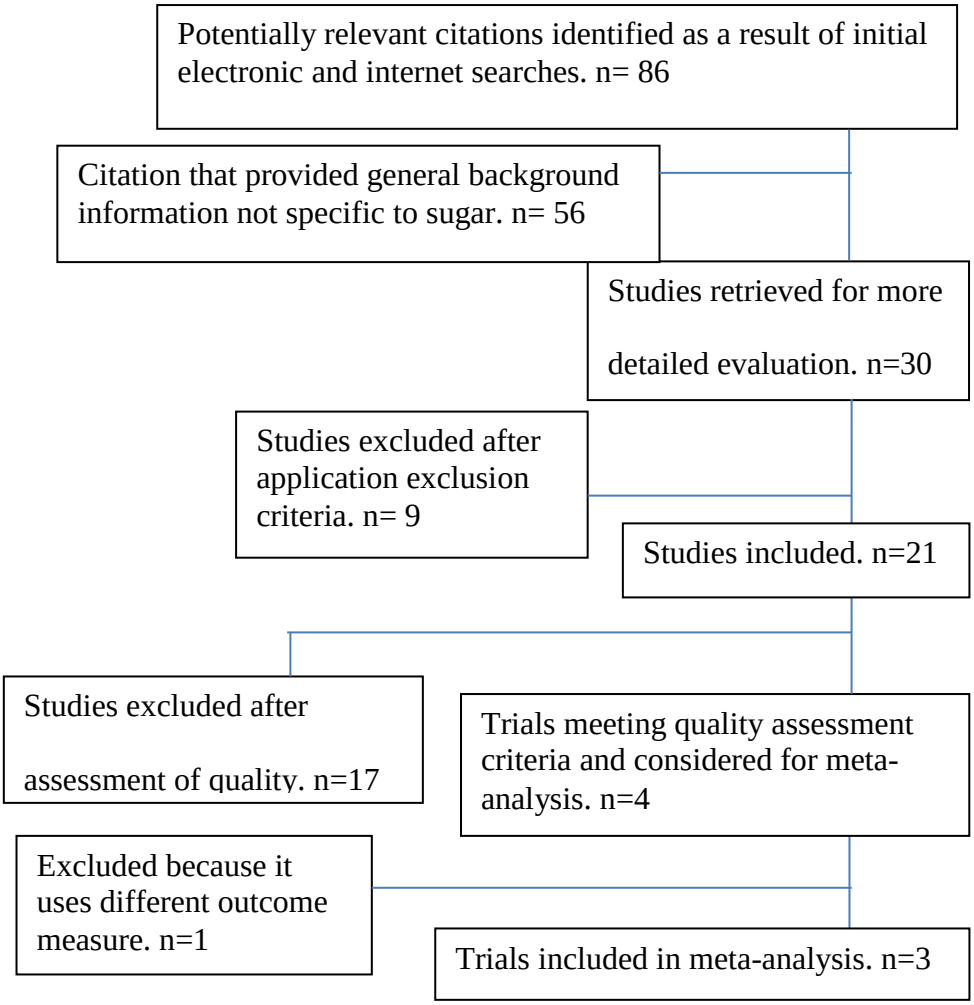
The overall difference between the sugar and control arms across the studies was represented using an odds ratio, with 95% confidence intervals. A Forest plot was produced to visualise

the results of the individual studies, as well as the pooled total. Statistical heterogeneity was assessed using the I squared statistic (Huedo-Medina et al., 2006).

3.7. Results

Eighty six (n=86) citations were identified as a result of the initial electronic and internet searches. Once titles and where available abstracts had been assessed 30 papers were considered. Further analysis through reading and applying exclusion criteria resulted in 9 studies being excluded because they did not explore use of sugar on wounds but gave general information related to different uses on sugar. Of the 21 papers identified as potential studies for inclusion into this review 17 were of poor quality. A total of 4 papers (see Table 3.2) met the inclusion and quality assessment for the review and meta-analysis; however, one study had a different outcome and was excluded from the meta-analysis (see **Figure 3.1**). The four trials explored use of sugar on wounds. The trials originated from developed and developing countries Japan; (Toba et al., 1997); Uganda; (Dawson, 1996): Malawi; (Mphande et al., 2007) and Nepal; (Bajaj et al., 2009). In terms of wound type all studies explored mixed aetiologies, however Dawson focused more on post infected surgery wounds while Toba and colleagues and Bajaj and colleagues (2009) focused mainly on pressure ulcers. Mphande and colleagues (2007) included leg ulcers. Details of the trials included are summarised in Table 3.2.

Figure 3.1: Flow summary of the identified papers for systematic review and meta-analysis



3.7.1. Excluded studies

From searching electronic databases there seem to be several studies involving sugar treatment. However, many of those identified papers were not eligible for inclusion. The common reasons for exclusion were study design (non-comparative observational and single or multiple case studies) and outcomes assessments were not clear. At times trials focused on subjective measure of wound healing. **Table 3.2** overleaf show studies that were closely considered for inclusion, but eventually excluded. All studies explored sugar on wounds but the sugar used was not standardised. The studies originated both from developed and developing countries.

Table 3.2: Summary of studies assessed for quality and excluded

Study Author & year	Country	Type of Study	Population (what type of participant, what type of wound etc)	Intervention	Acute/chronic wounds	Outcomes measured	Number of patients included	Duration of follow up	Reported outcome/conclusion	Reported disadvantage
Knutson et al 1981	USA	Case series	Various infected wounds	Sugar povidone-iodine	Both	Debridement and wound healing	605	5 years	Decrease drainage	Concern about contaminates in the sugar product
Chrife et al 1982	Argentina	Laboratory		Granulated sugar	Acute	Wound debridement and wound healing			Granulated sugar debridement infected wounds	Multiple dressing changes
Haddad et al 1983	Brazil	Descriptive		Granulated sugar	Both			Not specified	Inhibit bacterial growth	None reported
Troullet et al 1985	France	Descriptive		Granulated	Both				Inhibit bacterial growth	None reported
Debure et al 1987	USA	Case study	Infected surgical wound	Granulated sugar	Chronic	Debridement and wound healing	1	Not specified	Decrease odour	Lack of standardization on type of sugar product of the substance to which is added
Wiseman 1989	South Africa	Descriptive	Infected leprosy ulcers	Granulated sugar	Chronic				Inhibit bacterial growth	None reported
Archer et al 1990	UK	laboratory	Controlled wound model	Sugar paste	Acute				Wound debridement	None reported
Seal et al 1991	UK	Descriptive	Infected cavity wounds	Sugar paste	Chronic	Debridement and wound healing	1	Not specified	Stimulate granulation	May disrupt granulation tissue
Szerafin et 1991	Hungary	Observational	Mediastinitis after open heart surgery	Granulated sugar	Both	Wound debridement and wound healing	specified		Inhibit bacterial growth	None reported
Beadling 1997	North America	Observational	Deep infected wounds	Ordinary table sugar	Chronic	Wound debridement wound healing	1		Encourage epithelialization	May elevate blood sugar in persons with diabetes
Valls et al 1996		Observational	Infected pressure ulcers	Sugar paste	Chronic		1		Stimulate granulation	May disrupt granulation tissue
Grauwin et 1999	Senegal	Observational	Osteitis and septic arthritis	Granulated sugar	Both	Rate of wound healing	36	2 years	Granulated Sugar debrided osteitis and septic arthritis wounds	Lack standardisation; type of sugar
De Feo et al 2000	Italy	Observational	Recurrent Post open heart surgery Mediastinitis	Granulated sugar	Both	Rate of wound healing;	9	96 months	Granulated sugar is effective treatment option in patients with mediastinitis refractory to closed irrigation	Frequent dressing change
De Feo et al 2003	Italy	observational	Recurrent Post-open heart surgery mediastinitis		Both					Frequent dressing change
Ralf et al 2005	Netherlands	Observational	Post hernia repair- infected	1 kg granulated sugar	Acute	Debridement and wound healing	1	2 months	Wound debrided and healed in 2 months	Anuria, hyperosmolar hyponatremia
Chiwenga et al 2009	Malawi	Audit	Various infected wounds	Granulated sugar	Both	Wound debridement and wound healing	71		Reduced wound pain Wound odour removed Cheap	None reported
Ruhullah et al 2013	Nepal	Observational	Grade 3 & 4 Pressure ulcers	Granulated sugar	Chronic	Rate of wound healing; Reduction in wound size; Wound debridement	14	5-14 days	Wound debridement Enabled follow-up skin flap surgery Complete healing Cheap	None reported

Table 3.3: Summary of the four studies considered for inclusion in meta-analysis

Study Author & year	Country	Study design	Population	Intervention	Comparison Group	Outcomes measured	Total N	Duration of follow up	Allocation concealment	Randomisation Method explained	Blinding reported	Baseline comparability	Reporting Loss to follow up/Withdrawal	Intention To Treat Analysis
Dawson, 1995	Uganda	RCT	Infected post-operative wounds	Granulated sugar	Traditional gauze/Anti-septic packing	Rate of wound healing	11	Not specified	None reported	No	No	Not reported	Not reported	Not reported
Toba et al 1997	Japan	RCT	Elderly patients with MRSA decubitus lesion	Povidone Iodine sugar	Gential Violet and Dibutyrylc AMPoinment	Rate of wound healing; MRSA eradication; Reduction in wound size	19	14 weeks	None reported	Yes	Not reported	Yes	Not reported	Not reported
Mphande et al 2007	Malawi	RCT	Open or infected wounds	Granulated sugar	Local Honey	Time to complete healing	40	Not specified 14-133 days	None reported	Yes	Not reported	Not reported	Not reported	Not reported
Bajaj et al 2009	Nepal	RCT	Traumatic wounds	Granulated sugar	Eusol	Rate of wound healing; Reduction in wound size; Wound debridement	50	4 weeks	None reported	Not reported	Not reported	Yes	Not reported	Not reported

3.7.1. Quality of included studies

Of the 4 studies selected **Table 3.3** shows the details of the quality assessment. Sample sizes were highly variable ranging from 11-50 patients. All studies failed to report *a priori* sample size power calculation. Other aspects of quality were also variable with two trial providing their criteria inclusion and exclusion criteria (Bajaj et al., 2009 and Toba et al., 1997). Three studies (Dawson, 1996; Toba et al., 1997 and Mphande et al., 2007) did not include base-line comparability between groups. All studies reported collecting wound size as a baseline data, however only one study (Dawson, 1996) reported this characteristic on the results. Demographic data was poorly reported in three studies with only one study (Bajaj et al., 2009) providing such data.

Randomisation and allocation concealment

All four trials were described as randomised controlled trials, but only 2 trials reported how their allocation sequence was generated using a random number table; (number system, with corresponding registration numbers applied which was divided into two groups) (Toba et al., 1997). Mphande and colleagues used alternating admission for their allocation to either sugar or honey.

Allocation concealment

This was not reported in any of the trials.

Loss to follow up

Loss to follow up was not reported in any of the four trials.

Intention to treat analysis (ITT)

There were no reports of using ITT analysis in any of the studies.

Blinding

There was no reporting or employing of blinding on any of the four trials.

Baseline comparability

Baseline equivalence of the treatment groups was not reported in two of the trials. Two trials (Toba et al., 1997; Bajaj et al., 2009) reported baseline data, although the reported data was limited.

Risk of bias

Overall, the methodological quality of the trials was variable, with most trials failing to adequately report on randomisation or allocation concealment, study design elements that are known to decrease the risk of bias (Jadad et al., 1996; Schultz et al., 1995; Moher et al, 1998). Therefore, all trials were considered to have a moderate to high risk of bias.

Quality of life (QoL) assessment

None of the four trials reported on the QoL issues.

Studies Selected for Meta-analysis

Of the four RCTs (see Table 3.3), three reported the rates of wound healing as outcomes (Dawson, 1996; Toba, et al., 1999; Bajaj et al., 2009). Therefore, this was the common outcome that was included in the meta-analysis. One study was excluded as it reported a different outcome (Mpande et al., 2007)

Statistical results

Figure 3.2: Meta-analysis and Forest Plot

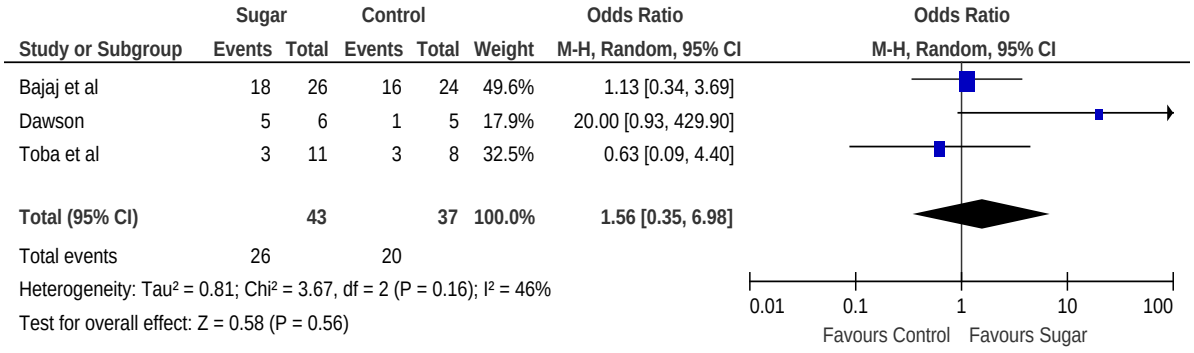


Figure 3.2 reports the results of the meta-analysis. It shows evidence of heterogeneity between studies (I^2=46%). This was not significant (p=0.16), due to the small sample size,

this significance test would have had low statistical power. Furthermore, the result of the Dawson study differed considerably from the other two, with an odds ratio for wound healing of 20.0 (95% CI=0.9 – 429.0), in favour of sugar. However, the small sample size in this study meant that, even though the difference between treatments was so large, it was not significant.

The overall pooled odds ratio for wound healing was 1.56 (95% CI=0.35 – 6.98) in favour of sugar. However, this overall effect was not found to be statistically significant (p=0.56).

3.8. Discussion

3.8.1. Treating wounds with sugar

Existing evidence does not support the treatment of exuding necrotic or sloughy wounds with sugar. The available evidence from RCTs (Dawson, 1996; Toba et al., 1997; Mphande et al, 1997; and Bajaj et al, 2009) does conclude that sugar has an effect on desloughing wounds but the findings are based on small studies where the possibility of type II error could not be excluded. Therefore, the role of sugar treatment in the management of exuding necrotic or sloughy wounds remains unclear due to methodological problems of the primary literature and lack of detail on baseline characteristics of participants. It must be pointed out that from the reviewed literature available there are no clear guidelines on the prescribing of the sugar products. The current available data is not standardized and lack of clarity on the type of sugar, dosage, or formula and frequency of dressing change pose difficulties in replicating studies. In addition; there are no clear guidelines on treating patients with diabetic foot ulcers. Sporadic reports suggest that use of sugar on diabetic foot ulcer wounds does not interfere with their blood sugar level (Tophan, 2000), but there are also other conflicting accounts of small elevation of blood sugar levels when treating these patients with sugar (Mphande et al., 2007). Furthermore, available research outcomes suggested that the use of sugar treatment is

not better than already available products such as honey (Mphande et al, 2007) and Eusol (Bajaj et al., 2009). Once again the methodological quality of these studies is poor. Both sample sizes were small with possibilities of type II error.

The above results (**Figure 3.2**) are all from small studies (range 11-50) in the smallest and the largest and it is likely that evaluations on this scale lack the statistical power to detect true treatment effects. It would be useful to replicate this area of research with a larger well-designed study. A further problem is lack of detail relating to baseline characteristics of participants and inadequate presentation of inclusion and exclusion criteria. In such trials focusing on sloughy, necrotic and infected exuding wounds of mixed aetiologies, it is important to have detailed reporting of baseline characteristics and results should be presented according to wound aetiology as well as in summary. Similarly, it is also necessary to report other adjuvant treatment.

3.8.2. Dosage of sugar

Various formulas of sugar have been reported by different researchers; sugar paste (caster sugar and polyethelene glycyrine) Matthew and Binnigton 1985; sugar paste (Povodone-iodine plus sugar) Knutson et al., 1981; Toba et al., 1997; Bajaj et al., 2009 and others used pure granulated sugar (Heszarge et al., 1983; Mphande et al., 2007; De Feo et al., 2000 and De Feo et al., 2003) but the dose and frequency is not replicable. It is imperative that further research is undertaken to determine the best preparation and dose of sugar and the type of sugar that are most likely to benefit from this product. To date there are several debriding wound care products in use, such as hydrogels, Eusol and hydrogen peroxide which has traditionally been used on cleaning exuding necrotic or sloughy wounds (Bajaj et al., 2009). Eusol and Hydrogen peroxide are no longer in use in the UK and many other developed countries because hydrogen peroxide and Eusol both have a caustic action that is dependent on the steady release of oxygen and can sting when applied on wounds. The damage may also

cause maceration to the surrounding healthy skin. There is also suggestion that there is a possibility of air embolism resulting from the action of the pressurised irrigation or used in enclosed body cavity wounds (Yarkony, 1994; Morgan, 1993). Hydrogel wound dressings have been used significantly when treating diabetic foot ulcers (Vuorisalo et al., 2009), however the variety of preparations used in the control group makes the results difficult to interpret. Furthermore, none of the control group included sugar. In Allen et al (1991) and Mphande and colleagues (2007) studies honey is considered to have antibacterial properties and has been compared with silver sulphadazine (Subrahamanyam, 1991) in the treatment of burns. Mphande and colleagues compared the honey and sugar in the treatment of wounds of mixed aetiologies (Mphande et al., 2007). In one of the longest and largest studies of 605 participants, Knutson and colleagues concluded that sugar combined with povidone-iodine was found to be beneficial in treating wounds of mixed aetiologies (Knutson et al., 1981). However, the type of sugar used and baseline characteristics were not described (Knutson et al., 1981). In 1997 Toba and colleagues undertook a RCT study to explore patients with pressure ulcers using sugar paste of povidone-iodine and findings supported those of Knutson et al (1981). But like previous studies the type of sugar used was not described. It can be argued that alternative approaches to managing exuding necrotic or sloughy wounds is of benefit, but their effectiveness and safety needs to be established with well-designed comparative studies before any conclusions can be made.

3.8.3. Complete healing

The frequency or rate of complete healing is the proportion of participants achieving complete healing (in most studies this means lesion closure), relative to the total number in the treatment arm. Between comparisons are then made by looking for statistically significant difference between the proportions of healed lesions in each arm. While this can be a useful measure, it can be argued that the choice of follow-up time can influence outcomes as

complete healing is more likely to occur with longer follow-up even in the absence of an intervention. To resolve this issue Altman (1997) advises using survival analysis strategy. This involves the estimate by regression of the time taken for all wounds to heal beyond the follow-up period and this according to Altman is the most reliable strategy if an account is taken of the frequency of healing and rate of healing. None of the four trials reviewed included a survival analysis model. This is important because if time to healing is chosen as the primary outcome a group that has predominance of smaller wounds/ulcers is most likely to achieve better results because larger wounds/ulcers take longer to close. It is therefore important to match groups for wound/ulcer size by using baseline wound/ulcer size as a stratification variable (Stacey et al., 1991). From the reviewed literatures it is apparent that other difficulties that can be encountered in this kind of research is subjectivity of measurement and different definitions of complete healing. Subjectivity can be that of judging whether complete healing has occurred or not and the inter-rater reliability may be poor, even when assessors are experienced in wound care management. Using definitions of complete healing per participant per limb and per wound may give different results in cases where patients have more than one wound included in the study.

3.8.4. Mean change in wound/ulcer size

In both studies Dawson (1996), Toba et al (1997), Mphande et al (1997) and Bajaj et al (2009) a between group comparison of the mean change in wound/ulcer size relative to baseline was used as one of the outcome. The wound/ulcer outline may be traced directly onto paper or acetate, or a photograph or slide may be used. If photographs or slides are used the image can be calibrated by placing a centimetre scale at the side of the wound. The area within the tracing can be calculated by counting grids on graph paper, uniform density tracing paper planimetry or by using computerised image analysis. Technologies, such as computerised image analysis or the use of digitisers have now advanced and are slowly

replacing most of the traditional methods of wound measurement. However, the most commonly reported method is that of measuring the longest and shortest part of the wound using a clinical ruler and multiplying the two readings to find the surface area of the wound in centimetres or millimetres. Although these are the most commonly used methods of measurement in wound care a comparison of different measurement tools showed that direct acetate tracing produce more accurate measurements as compared with photographs combined with image analysis (Thomas and Wysocki, 1990).

3.8.5. Bias arising from wound/ulcer size

Bias may arise unless treatment groups are matched at baseline for wound/ulcer size. Failure to do so may render results unreliable. This is because a group containing many smaller wounds/ulcers which are likely to heal quickly will be favoured if complete healing and time to healing are selected as study-end point. Groups with predominance of small ulcers are also likely to achieve better treatment outcomes if the primary outcome is the change percentage in wound/ulcer surface area. Conversely, a participant group with mainly large wounds/ulcers will appear to produce better healing outcomes if absolute change in wound/ulcer surface healed is the outcome of interest (Stacey and Burnand, 1991; Gorin et al., 1997). In the evaluations of pressure ulcers and cavity wounds the baseline comparability of wound volume should also be considered. Although the reviewed RCTs explored wounds of mixed aetiologies Mphande et al (2007) and Bajaj et al (2009) and Toba and colleagues (Pressure ulcers) the comparable surface area and volume baselines respectively were not mentioned. Average baseline estimates of wound sizes within groups can mask the true distribution and heterogeneity between groups. Therefore, more detailed information on the relative frequencies of different categories of wound size per group is necessary. In the reviewed trials, the researchers did not mention any wound categories and this indicates poor quality of

the methodology that can affect the findings, considering that wound measurements are taken on estimates.

3.8.6. Comparison with other systematic reviews

Two systematic reviews concerned with the use of sugar on wounds were identified. Pieper and Caliri (2003) undertook a review on non-traditional wound care products including sugar, papaya/papain and fatty acids from 1981-2000. The findings were that sugar was safe to use on necrotic exuding wounds. It helped debride wounds, reduce wound oedema, decrease exudate, inhibit bacterial growth, caused little pain on dressing change and encouraged epithelialisation. The review also highlighted the disadvantages as a lack of standardisation on the type of sugar; difficulties in holding sugar in place may disrupt granulation tissue. There were issues related to lack of description of subjects/patients wounds, contaminates in the sugar and multiple dressings changes. Some studies were concerned about elevation of blood sugar levels, renal insufficiency and lack of randomised clinical trials. Although the findings of this review were encouraging, overall, the review is very basic and a multifocal (sugar, papaya/papain and fatty acids) lacking depth in sugar on its own. Because the review's focus was on several different products there is justification for further exploration of literature focusing on sugar as a wound care product.

A more recent review was done by a group of American surgeons (Biswas et al., 2010) into the wound management of diabetic foot ulcers. The review is divided into two parts. The first part reviewed fifteen studies of the physiological rationale for the use of sugar in wound healing, ranging in date from 1953 to 2007. There was clearly a peak of interest in sugar from the mid-1980 to the end of the 1990's. The 15 studies in this section cover a wide range of material, from the anecdotal to the scientific. Two studies have honey as their focus, two are animal studies and three are *in vitro.* There is a clear account of the material used and the theories that are postulated. There was an overall conclusion that multiple reports

documented the effect and the ability of sugar to reduce wound exudate, odour, and oedema. But, this evidence lacked evidence on cellular and molecular interactions between sugar and wound environment.

The second section reviewed eleven case studies. Again the dates range from 1958 to 2001, with the majority in the mid 1980's. There is a critical appraisal of the material and a detailed account of case studies. However, the focus in this section is on diabetic foot ulcers, which is understandable given the aim and the title of the review.

The reviewers Biswas and colleagues (2010) did not comment on the quality of the papers or the statistical significance of the evidence or whether sugar treatment affects blood sugar levels of diabetic patients, instead concluding that more evidence was needed in this area. They further suggested a prospective trial for the treatment of diabetic foot ulcers. This was a fairly comprehensive review of the state of knowledge in 2010. However a few studies were missed (Keith & Knobel, 1988; Haughton & Young, 1995; Topham, 2000; Mathews and Binnington, 2002; Topham, 2002; De Feo, 2003; Booth, 2004; Hampton, 2007 and Ambrose et al., 1991; Grauwin, Cartel & Lepers, 1999; Mphande et al., 2007 and further work has now been done Ammons, Ward & James 2011, Al-Waili, Salom & Al-Ghamdi, 2011; Murandu et al., 2011; and Ruhullah et al., 2013).

In both reviews there were notable methodological problems. The search strategy as well as search terms were not clearly stated in both studies. In addition, only English language reports were mentioned. Both studies' inclusion criteria were not specified. In Biswas and colleagues' review two of the included studies overlap with this review Dawson (1996) and Toba et al (1997).

Quality of life

No trial was found reporting data on health related quality of life (HRQoL) using a specific (HRQoL) tool. It is important that future research incorporates this aspect of wound care as it

allows participant concordance and assessment of patients' acceptance of the intervention treatment.

3.9. Adverse events

None of the studies included reported adverse events associated with sugar intervention or comparator. It is important that future research studies address this issue as the incidence of adverse events may impact on the extent to which patient feel able to adhere with treatment regiments. In particular localised skin reactions may be a problem for people using topical preparations such as sugar or sugar-paste.

3.10. Conclusion

At present, there is no existing good quality evidence to support the routine use of sugar dressings to promote wound healing in non-healing acute or chronic exuding necrotic or sloughy wounds. The lack of reliable evidence means that it is not possible to recommend the use or the discontinuation of the sporadic use of the sugar reported in different formats from different developing and developed countries. It is possible that sugar treatment may be effective as reported in some literature (Dawson, 1996, Toba et al., 1997, Mphande et al., 2007 and Bajaj et al., 2009), however rigorous evaluation is needed.

The four RCT studies gave promising results however the small sample size as well as the poor methodological quality of the studies raises many questions. There is no clear evidence on the type of sugar, dose and frequency of use as mentioned earlier.

3.11. Implications for future research

All results reviewed are from small trials with methodological problems. Therefore, future research should focus on the following:

- Larger well-designed studies.

- Clearly define the inclusion and exclusion criteria for participants.
- Consider sample size with sufficient power to detect true treatment effects.
- Clearly report on *a priori* power calculations of the sample.
- The trial must make use of true random numbers with clear method of randomisation with allocation concealment.
- Consider using either opaque sequentially numbered sealed envelopes or computer-generated codes.
- Must stratify wound/ulcer size and aetiology.

Future researchers must guard against factors that may affect healing outcomes by using survival analysis, intention to treat protocol and analysing complete healing rates. It is also important to report of incidence of adverse events and detailed numbers and characteristics of withdrawals from the treatment group.

It will be of use to carry out comparisons between other debriding agents such as hydrogels in order to evaluate both the relative effectiveness and the cost-effectiveness. The cost-effectiveness of sugar treatment needs to be established taking into account the patterns of healing and recurrence that can occur with non-healing acute and chronic exuding necrotic or sloughy wounds.

The next chapter is the feasibility study. The researcher will explore the suitability of using sugar as a wound care product in an NHS hospital. It is also important to determine the effects of sugar treatment on diabetic patients' blood sugar levels. In addition, the study explored both nurses and patients' acceptance of the treatment. Finally, a sugar dressing protocol needed to be developed.

4. Chapter: Feasibility study

4.1. Introduction

Chronic sloughy, necrotic and infected exuding wounds are a major problem in any wound care setting. They affect the quality of life of patients (Gardner and Cook, 2004; Madeo, 2001) to the extent that, some patients decide to isolate themselves. These wounds at times are the cause of extended hospital stay for patients as acknowledged by (Plowman et al., 2001). Finding an appropriate dressing product that can facilitate healing and improve the quality of life of these patients is an ongoing process. To this effect sugar has been explored previously when managing these types of wounds (Herszage et al., 1980; Chirife et al., 1983; Archer et al., 1990; Mphande et al., 2007; Chiwenga et al., 2009). The researcher had had an experience of using sugar precedingly in Zimbabwe. However, there was uncertainty as to how its use would translate to NHS hospital; therefore this study was proposed to assess the feasibility and acceptability of sugar treatment on a vascular ward in a modern NHS hospital. It must be pointed out that sugar (in the form of sugar paste) had been used before in the UK as a wound care product with sporadic reported case studies (Middleton, 1985; Gordon et al 1985; Booth, 2004) available. There was not specific sugar protocol developed from the reported sugar studies. That made it very difficult to adopt this method of wound treatment. Furthermore, there does not seem to be any mention of the relationship of diabetic patients receiving sugar treatment and the level of their blood sugar. Does sugar treatment raise blood sugar level of diabetic patients? To date not many nurses in the UK are aware of the use of sugar treatment on wounds therefore it is important to determine their perception of the acceptability of this method of treatment. Patients suffering from long standing wounds often times accept any alternative treatment especially when the wound has been delayed in healing. However, this assumption was to be determined before any further large studies were to be conducted as patients might be sceptical in opting to use sugar. Although there is

theoretical basis to support the use of sugar (Chirife et al., 1983), there is no data upon which to base a design for a definitive randomised controlled trial to test its efficacy in the UK, so this study is undertaken to assess the possibility of using sugar treatment in a modern NHS hospital and develop a standard sugar dressing protocol.

Aims/Objectives summary

The study aims to:

- Determine wound sizes, sugar dosage and acquisition of single use aliquots
- Make sure the study complies with Ethical and MHRA guide-lines
- Train doctors and nursing staff on the use of sugar dressing
- Establish types of patients and research site appropriate for a full trial
- Monitor recruitment and drop-outs rates
- Determine acceptability of sugar to patients
- Determine the effects of sugar on microorganisms
- Determine effects on diabetic blood sugar levels
- Determine appropriateness of methods of data collection
- Determine appropriateness of the dressing in an NHS hospital
- Calculate the appropriate sample size for a randomised controlled study
- Develop a protocol for managing exudating wounds with granulated sugar.

Outline of overall outcomes of the study

The overall outcomes of this study are illustrated in **Table 4.1** below.

Table 4.1 Summary of primary & secondary outcomes

Primary outcomes	**Secondary outcomes**
Effects on wound--- debridement, malodour, exudate and pain (using TELER indicators)	Acceptability to patients, doctors & nurses (using purposely designed questionnaire) see Appendix 11.
Effects on wound infection (laboratory wound swab analysis)	Completeness of data and appropriateness of data (using case report form)
Effects on diabetic patients' blood sugar level (using routine diabetic blood sugar test)	Ease of dressing change (using TELER)
Serious adverse effects (using adverse effects report forms)	

4.2. Determining wound sugar dosage and acquisition of single patient dose aliquots

It was vital that wound sizes and sugar dosages were determined prior to commencing the feasibility study. This was to help in developing an appropriate sugar treatment protocol. In order to achieve this task, 'White' cane/beet granulated sugar (see **Figure 4.1** A) was acquired from Tate & Lyle and British Sugar companies respectively, and was supplied with certificates of conformity (see Appendix 5: Tate & Lye Certificate of conformity). The researcher undertook assimilation of wound dressing using sugar on wound models in the clinical skills laboratory (see **Figure 4.1)**. Wound models were measured of their length and width (**Figure 4.1** B & D); these were multiplied to find the wound surface area in centimetres. Granulated sugar was gently poured on the wound models (see **Figure 4.1.** C & E), fully covering all the wound areas. Sugar was poured from the wound model onto a digital kitchen scale (see **Figure 4.1** .F) GT- KSg-02; approximate size 15 x 22 x 1.7cm with coin battery CR2032 / 3 V. / 3-5 mA operation. The digital scale's measuring range was 5g to 5000g with measuring intervals of 1g / 1 ml with measuring precision of +/- 0.2 %. The ambient temperature was +10 ^{0}C to + 40 C. From this exercise, it was possible to categorise

wounds into $5cm^2$-$10cm^2$ (small-medium) and $10cm^2$-$20cm^2$ (medium- large). The amount of sugar needed for each wound was found to be as follows: Small wounds =15g sugar and Medium to large wounds = 30g sugar.

Figure 4.1: Determining the therapy dosage

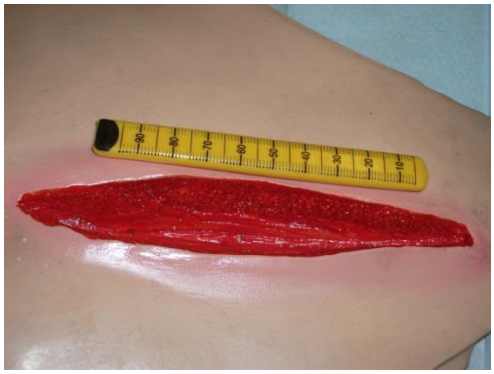
(A)

A – bag of granulated sugar

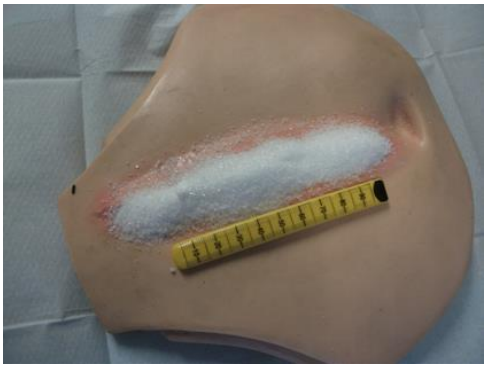
B & D – different types of wound models measured

C & E – sugar poured on wounds

F – amount of sugar used



(B)



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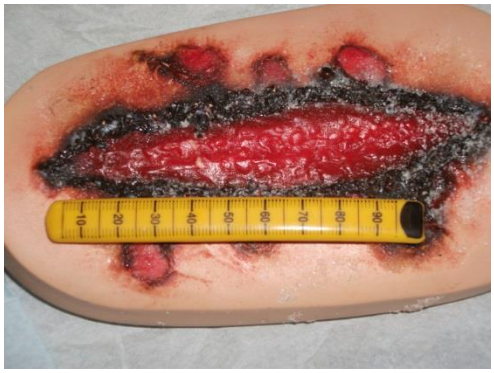
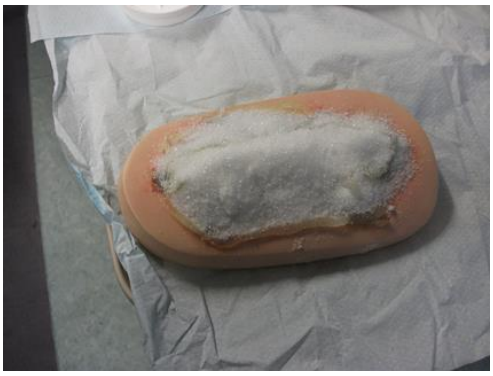
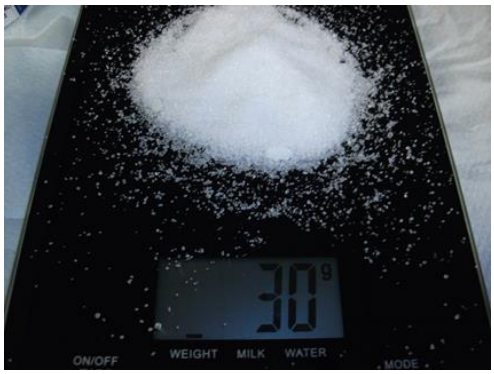


(D)

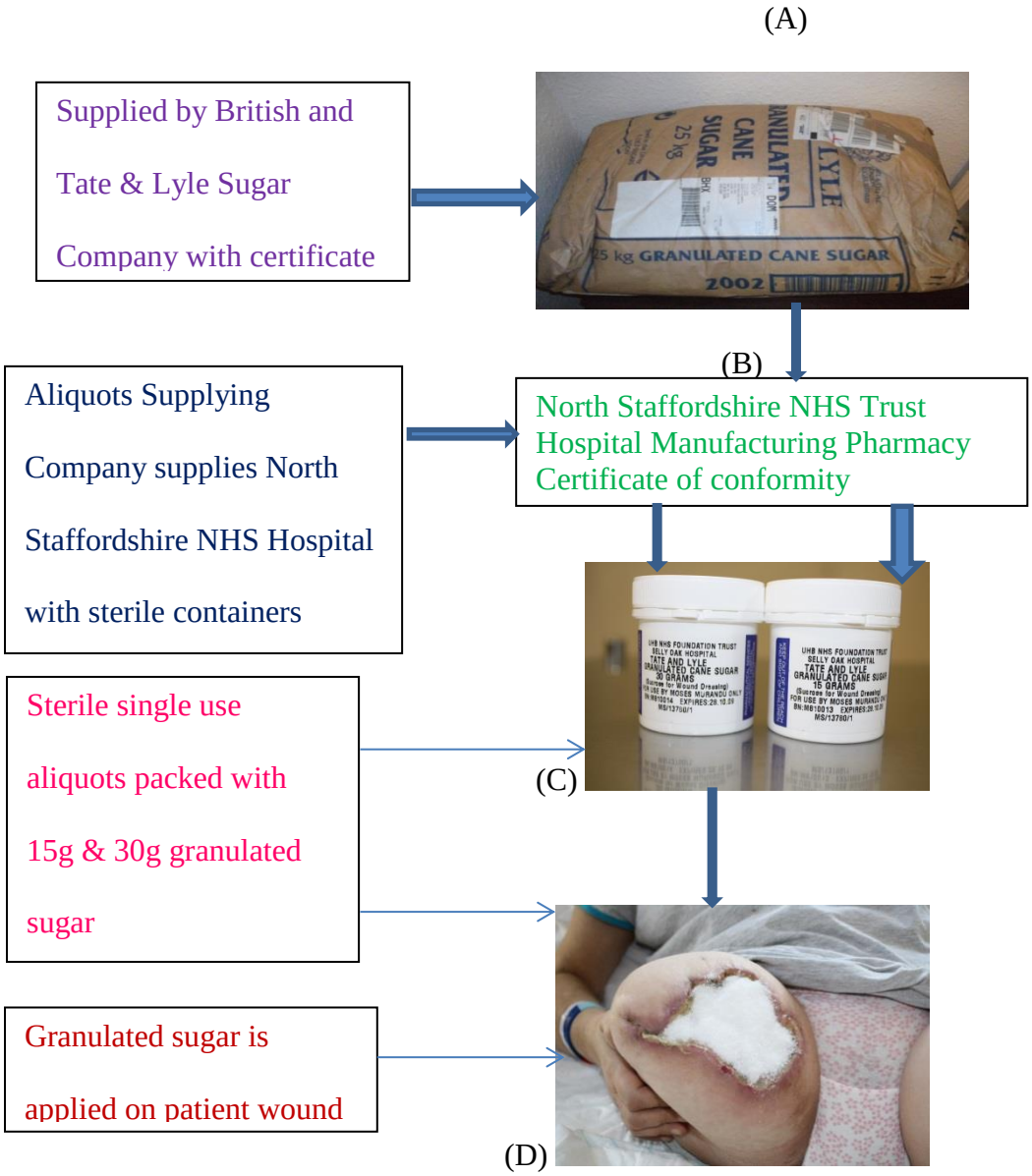


(E)



(F)

Figure 4.2: Illustration of supply chain flow of sugar from manufacturer to patient use.



4.3. Acquisition of 15 and 30 grams single use aliquots

Having determined the specific wound sizes and sugar dosages needed for each wound category, the 25kg bags of sugar acquired from Tate & Lyle and British sugar (with certificate of conformity (see Appendix 5) was delivered to the Manufacturing Pharmacy and wound specifications and dosages where given to the lead production manager and the sugar

was packaged into single use sterile aliquots of 15g and 30g (see **Figure 4.2**) under sterile conditions. Packages were serialised so that any adverse effects during clinical usage could be monitored and tracked to the packaging pharmacy or manufacturer. **Figure 4.2** illustrates the schematic diagrams of the supply chain of the sugar from manufacturer to the patient.

4.4. Medical and Nursing Staff training on use of sugar dressing

A series of meetings and training sessions were held to inform nurses and medical staff about the application and dressing changes. Both nurses and medical staff were concerned about the effects of sugar with diabetic patients, in particular hyperglycaemia. This was discussed and it was resolved that diabetic patients would be monitored for their blood sugar levels on admission and at regular intervals during the study. Although, there is evidence to suggest that sugar (sucrose) has no effect on blood sugar levels when applied topically (Yudkin et al., 1971; Knutson et al., 1981; Ambrose et al., 1991; Toba et al., 1997; Tophan, 2000) it was necessary to monitor every diabetic patient who was recruited into the study whether they were non-insulin dependent or insulin diabetic. All diabetic patients admitted into the trial had their blood sugar levels checked on admission into the trial as a baseline reference. The monitoring of the blood sugar continued throughout the period of the study.

4.5. Compliance with Ethical and Medicine and Health Regulation Authority (MHRA) issues

Researchers are bound by ethical and good clinical governance guidelines and this study was no exception. Therefore ethical approval was granted from the North Birmingham and Solihull Local Research and Ethics Committee prior to commencing the study. Ethical principles laid down in the National Health Service (NHS) Research Governance framework (DoH, 2008) were adhered to. The researcher had an honorary contract with the University Hospital Birmingham National Health Service Foundation Trust (UHBNHSFT). Full informed consent procedures were followed. Prospective participants were given time to read

the information (see Appendix 3) about the proposed study prior to inviting them to take part. The researcher was aware of the diversity of the population to be studied and the need for an informed decision to take part in the study. The UHBNHSF Trust has a robust and effective interpretation services that the researcher was able to use if there was language barrier. However, this was not required as all recruited participants understood English language sufficiently to make informed decision. All prospective participants were asked to sign consent form (see Appendix 7).

Patients were informed of their right to withdraw from the study at any time. Confidentiality of data, subjects and study settings were maintained throughout this study in accordance with the Data Protection Act (Great Britain Parliament 1998). Anonymous data were stored at the research centre (the UHBNHSFT Research and Development offices) on a computer with a protected password. Hard copies of data were stored in a locked facility at the centre and the keys kept in a safe supplied by the Research and Development Supervisor. Following completion of the study all data were kept securely according to the UHBNHSFT Research and Development protocol.

In addition to the ethical approval this study required authorisation from the Medicine and Health Regulation Authority (MHRA) as sugar when used on a wound is considered to be a drug. Permission was sought from MHRA before commencing. Authorisation was given on condition that patients will not be charged if there was to be an effect on the wounds, see MHRA correspondence in (Appendix 2).

4.6. Establishing data collection methods/tools/TELER system

It is worth noting that, no study is superior to the quality of its data. This point is supported by Friedman and colleagues who stated that, “during all phases of a study, sufficient effort should be spent to ensure that all key data critical to the interpretation of the trial are of high quality” (Friedman et al., 1998, p. 157). Therefore, it was vital that an appropriate data to be

collected was identified clearly and data capturing tools determined prior to commencing the study. This study's wound evaluation was based on treatment evaluation by Le Roux (TELER) system (Le Roux, 1995). The aim was to get a broad picture of the impact of sugar on the wound. The TELER is a generic system for making clinical notes and measuring patient centred outcomes of treatment and care (Le Roux, 1995). The system has two main elements, clinical note making and clinical measurements. These domains assess information regarding the pattern of change, or lack of, in a patient condition. This is coded at individual patient level using indicators based on measurement theory. The TELER indicator is an ordinal measuring scale for tracking change using six clinically significant reference points, or codes from 0-5 (see **Table 4.2**). These indicators are used to determine whether outcomes have occurred by chance or not.

Table 4.2 An example of *TELER* indicator: Pain Impact of Dressing Change.

Code	Indicator Definition
0	Unbearable dressing change medication needed during pre & post dressing change
1	Distressing dressing change, medication needed
2	Unpleasant dressing change, medication needed
3	Disagreeable dressing change, no medication needed
4	Some unpleasantness
5	Dressing change alright

Code 5 defines the goal of treatment and care, and is agreed upon with the patient. For example, 'Dressing change alright' (see code 5 in Table 4.2). When a starting code is 0 and an outcome code is 4 or 5, the latter is statistically significant, denoting 4 or 5 significant improvements. When a starting code is 1 or 2, and the outcome code is 5, this denotes 4 or 3 clinically significant improvements respectively (Le Roux, 1995). Data recorded measures whether a patient outcomes are attributed to the care received or by chance (Brown et al., 2004). With five clinically significant improvements the probability that the outcome occurred by chance is believed to be less than 2.5% (Le Roux, 1995; Grocott, 2000; Browne et al., 2004). The system is believed to discriminate treatment effects, dressing performance failure, gaps in clinical knowledge and wound care skills, including product use (Grocott and Browne, 2005). The definitions capture observable, patient-centred treatment and objectives. This forms outcomes that are clinically significant because they can be justified by appropriate theory or knowledge. Without clinical knowledge, the definitions lack meaning and will not be repeatable and fail.

The decision on whether the wound was debrided and healing was made by the clinical staff (doctors and nurses) following ward round wound assessments. It is during this clinical round

that expert opinion on wound healing was significant as judgement was based on subjective and objective observation required by TELER system.

4.7. Digital photography

Digital photography has increasingly become part of healthcare management within the 21st century providing much needed aid in patients' diagnosis. In wound care, digital imaging has proved invaluable as clinicians can share knowledge internally and externally allowing easy exchange of knowledge and ideas. This is the reason why it was decided to use digital photography in this research. This process was to help with the monitoring of wounds and comparing the initial photography to the subsequent images. It helped with review of wounds by those senior surgeons who would have missed the ward round review/assessments due to other commitments. Digital photography varies from amateur to high-tech photographers. In this research, it sufficient to have clear and consistent photographs, and there was no need for formal training in photography.

During admission, the admitting nurse or the researcher without any formal photography training photographed all wounds using a digital camera (Canon EOS-1000- ESF 18-55mm with 0.25m/0.8ft that complies with the Canadian ICES-003 Class B specifications; CANON INC. MADE IN JAPAN with single CCD chip ..32megabites colour. There was no specific protocol on imaging. However, there were basics guide-lines to follow:

- **Camera**- Auto focus, auto flash, auto exposure
- **Lighting** -window shade closed, overhead examination light on
- **Position of patient** – supine and comfortable to patient
- **Wound presentation** – Incontinent pad under extremity; yellow disposable ruler and identifier number adjacent to the wound
- **Photographs** taken (image set)

- **View of wounds** (camera 25-35cm from wound)

All 22 wounds were photographed initially followed by interactive and convenience photography. Wounds were photographed weekly for a period of four weeks, however some wounds were considered debrided earlier than four weeks so their wounds were photographed at that point. Images were stored as highest-quality JPEG (PC Webopaedia 1997 online) files (Joint Photographic Experts Group, a comparison algorithm for digital images) and were converted to a Microsoft PowerPoint slide presentation to be viewed on a computer monitor at the maximum attainable resolution).

Wound descriptors that guided clinical staff regarding wound progress and non-progress were wound exudate, odour, gangrenous, necrosis, erythematous tissue, cellulitis/infection, pain, ischaemic or granulating tissue presence. The wound management decision would either be wound healing without problems, wound not healing, there is need for alternate management or there is granulation and sugar is no longer required. At times the decision was the study period is over; however continuing with the sugar if there was patient benefit.

4.8. Other auxiliary data collection tools

In addition to the TELER system and digital photography, there were two other tools: a purposively designed patient satisfaction survey questionnaire (see Appendix 10) that was aimed at reporting the opinions of patients on the use of sugar, and a purposively designed staff satisfaction survey questionnaire (see Appendix 11). These were administered at the start and end of the trial.

4.9. Patients' classification and site of recruitment

Patients were mainly recruited via the vascular surgeons who supported the project; however there were some referrals from different wards with patients with wounds of other aetiologies

beside vascular. Recruitment took place from January 2009 to July 2009. Eligible patients included those who had recently undergone a lower extremity bypass procedure or amputation or were admitted for a wound healing problem (non-healing ulcer, necrotic or gangrenous toes, cellulitis, fasciotomy, pressure ulcer, or abdominal surgery). **Table 4.3** illustrates the inclusion and exclusion criteria.

Table 4.3: Patient selection criteria

Inclusion
Patients who independently and willingly consent
ABPI* of 0.8-0.6
Exudating wounds
Necrotic escar not present
Diabetic & Non Diabetic with all of the above
Exclusion
ABPI less than 0.6
Presence of necrotic escar
Pregnant + nursing mothers

**ABPI =arterial brachial pulse index*

In addition to the above list, a known allergy to sugar products (*although very rare on my previous experience and that of reported literature*) or those already recruited for another trial were excluded.

All patients who fitted the above inclusion criteria were invited to take part, any eligible patients who did not participate were excluded as a result of factors beyond the control of the study, (see study flow diagram **Figure 4.3**). Reasons included clinical staff scepticism of the suitability of sugar to treat the wound; busy clinical activity and oversight; scepticism of patients and refusal to consent (2 patients). The number of wounds per extremity and wound category were assigned on the basis of the clinical staff examining and documenting on wound care chart (see Appendix 8). If a patient had more than one wound, all the wounds

were considered for the sugar trial if he/she had consented to the study. For post-operative incisions, any area of the incision with a wound complication that might independently influence wound evaluation was considered a separate wound. A brief history of age, gender, reason and date of admission, medical and surgical history, diabetic history and treatments rendered from admission to the time of admission to the trial on each patient was obtained and recorded on patients' notes and only relevant history was recorded on the purposely designed wound assessment chart.

Figure 4.3: Feasibility of sugar dressing a Study Flow diagram

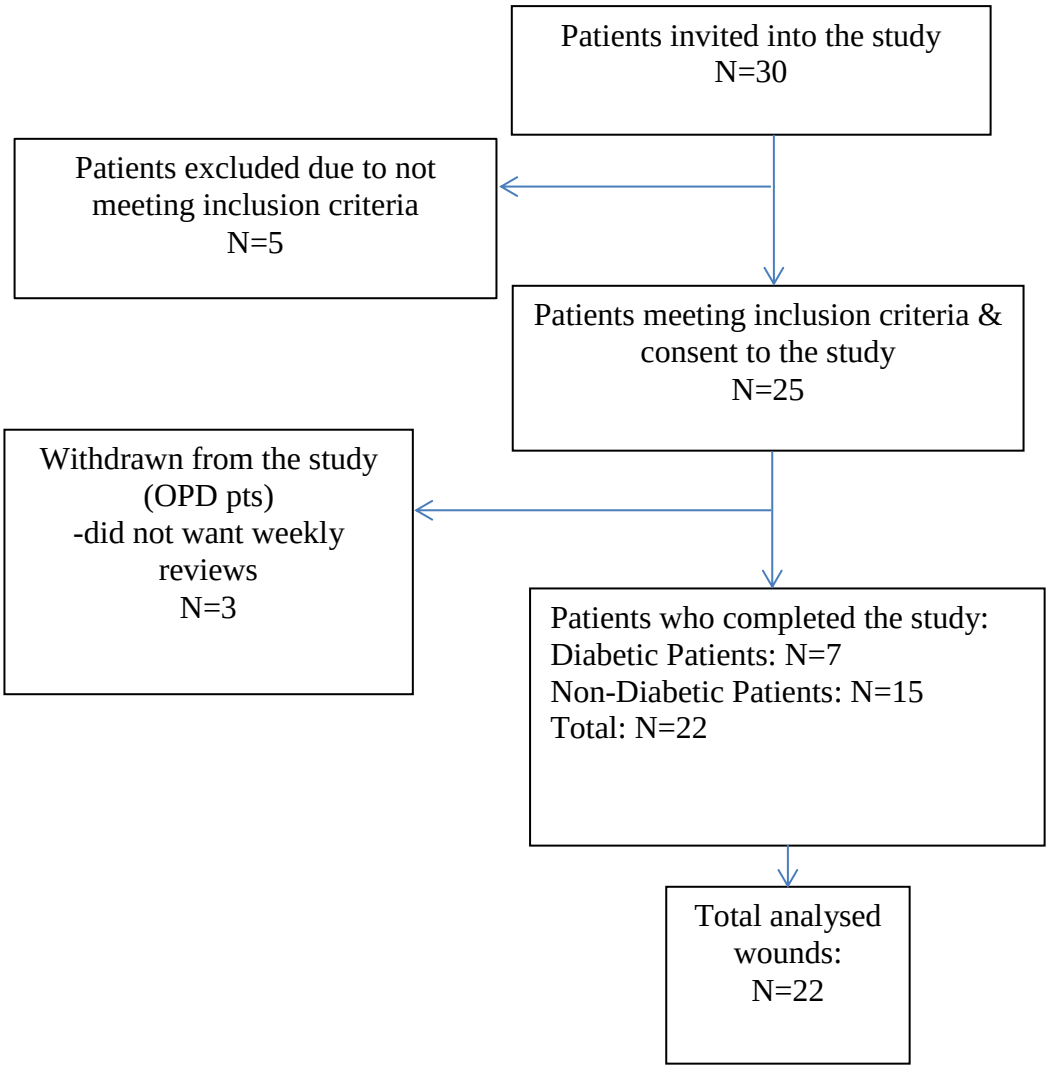
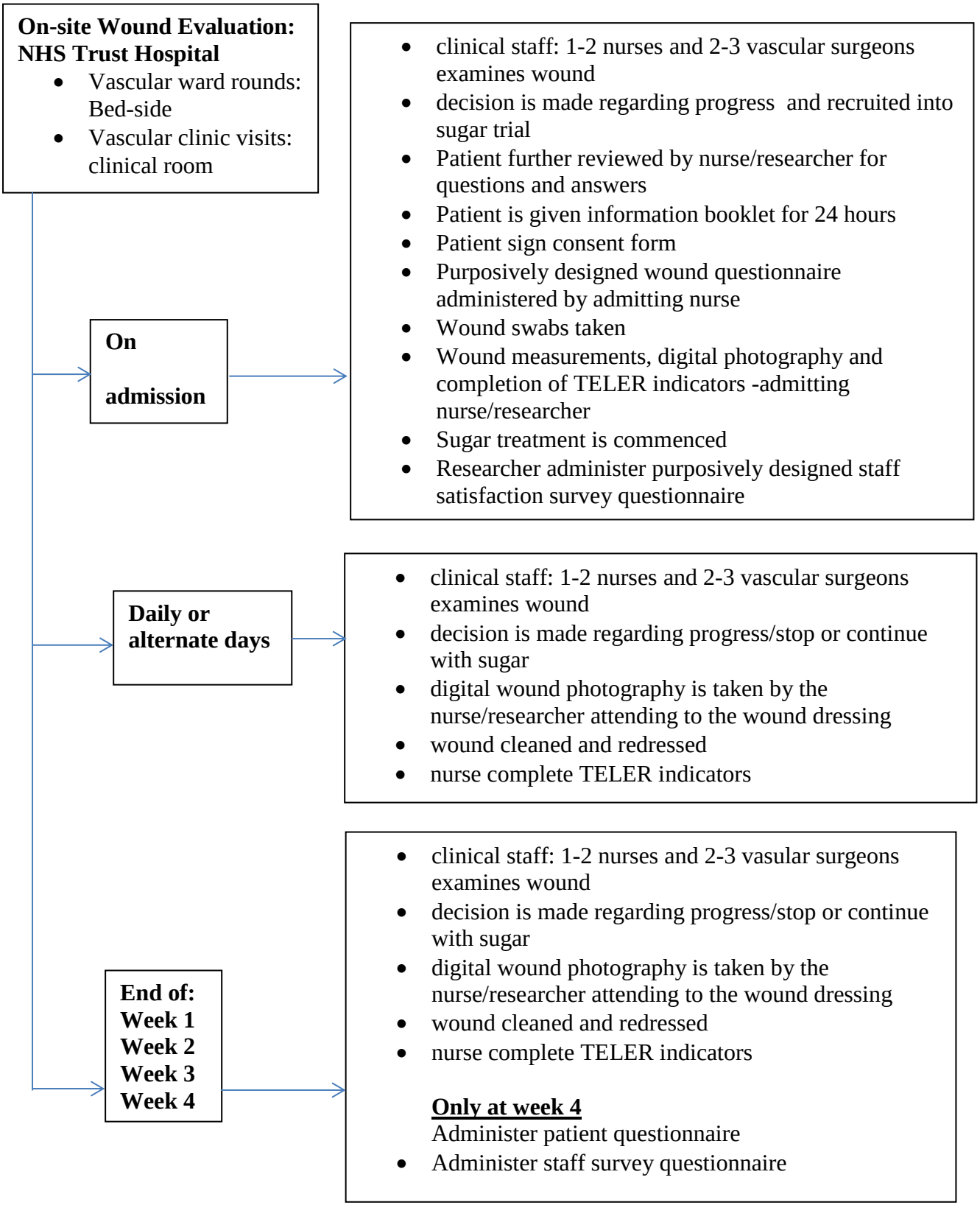


Figure 4.4: Study design. Using the adapted TELER system indicators and purposively developed questionnaire and bedside wound examination as the gold standard, the feasibility of sugar trial for wound management in an NHS hospital was measured by concordance between the patient and clinical staff at the bed-site evaluation



4.10. Wound swabs and microbiological assessment

It is known that a healthy skin is home to natural commensals ranging from Staphylococcus epidermis, Mycobacteria, Propionibacterium (anaerobic) and Corynebacterium most of which are gram positive aerobes. According to White and Cutting (2008) chronic wounds often contain necrotic or sloughy tissue which can harbour bacteria and act as a barrier to healing. It also follows that all open wounds will be colonised by commensal flora and depending on a range of factors both internal and external to the patient, may or may not cause infection. Wound infection is caused by pathogenic microorganisms evading the victim's immunological defences, entering and establishing themselves within the host's tissues, thereby multiplying causing a host reaction (Gardner et al., 2001; Gardner and Cook, 2004; Edwards and Harding, 2004). Accurate management of wound infection is dependent on identifying and treating the infecting organism. It was on this basis that swabs were taken on admission to the study and weekly to determine the colonising microorganisms and subsequently checking the effect of the sugar on the reduction or increase of microbial activity on the trial wound. Gardner and Cook, (2004) and Edward and Harding, (2004) go on to describe devitalised tissue as an increased risk of harbouring infection as microorganisms evade the host immunological defences and establish themselves, multiplying causing host reaction. Therefore early removal of necrotic tissue should reduce the risk of contamination and infection thereby facilitating healing, and this is what sugar is believed to facilitate (Tophan, 2000; Tophan, 2002; De Feo, 2003).

Base-line wound swabs were taken for every patient admitted on the trial. These were collected after signing the consent form. Swabs were subsequently collected weekly after commencing the sugar until end of week 4 but whenever any patients showed signs of infection additional swabs were collected and send for microbial assessment.

In addition to collecting and analysing wound swabs, clinical staff evaluated the wound during ward rounds for signs and symptoms of infection as mentioned earlier. Follow up weekly swabs were taken if the initial swab was positive of staphylococcus aureus and the wound had signs and symptoms of infection. This was stopped if there were two consecutive negative swab results with no sign of clinical signs and symptoms of infection. If the wound swabs remained positive and there were signs and symptoms of infection or at end of the study if the wound showed signs of infection like inflammation, painful, covered with 50-100% necrotic malodourous or non-malodourous tissue then an alternative wound care product and antibiotic was to be commenced.

Swabs were cultured for MRSA and other routine and serious wound pathogens in concordance with standard laboratory wound management policy of the trust. Swabs were taken before the wound were cleaned to maximise the size of microorganism collected; the swab was zigzagged across the whole wound under gentle pressure while being rotated between the fingers (Cooper and Lawrence, 1996) and immediately stored in transport medium and dispatched to the laboratory as soon as possible. All identified ward nurses who participated in the study were educated before the trial on how to swab the wounds.

4.11. Definitions of importance in this study

Wound infection is defined as a positive swab associated with pain at the wound site, increased exudate, odour, swelling, heat, or local redness. Colonisation was defined as a positive wound swab with no clinical indication of infection.

Debridement is defined as the removal of sloughy, necrotic, or damaged tissue from a wound until the surrounding healthy tissue is exposed (Mudge et al., 2014).

4.12. The method of applying sugar dressings

All wounds were cleansed using standard wound cleaning methods (cleaning with normal saline or washing with tap water in a wash bowl). After dabbing dry with sterile gauze, sugar was dusted over the wound until it was fully covered see

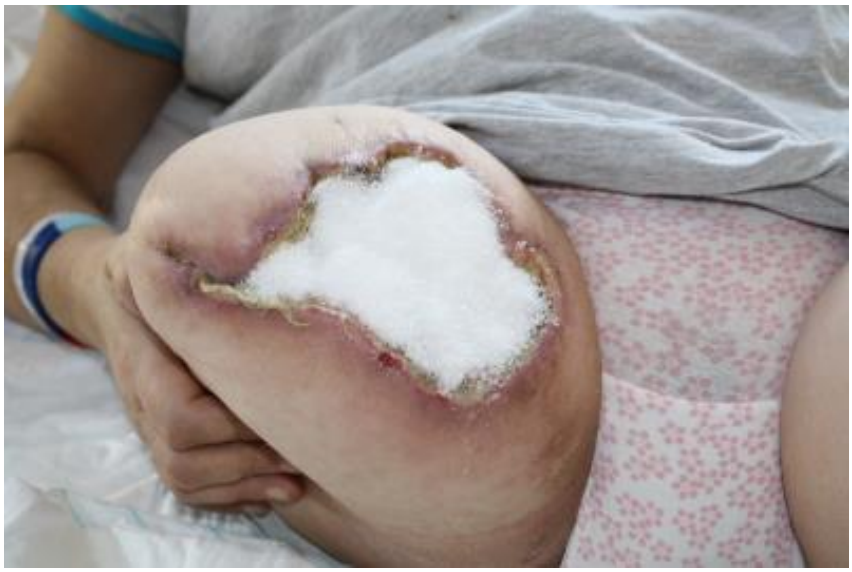
Figure 4.5 a. Any excess sugar was discarded. The sugar was held in place by an absorbent pad secured with a tape or bandages see

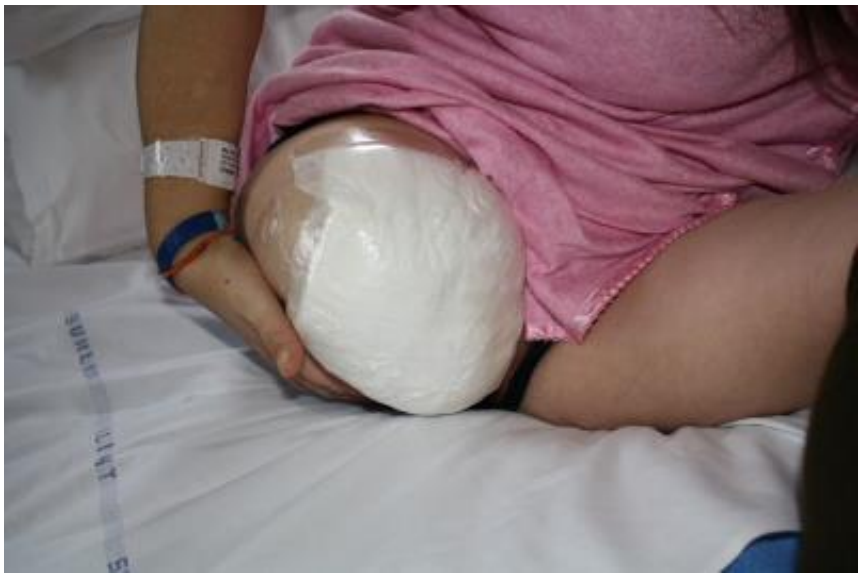
Figure 4.5 b). Dressings were changed daily or twice a day, depending on the exudate level.

4.13. Sugar dressing on leg ulcers

Applying sugar on leg ulcers or superficial wounds posed difficulties. To ensure sugar was held in place, a ridge of yellow paraffin was made around the periphery of the wound. The ridge enabled the sugar to stay on the wound without spilling on clothes and bed. Thereafter a wound absorbent pad was applied and secured with a bandage. The rest of the procedure followed that mentioned above. The treatment continued until there was completely clean, red granulating tissue, with residual sugar remaining in each dressing for two consecutive days.

Figure 4.5: Sugar covering the wound of an above-knee amputee (a), secured in place with a film dressing (b)
(a)





(b)

4.13.1. Additional wound care treatment required

Pain is a significant problem in wound care and needs to be routinely assessed and treated in both young and older adult population. Therefore patients were given analgesics such as paracetamol, co-codamol, and tramadol or morphine sulphate as prescribed by the medical team. Those with leg ulcers and receiving sugar treatment were nursed without compression

bandaging, but with their legs elevated for the duration of the treatment. Patients with methicillin-resistant *Staphylococcus Aureus* (MRSA) and *Staphylococcus Aureus* infections were treated with sugar alone. No patients received antibiotics during treatment or immediately after treatment period.

4.14. Clinical team wound evaluation

Wound healing progress

All wounds were evaluated by clinical staff (1-2 nurses and 2-3 vascular surgeons) at the bed-side or in vascular out-patient clinic rooms. Following the clinical team evaluation, the researcher or attending nurse trained to use the sugar would take digital photography, and wound measurements (if it was time for these procedures to be done) otherwise, they cleaned and redressed the wound with sugar and complete the TELER indicators.

Ease of dressing change

Dressing change is one of the procedures that clinicians rely upon to enable wound healing. It is also the time when some patients dread as some dressing products adhere to the wound causing severe pain on removal. This experience does affect the quality of life of most patients. Ease of dressing change was assessed during wound dressing times. Patients were asked questions related to pain on removal of dressing and after applying sugar according to TELER indicator component. The responses were recorded on the case report form. During ward rounds patients were constantly asked about the treatment and how they were feeling and their feedback was recorded in their study.

Patient acceptability of sugar dressing

Patients' attitudes towards sugar dressing were assessed using before and after adapted Naylor (2002) questionnaire (see

Appendix 10). The questionnaires were administered by either the researcher or trained nurses who had received training on the study. In addition to the questionnaire being completed, patients were asked for their feelings about the treatment and this was documented on the clinical notes. Besides asking then during ward rounds, patients were also asked informally in case they felt intimidated during wards rounds and failed to explain fully how they felt; and the responses noted in their clinical notes.

Blood sugar levels

One of the concerns of many clinicians was the possible rise in blood sugar levels of diabetic patients when commenced on the sugar trial. This issue became one of the focus areas of the study. Patients with insulin/non-insulin dependent diabetes mellitus had their blood sugar level checked before the start of the study and routinely according to the trust policy and diabetic management protocol until the end of the study. This was logged using the diabetic chart.

4.15. Other wound evaluations undertaken during ward rounds

Wound Appearance, Malodour, Exudate and Debridement

Lack of blood supply causes death at a cellular level and the dead cells accumulate in either a dry or wet mass which is recognised as necrotic tissue or slough. Slough and devitalised tissue will act as a bacteriological culture medium and inhibit the action of leucocytes in a wound and thus predispose a wound to infection (White et al., 2006; Kirketorp et al., 2008; Percival and Dowd, 2010). This process will influence the appearance, malodour status, and exudate production of a wound. Consequently, evaluating these characteristics was vital to the clinical team as a guide to wound healing progress. Evaluation was undertaken during ward rounds and dressing change times and findings were recorded in clinical notes and case

report form. This continued until the wound was debrided and sugar was no longer required or when the study period ended.

4.16. How patients were managed during out-patient appointment

The study was not limited to in-patients only. There were two patients recruited from a vascular out- patient clinic. Here participants' wounds were dressed as described earlier. They were shown how to re-dress the wound at home. Thereafter, they were given a week's supply of sugar, together with dressing packs for their use at home. They were also advised to discard all left-over sugar once the container had been opened. They were asked to attend their normal weekly check-up at the hospital, on the day of the out-patient appointment, the nurses and doctors assessed the wound progress as described earlier and documented findings on clinical notes and case report forms accordingly.

4.17. Staff acceptability of the sugar dressing

The nursing staff were given a purposely designed self-administered Likert scale satisfaction questionnaire (see Appendix 11: Nurses Questionnaire) at the start and end of the trial to complete. This was to determine whether there was a change in attitude and knowledge from that of initial recording.

4.18. Overall findings of the feasibility study

A total of 25 purposively sampled patients were admitted into the study. Two were admitted from the out-patient department and the rest from in-patients. One patient withdrew from the study after a day of treatment because the clinical staff preferred to use Vac therapy. Two patients both from out-patient withdrew; one did not attend the follow up appointment and the other refused to continue citing it was too much work. The rest of the patients' results

were included in this analysis. **Table 4.4** below illustrates recruited patient characteristics.

Table 4.4 Table: Recruited patients characteristics recruited.

Age range(s)	34-96
Average age(s)	68
Diagnosis	
Diabetes –on insulin + Leg ulcer	3
Diabetes-Non-Insulin + Leg ulcer	1
Diabetes –on insulin + Pressure ulcer	3
Leg ulcer	5
Pressure ulcer	3
Surgical wounds – incisions + amputees	7
Total	***22***

The age distribution was fairly inclusive (34-96 years) of young adults and old. In addition patients had wounds of different aetiologies that gave a broader understanding of the impact and applicability of the sugar. There were more of the leg ulcers and surgical wounds that portray the nature of the ward on which patients were recruited (vascular ward). One of the aims of the study was to determine the effects and acceptability of the sugar treatment to the patients.

The patients' self-reported attitudes using the adapted Wayne Naylor (2000) (Appendix 10) wound symptoms Self-Assessment Chart indicated that, wound pain and wound pain during dressing change, fluid leak, and malodour and itchy strongly interfered with their everyday life before the sugar treatment. When the same questionnaire was completed at the end of the sugar treatment, the self-reported responses strongly indicated less wound pain and less pain during wound dressing change. The wound leakage had decreased, with none of the initially

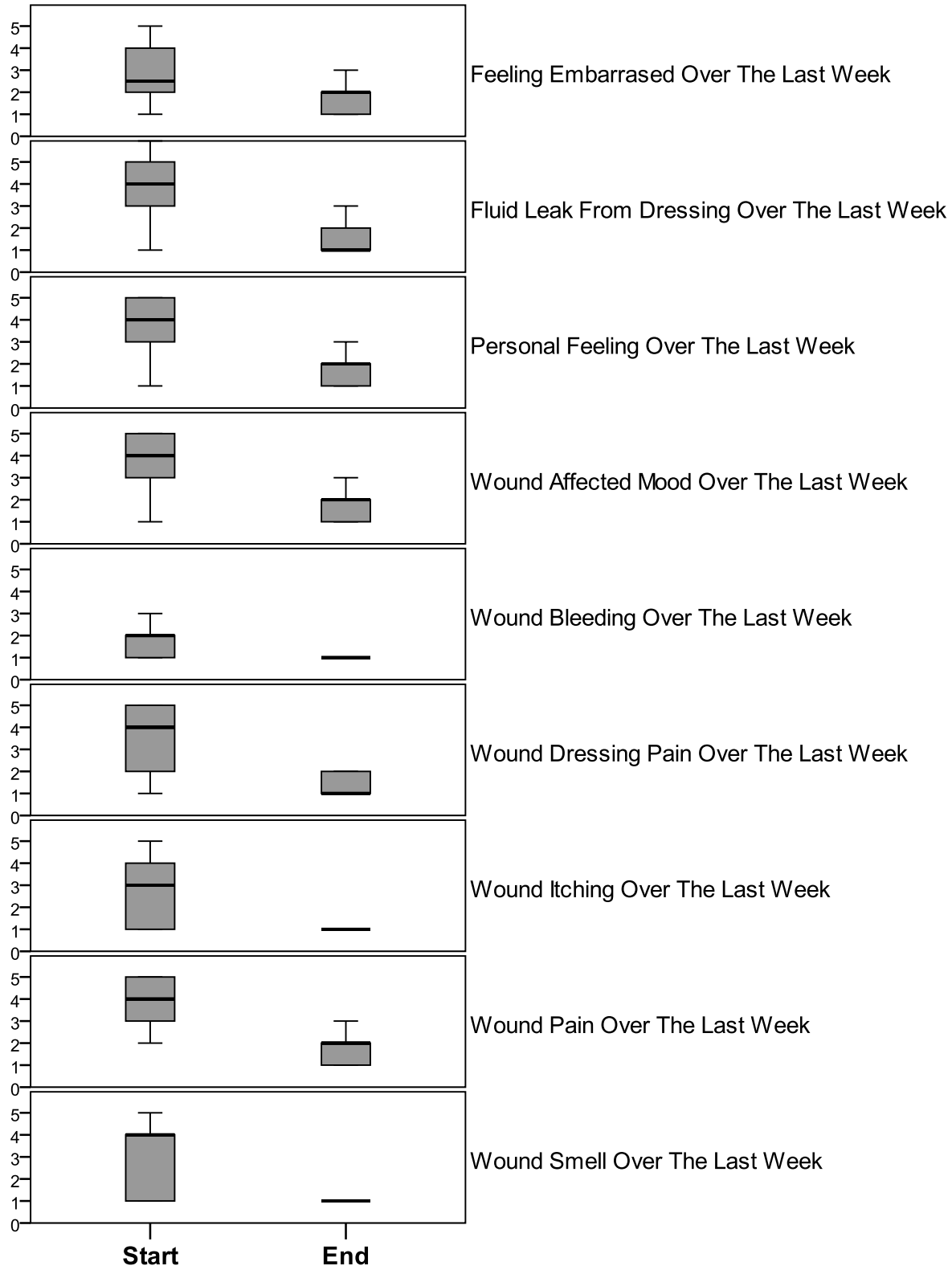
reported wound smell to patients whose wounds had an odour before the trial. The mood of the patients was improved according to the responses see

Figure 4.6. The most noted improvement was on wound bleeding, smell and itching that ceased to exist or did not bother patients sufficiently for them to report. Overall, patients' attitudes, mood and feeling of embarrassment were improved. For this reason, the data was summarised as a whole, using boxplots on page 80.

The study aimed at exploring the suitability and acceptability of the sugar by the patients; therefore it was important to understand how patients felt on their wound dressings were being changed. From the results it is clear that patients felt that dressing changes were satisfactory. The 22 patients experienced little or no pain at all, see

Figure 4.6. Again informal reports during ward rounds and dressings changes did support this phenomenon. Most patients had reported some form of pain at baseline information and the follow-up questionnaire illustrated that the patients had their pain intensity improved. They even reported a better sleeping pattern. Within this figure the bold line indicates the level of feelings as scored by participants.

Figure 4.6: Illustration of Patient feeling pre and post study



4.18.1. Effects of granulated sugar on necrotic exuding wounds

In this feasibility study, there was a need to explore the effects of sugar on sloughy, necrotic and infected exuding wounds. The researcher wanted to understand whether sugar would help in cleaning the wound in preparation for a larger study. The following are the general findings that illustrated the outcome of the study.

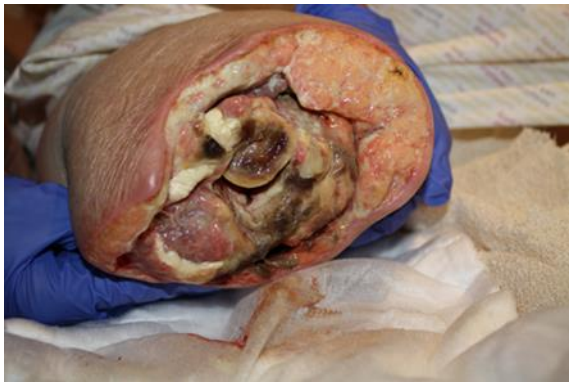
Wound debridement:

All wounds of the 22 patients admitted into the study were heavily or moderately exuding, with 50 -100% sloughy and/or necrotic tissue categories 0-3 of the TELER system. Ten (45.5%) patients had clinically infected wounds; 14 (63.6%) patients had necrotic tissue, and one patient had hard necrotic tissue and moderate slough.

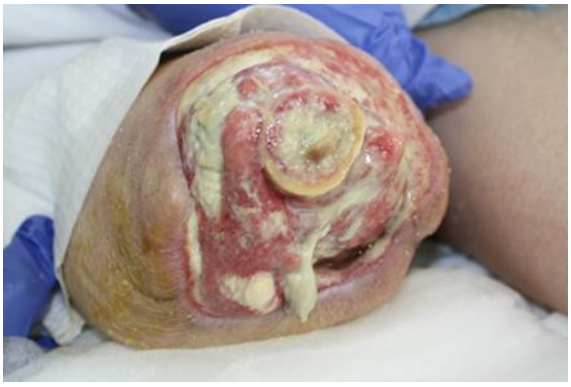
On day 14, the wounds of 9 (40.9%) patients wounds were granulating, 3 (13.6%) patients wounds had healed and been discharged, 10 (45.5%) wounds had either non odorous necrotic slough, or thin layer of slough.

Figure 4.7: (A1 -F1) illustrates the before and after debridement effect of sugar on a variety of wound profiles treated. E1 illustrates the debriding effect of sugar and the residual sugar left when the wound is debrided. There will not be any devitalised tissue for the sugar to dissolve into so sugar remains intact on the wound, a clue for stopping the sugar treatment.

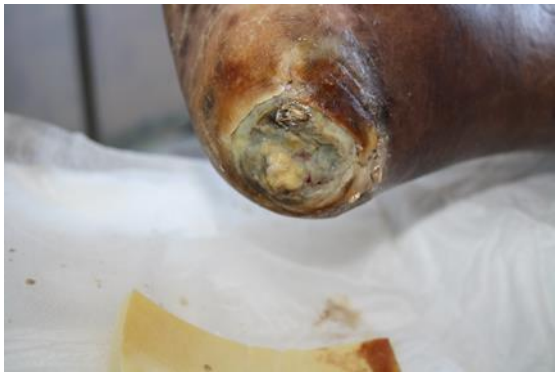
Figure 4.7: Wound samples showing debridement effect of sugar



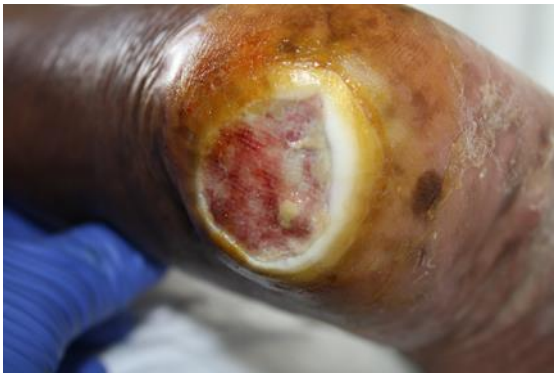
A1: Above knee amputee (before treatment)



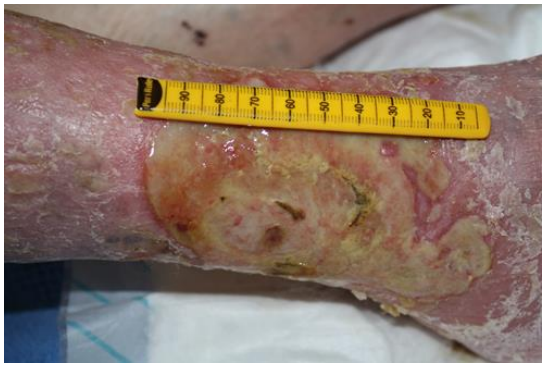
A1: (after 14 days sugar treatment)



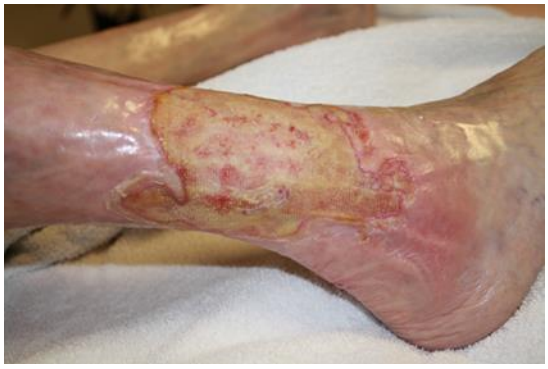
B1: Diabetic leg ulcer (after treatment)



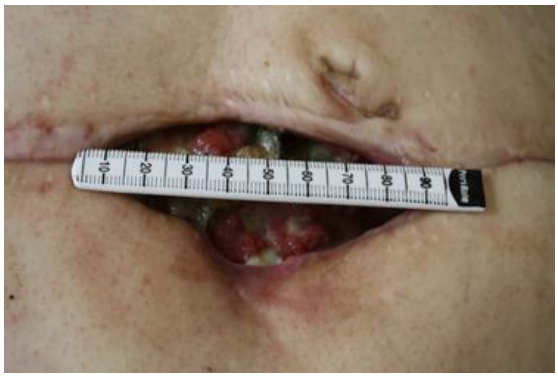
B1: (after seven days sugar treatment)



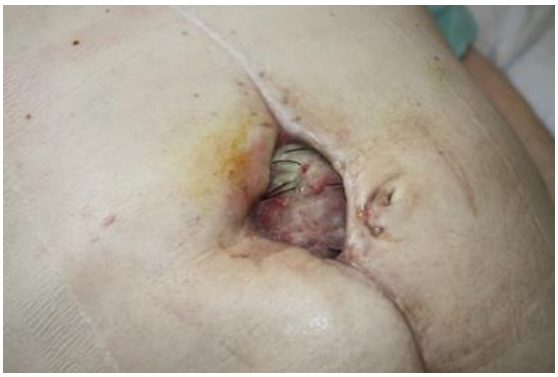
C1: Leg ulcer (before treatment)



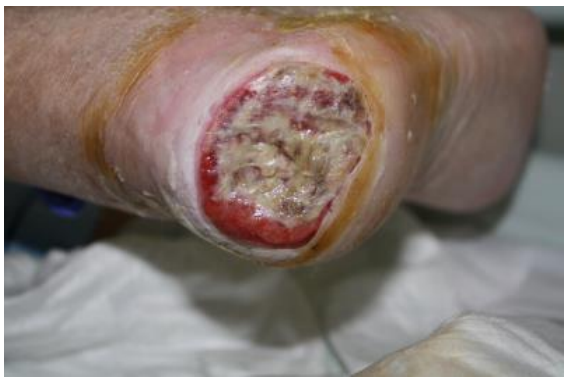
C1: (after seven days sugar treatment)



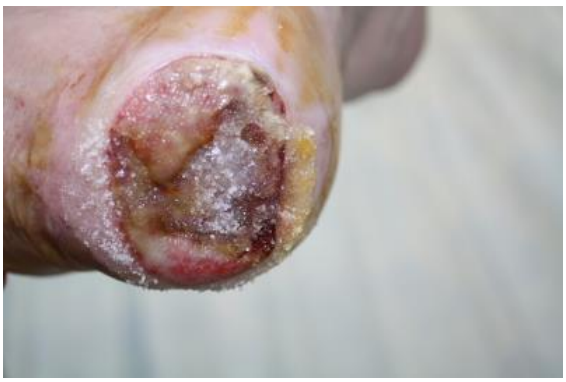
D1: Infected laparotomy wound (before treatment)



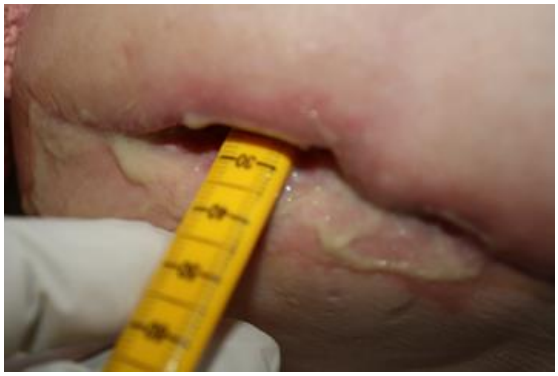
D1: (after seven days sugar treatment)

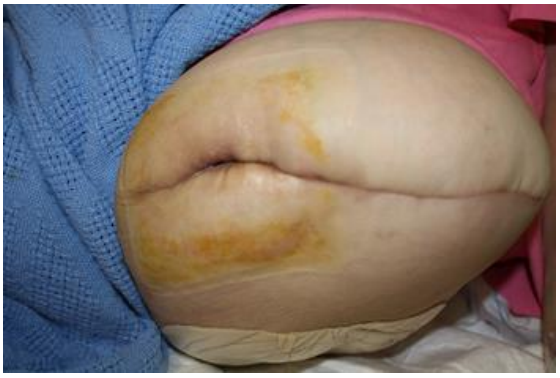


E1 –pressure ulcer (before treatment)



E1 – (after seven days sugar treatment)





F1: Infected above knee amputee (before treatment) F1: (after seven days sugar treatment)

Further to exploring debridement, it was vital to understand the effects of granulated sugar on exudate management. Base-line data using TELER system and the before and after questionnaire showed that 15 (68%) patients had categories 1-2 exudate and 7 (32%) had category 3. In all 22 (100%) patients, varying degrees of strikethrough and some heavy exudate was reported at the start of the study but exudate leakage had decreased by day 7.

Figure 4.7 A1 before and after photographs illustrates this outcome. There were similar results from other 21 patients treated, although their wounds were of profiles were different.

Although the study did not set to explore wound odour and pain specifically, these two wound characteristics were reported. Eleven (50%) patients' wounds were malodorous at base-line assessment by the end of the study none (100%) reported malodour. Similarly, at base-line assessment 22 (100%) patients scored 2-5 moderate to severe wound pain. At the end of the study all 22 (100%) patients indicated 0-2 pain score, showing a reduction in wound pain.

4.18.2. Effects of granulated sugar on blood sugar levels in diabetic patients

One of the key areas of this study was to understand the effect of sugar on both non-insulin and insulin dependent diabetic patients. Base-line capillary blood sample results tested; mean level 5.6mmol/l (range 3.8-10.1) versus 5.6mmol/l (range 3.6-7.83) at the study end. Insulin dependent patients required no additional insulin throughout the study.

4.18.3. Effects of granulated sugar on bacterial load

All 22 patients' laboratory wound swab results were monitored; 4 (18.2%) showed MRSA colonisation and the rest 18 (81.8%) patients were of mixed flora/microorganisms of no significance. At the end of the study the four wounds with MRSA were found to be negative to MRSA.

4.18.4. The nursing staff's reaction to the sugar treatment.

This feasibility study explored nurses' experiences and acceptability of the sugar treatment. Twenty one nursing staff of various years of experience was purposively recruited into the study. For a full list of the characteristics see **Table 4.4** underline. There was a general

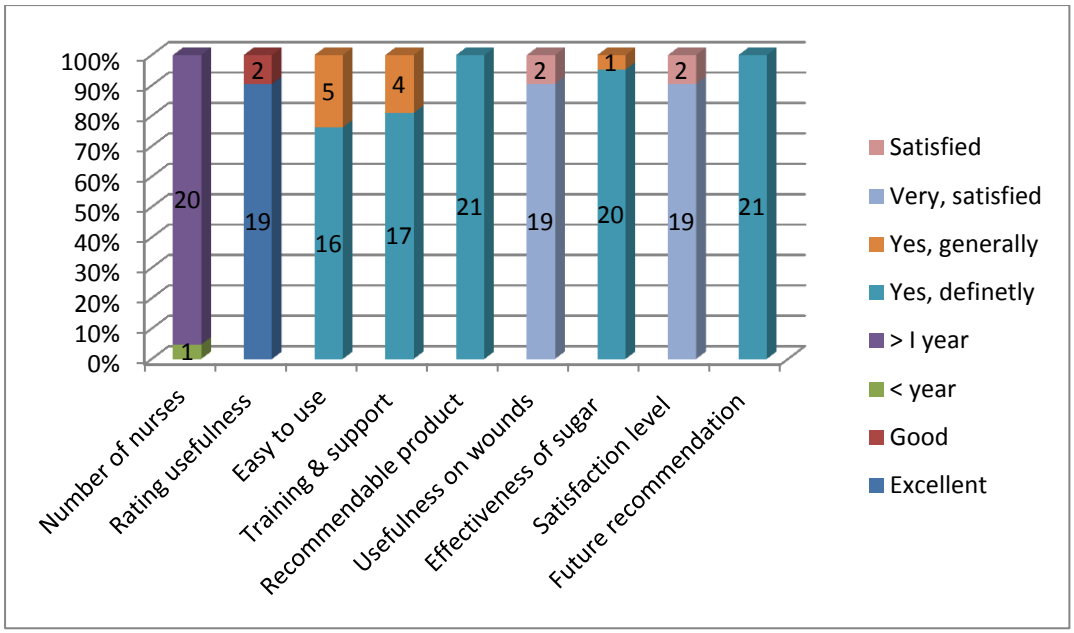
distribution of the nursing grades and experience in line with the number employed whole time equivalent staff in that vascular ward. The majority of nurses were from band 5, (qualified registered nurses who have 6 months and over post qualifying clinical nursing experience) a category that mainly deals with wound dressings. It can be noticed from the same table that, the years of experience ranges from 5-10 years.

Table 4.5: Illustration of recruited staff characteristics

Category	Staff	Years of Experience		
		≤10 Years	***10-20 Years***	***≥20 Years***
Nursing Band 7	1	0	0	1
Nursing Band 6	4	1	3	0
Nursing Band 5	10	6	5	0
Student Nurse	1	1	0	0
Nursing Band 1-4	3	2	1	0
Total Recruited	***21***	***11***	***9***	***1***

Initially, the responses to the questionnaires completed at the end of the trial were compared between those nurses with less than 10 years' experience, and those with a longer duration of experience. However, none of these comparisons were significant. For this reason, the data was reported as a whole (in **Figure 4.8**), to indicate the questions where there was most agreement.

Figure 4.8: Nursing staff responses to use of granulated sugar



From

Figure 4.8, it is clear that the vast majority of nurses are satisfied with most of the questions having over 80% of nurses giving the highest possible score. All of the nurses expressed that they would definitely use granulated sugar again on exudating wounds, and would recommend the treatment to a ward that needed it. Only one nurse was unsure on the treatment and this related to how easy the protocol was to follow.

4.18.5. Does granulated sugar have adverse effects on patients?

Adverse effects in this study were defined as any event/experience that was not only life threatening but caused severe wound pain and damage leading to deterioration in wound healing. This issue was monitored closely and none of the 22 (100%) patients recruited and treated with sugar experienced any of these events during the trial period.

4.19. Discussion

The practical usage of granulated sugar for managing sloughy, necrotic and infected exuding wounds in the modern day NHS health care systems was questionable given the advanced technology available within this area. Historically, sugar dressing has been used to treat varying wounds aetiologies and reports has been slowly emerging (Herszage et al., 1980; Trouillet et al., 1985; Gordon et al., 1985 Ambrose, 1986; Archer et al., 1990; Mphande et al., 2007). Even with available evidence, there is little knowledge to guide expansion of this method of wound care. The principal attainments of this study were that it is feasible to use sugar in modern day NHS hospital. Ethical and the Medicine and Health Regulatory Authority does allow sugar to be used as an alternative wound care dressing product. It is also feasible to use sugar as a dressing product for diabetic patients without affecting their blood

sugar levels. Furthermore, both health care professionals and patients exposed to the use of sugar accepted this method.

The process of establishing the study was robust, seeking both MHRA and ethical authorization. Sugar when used as a wound care product becomes a drug (MHRA 2010); therefore it was important that, the study follows the guidelines of good clinical principles of research study. The study was given a EudraCT number for future reference.

Determining the sugar dosage was important if the study was to develop an applicable sugar protocol. There is evidence from this study to show that sugar treatment used on both cavity and non-cavity sloughy or necrotic wound tissue seems to be an effective way of wound debridement and is capable of debriding a wound of small or large surface area. However, the most appropriate follow up dressing product after wounds are debrided is not very clear. It was noticeable in the study that after applying sugar on the wound for a couple of days or weeks when the wound is debrided the sugar remained undissolved on the wound. This is an indication showing the wound is adequately cleaned of slough. It is important to clarify the follow up treatment in order to minimise re-sloughing. This will enable developing an effective clinical protocol.

It was also feasible to establish ways of preventing cross infection and maintaining a chain of sterility by designing the use of different sizes of single use aliquots containing 15 and 30 grams of sugar (**Figure 4.2 see page 60**). These aliquots came with certificate of conformity and batches serial numbers that enabled tracing back to the manufacturer as well as the re-packaging NHS Pharmaceutical respectively if there was any adverse effect.

There is evidence from this study that sugar administered on type 1 and type 11 diabetic patients does not influence their blood sugar level concurring with the work by Yudkin and colleagues (1971), that simple sugars are the forms in which carbohydrates are absorbed into the blood stream and hydrolysis of dietary carbohydrates is an important digestive function that involves catalytic enzymes (Yudkin et al., 1971 p. 156). In this study, sugar is administered topically and there is no enzymes (amylase) involved to convert sucrose into a monosaccharide glucose and fructose that are easily absorbed. However, it is further explained (Yudkin et al., 1971 p. 168) that simple sugars glucose and galactose are actively absorbed using a carrier mechanism similar to that of sodium gradient movement in and out of the cell, and this dependent on cellular metabolism; a process not supported by topical application of sugar on a wound. This notion is further evidenced by the studies of (Trouillet et al., 1982; Tophan, 2000; Biwas et al., 2010) who did not encounter any rise of blood sugar levels in patients receiving sugar treatment but already suffering from diabetes mellitus.

Previous research of sugar, Mphande et al (2007) cited patients experiencing pain using sugar. Subjects' pain experiences were therefore assessed at each dressing change as well as weekly evaluations. Patients' reported varied experiences some had tingling pain when the initial dose of sugar was applied with no further pain. The majority of subjects did not experience pain at all, reporting feeling reduced pain sensation. Overall, there was no patient withdrew due to pain issues. Although this was a small study a visual assessment score of pain was monitored as Sussman (2001) concludes that pain and discomfort can be a deciding factor when choosing reliable and efficient dressing. However, Gardner et al (2001) found increasing wound related pain and wound breakdown to be among the sensitive indicators of wound infection. They advocate relieving pain as an encouragement to concordance with other adjuvant treatment, like compression bandages.

Subjects' reports indicated that there was good adherence with the study treatment, with the majority stating that malodour and exudate management was good. The level of comfort of the dressings was varied but the majority of subjects rated the treatment as comfortable and rated the level of comfort on the high level, a state that we did not anticipate. The majority of subjects described satisfaction with the study treatment. Positive evaluations of the treatment were also provided by the majority of nurses who rated ease of application and removal of dressing as "very simple" and "simple".

This study provided evidence to show that sugar treatment debrided wounds of various aetiology considerably more quickly (3-14 days) although this needs verifying with a larger comparative study. The results also showed a lower incidence of wound infection signs using sugar treatment. However, it was not possible to analyse the actual quantity of colonising microbes before and after. This proved costly given the small budget available. But, it must be pointed out that the four MRSA positive swabs at the start of the trial were negative at the end of the study without any use of antibiotics. This experience is encouraging, but needs further verification with a larger sample size.

There was a systematic evaluation of side-effects or complications and none were concluded during the intervention. This study participants did not experience any adverse effects or complications, concurring with the findings of the previous researchers (Seal and Middleton, 1991; Tophan, 2000; Mphande et al., 2007 and Chiwenga et al., 2009. Chirife et al., 1982) who did not experience either adverse effects or complications. The results of this feasibility study enabled the development of a protocol on the use of sugar in the management of sloughy, necrotic and infected exuding wounds in readiness for a RCT.

4.20. Conclusion

To the best of our knowledge this trial was the first sugar study to evaluate the possibility of sugar dressings affecting/not affecting the diabetic patients' blood sugar level. The researcher concluded that patients who are on insulin or treated with diet and tablets can be treated with sugar dressing without affecting their blood sugar levels.

The study enabled us to determine the sizes of the wound and their respective sugar dosages. We concluded that wounds will be categorised as small- medium and medium to large and treated with doses of 15 and 30 grams respectively. Although this study was not aimed at exploring debridement effect as a primary outcome, the researcher noticed that sugar was effective on wound debridement. The positive outcome of the short survey of nurses' acceptability of the sugar added on to our assumption that clinical staff would support undertaking a RCT.

This study failed to produce a tangible mechanism of monitoring the quantity of colonising bacteria and this meant it was impossible to explore this in the larger study. It was concluded that the reduction or increase of wound infection using laboratory analysis was to be omitted in a future study, since the funds were not sufficient at the time. But the trial would assess the clinical signs and symptoms of infection coupled with routine microbial analysis of wound swabs periodically.

The patient survey suggested that sugar dressings were tolerated with or without minimal pain reported. But it must be noted that it is unusual for any pain associated with changes in dressing to cause patients to withdraw from studies that involve chronic wounds (Jull et al 2008), as patients would try to persevere in order to find a cure for their wound. One of the

unexpected findings was a reduction in the use of opiates. Systematic effects in a small study could not explain this, but if it really were reduced even by frequency of use it would lessen the cost of medication and improve the quality of patients' lives. Of course there are many factors that may contribute to the reduction of pain and use of opiates and further research is required to account for any possible confounding factors for example adhesive dressings, infections or cultural issues.

This study has shown that a randomised trial is feasible in this group and that a single non-comparative study cannot draw any firm conclusions about efficacy of sugar dressings. However, a full RCT is feasible with minor modification to the study design.

Finally, the proposed RCT is to be a multi-centre involving different study settings, so this has to be accounted for in the planning. The results and experience allowed for a comparative study to be developed. A power calculation was done from the given study results. Therefore the following chapter will describe the RCT.

5. Chapter The use of granulated sugar on managing sloughy necrotic and infected exuding wounds: a pragmatic randomised controlled trial (RCT)

5.1. Background

In chapter 4 the use of granulated sugar was demonstrated to be useful for debriding sloughy, necrotic and infected exuding wounds. The study also concluded that granulated sugar in direct contact with the wound creates a wound bed environment of higher sugar osmolality that interferes with bacterial growth. This process results in an increased volume of exudate

production initially, reducing in amount as the treatment continues. This process enables easy cleaning of wound debris and allowed new tissue to develop i.e. granulation. Chapter 4 illustrated the method and feasibility of undertaking a sugar trial in a modern NHS hospital. However, the study was not randomised and lacked comparison with current treatments. It was important to undertake a RCT in order to determine the effectiveness of sugar on wound debridement. According to Silverman et al. (1992) and Jadad and Rennie (1998), the RCT is one of the simplest and most powerful research tools to assess effectiveness of treatments. Therefore, this trial was to employ this gold standard study design to compare granulated sugar and standard wound dressing care, to determine whether there was any difference in the wound debridement times. It is understood that the destructive action of bacteria on wound-bed tissue influences an increased production of slough and necrosis, hence wounds in which slough is the predominant tissue will heal more slowly than clean granulating wounds (Falanga, 2000). This chapter describes the RCT undertaken to assess the effectiveness of granulated sugar dressing on managing sloughy, necrotic exuding wounds in a modern NHS trust hospitals and Community Healthcare NHS trust setting.

Aim

The aim of this study was to evaluate the clinical effectiveness of granulated sugar therapy compared with standard autolytic debridement dressings.

Objectives

The objectives were set within specific research questions as follows:

Primary:

- How effective is a granulated sugar dressing on debriding, sloughy, necrotic and infected exuding wounds compared with standard treatment in terms of debridement at 4 weeks?

Secondary:

- Does use of granulated sugar reduce pain and odour?
- Does of use granulated sugar reduce the wound surface area
- Does use of granulated sugar reduce amount of exudate and percentage of slough?
- Does the use of granulated sugar dressing improve the quality of life of patients with sloughy, necrotic and infected exuding wounds?

5.2. Methods

Trial design

The study was a prospective pragmatic stratified multicentre open randomised controlled trial with equal randomisation, carried out in 3 centres in the United Kingdom from June 2010 to June 2013. Randomisation was stratified by wound size and type (chronic or acute). The methods used were based on those developed by Dumville et al (2009) and Toba et al (1997) for similar pragmatic randomised controlled trials of wound management products.

Participants

Participants were recruited from two acute NHS hospitals from the vascular surgery wards, leg ulcer clinics and one NHS community hospital, as well as community caseloads including home treatments. All patients had sloughy, necrotic or infected exudating wounds and were either hospital in patients or attending out-patients clinics. Eligible participants had wounds between 5 cm^2 and 40 cm^2 in area, with at least 25% of the wound covered in by slough or necrotic tissue. Diabetic and non-diabetic patients were included. Patients who had arterial brachial pulse index (ABPI) less than 0.6, pregnant patients and patients whose wounds had necrotic eschar were excluded. See **Table 5.1**: below.

Table 5.1: Inclusion and Exclusion Criteria

Inclusion
Wounds with a minimum of 25% slough with infected or necrotic tissue present Exudating wounds between the sizes 5 - 40cm^2
Exclusion
Patients who had previously been in this trial ABPI less than 0.6 Presence of hard necrotic eschar Pregnant patients

**ABPI =arterial brachial pulse index*

Interventions

Trial group A (Sugar arm)

After the initial wound assessment and past medical history was recorded, a short EQ-5D QoL questionnaire (see Appendix 13) was given to all patients in both arms to complete. Following completion, the dressing procedure and wound swabs were performed as follows:

Wound photographs:

Nurses/researcher took digital photographs using auto focus mechanism (as previously explained in chapter 4) at the start of the study then weekly, when the wound was considered to be debrided or at the end of the study period (end of week 4).

Wound swabs:

Before cleaning the wound; swabs were taken by moving the swab probe zigzagging gently across the wound; thereafter swabs were placed into the transporting media labelled and dispatched for laboratory analysis as per trust policy.

Wound dressing procedure:

Wounds were cleaned according to normal trust wound cleaning procedures. However, nurses were requested to wash wounds with plenty of water or irrigate with normal saline as earlier explained in chapter 4. Sugar was applied and secured as illustrated in chapter 4. The frequency of dressing change was every day or every other day decided by the treating nurse. The approximate sugar dosage was 30 gram aliquots or more depending on the wound size for all categories of wounds. For smaller wounds, the remaining sugar was discarded.

Control group B (Standard dressings arm)

Dressing procedure followed a similar process to that explained above, except that participants received debridement agents (according to local trust protocols). Frequency of dressing change was decided by the treating nurse.

Adjuvant treatment

Patients with leg ulcers had compression bandage as well as assigned wound care products as adjuvant treatment in both arms. Those with pressure ulcers were treated with pressure relieving methods accordingly.

Post debridement

The nurse assigned to attend to the wound dressing made most of the decisions on the day to day care of the wound, according to the sugar protocol including whether the wound had debrided or not. On some occasions there was disagreement between assigned nurses on whether the wound was debrided or not and the disagreement was resolved by members of the clinical team (doctors and nurses) during ward rounds. The ward round team would assess the wound and make the final clinical judgement on whether the wound was debrided or not. Sugar treatment was applied during the period of achieving debridement only. In the phase

after debridement, all participants received appropriated available trust formulary dressings decided by the treating nurse. The date on which this occurred was recorded.

Wound photography was taken and recorded in the case report form (CRF) (see Appendix 8). At this point participants were asked to complete validated Euro-quality of life (EuroQoL 2010) health questionnaire (EQ-5D) see Appendix 13**.** The maximum length of follow up was 4 weeks. After four weeks, collection of study clinical data stopped on both arms.

Outcome measures

Primary outcome

The initially proposed primary outcome in the registered protocol was "*time to debridement truncated at four weeks*" monitored and recorded on case report forms using the TELER indicator system, as in the text box below and Appendix 6. However, this was amended to "*debridement rates at week 4"* in the two groups because it was impossible to follow up every day. Date of debridement was determined by the nurse doing the dressings and confirmed by discussion with doctors on their daily ward rounds and recorded on the case report forms using the TELER indicator system, as in the text box below and Appendix 8.

0 Deep necrotic offensive, infected wound, down to bone

1. deep infected wound, heavy exudates, and damage to muscle
2. sloughy wound, infected and offensive, to subcutaneous fat
3. no infection, no exudate, granulating, odour free
4. superficial damage, some inflammatory change, broken "healthy" skin
5. Healthy "pink" unbroken skin. Healed wound

Based on the TELER indicator, scores between 3-5 was considered indicative of debridement.

Secondary Outcomes were:

Reduction in wound area in cm^2; wounds were measured by the attending nurse using flexible wound dressing paper tape measure on admission into the study, then at the end of each week until the end of the study period (4 weeks). The longest and shortest size of the referral wound were measured and then multiplied to find the area in centimetres.

Wound exudate leakage and wound exudate appearance*:* both wound exudate volume and exudate characteristics were assessed on admission into the study and at the end of each week. In addition regular monitoring of exudate volume and characteristics were carried out during dressing change using the TELER indicators on a Likert scale of 0-5, as shown in the text boxes overleaf as well as Appendix 8: Case report form and TELER Indicators.

The **exudate leakage** scoring was as follows:

0.	Dressing(s) and bed clothes are soiled
1.	Dressing(s) and bed clothes are wet
2.	Dressing(s) wet and bed clothes are damp
3.	Dressings wet and clothes are soiled in patches, size of 50p piece
4.	Dressing(s) only is wet
5.	Dressing only is soiled.

Exudate appearance was scored in a similar format;

0. With sanguineous, predominantly blood
1. Serosanguineous, i.e. blood stained but not bleeding frankly
2. Odorous purulent, i.e. odour + cloudy, thick yellow/blue/green tinge
3. Non-odorous purulent, i.e. cloudy, thick, yellow
4. Serous, i.e. thick, pale, straw/clear
5. No exudate to describe

In both categories assessments were done at every dressing change. However, the initial and final week four assessment or the final recorded entry was used for the statistical analysis. Patients whose score movement points were between 2 to 4 were considered to have experienced some change equivalent to the minimally important clinical significance for their state of health at the time of the final assessment within the study period of 4 weeks.

Wound slough was assessed using a subjective slough percentage (%) estimation of wound surface area covering, as well as digital photographic evidence on admission into the study, and at the end of each week, until end of the study (4 weeks). In addition, regular monitoring and recording were carried out during dressing changes and recorded on the CRF. The

percentage of slough was to be independently assessed using the supplied digital photographic evidence by an assessor who was blind to the study arms. The results were to be compared to those reported on the CRF by the nursing staff.

Wound Pain assessment on three domains; (a) wound pain and its interfering with daily life activities, (b) wound pain disturbing sleep and (c) wound dressing pain. The score was measured using TELER indicator system with a Likert scale of 0-5, higher scores showing a desirable outcome. For example (a) wound pain interfering with patient's ability to: relax (0), mobilise (1), concentrate (2), socialise (3), sleep (4) and no pain at all (5).

Other pain domains were wound pain disturbing sleep and were scored as wakes frequently difficulty to sleep (0), wakes frequently (4 or more times a night) (1), wakes infrequently (3 or less times a night) (2) sleeps through 1-3 nights a week (3), sleeps through 4-6 nights a week (4) and sleep undisturbed every night (5). The third domain was, wound dressing pain and was measured on how dressing changes were affecting the patient such as; unbearable dressing change, medication needed during pre and post change (0), distressing dressing change, medication needed (1), unpleasant dressing change, medication needed (2), disagreeable dressing change, no medication (3), some unpleasantness (4) and dressing change alright (5).

Patients whose overall TELER indicator movement points of between 2 to 4 were considered to have experienced some change equivalent to the minimally important clinical significance for their state of health at the time of the final assessment within the study period of 4 weeks. At every dressing change the nurse/researcher asked the questions using the TELER indicators and recorded the scores in the CRF as well as the weekly evaluation scoring.

Odour was recorded using the same TELER system indicator with a Likert scale of 0-5. The worst result being, odour is obvious in the house/clinic/ward and scored as (0), odour is obvious at arm's length from patient (1), odour is obvious at less than an arm's length from

patient (2), odour is detected at arm's length (3), odour is detected by patient only (4) and no odour (5).(see Appendix 8). As mentioned earlier, a 2 to 4 point movement was considered clinically significant as compared with the baseline score. Assessing and recording of odour stopped when there was three consecutive recorded scores of 5 (*no odour*) on daily dressing change assessments. When the score was agreed by the clinical team, the final agreed score, day and date was recorded in the case report form (Appendix 8). The initial and final recorded score were compared statistically at the end of the four week period.

Health-Related Quality of Life (HRQL) was measured using EQ-5D (Appendix 13) (The EuroQoL Group, 1990). In previous studies, this tool was found to be sensitive to changes in the healing statistics and participants' perceptions of health related quality of life both at baseline assessment and end of trial. The patients scored on a visual analogue scale, marked with 100 increments, such that a score of 100 indicated "full health".

In addition to the visual analogue scale, on entry into the study and at 4 weeks, patients were asked questions relating to the five domains of the EQ-5D, namely mobility, self-care, usual activities, paint/discomfort and anxiety/depression. The response to each of these questions was on a 3-point Likert scale. The changes in scores from baseline to four weeks were compared between the treatment arms.

Participants in both arms completed their first HRQoL questionnaire after signing the consent form. They were given the second questionnaire after the wound was agreed by the clinical team to be debrided and the sugar was no longer required or after 4 weeks if sugar treatment continued till the end of the study period. The questionnaire is validated in English language, and all patients were encouraged to complete on their own, but some used relatives to assist, due to poor sight or arthritis problems. Where relatives were not available and the patient needed help with the questionnaire, the nurse assessing and dressing the wound asked the patient questions from the questionnaire and completed according to the patient's response.

5.3. Sample size

In consultation with hospital's statistician, the study was powered based on a proportional hazards survival analysis model, comparing the times to debridement in the two treatment groups. The statistical methodology described by Brysbaert (2011) was used as the basis for the calculation. The median times to debridement were assumed to be 11 days in the sugar treatment group, based on the information from a feasibility study chapter 4, (Murandu et al., 2011 see Appendix 17), and 21 days in the standard treatment group, based on Gethin and Seamus (2008). For a total of 28 days of follow-up for each patient, a sample size of 54 patients per group was found to be sufficient to detect a difference between treatments at 80% power and 5% alpha if the median times to debridement are 11 and 21 days, as forecasted. Hence, the target for recruitment in the study was 108 patients to randomise between the two treatment groups.

5.4. Randomisation

Randomisation was performed centrally and the block randomisation table was designed by the hospital statistician. This type of design makes it difficult to reveal the allocated number of the patient which can occur when smaller equally sized blocks of randomisation are used (Schulz and Grimes, 2002). Consecutively numbered opaque envelopes were prepared for all hospitals. Equal numbers of blocks of 2, 4, 6 and 8 were prepared with block sizes determined using a random numbers.

Sequence generation

Within each block, a further series of random numbers was generated, one for each patient in the block. Those falling between 0-0.499 resulted in an allocation of intervention and those

between 0.500-0.999 resulted in a control. Once half of a block had been allocated to either an intervention or control, the remaining places in the block were allocated so as to result in equal distribution of intervention or control within each block. Further stratification was performed according to type of wound/s; “chronic or acute” and wound size using separated sets of numbered envelopes for those with chronic or acute wounds. The initial randomisation tables were constructed by the lead hospital trust’s senior statistician four months prior to the start of randomisation and the consecutively numbered envelopes prepared by the administrative secretary.

5.5. Allocation concealment

Allocation took place away from the research sites. When the patient was assessed by the clinical team and found to be suitable, that is, meeting the inclusion criteria as mentioned earlier in **Table 4.3** the patient was informed of the trial taking place by the doctor or nurse. If the patient was willing to be considered for the trial, a nurse/researcher with the knowledge of the sugar trial was informed. Either the nurse or the researcher explained in detail the trial procedure and gave the patient an information sheet (Appendix 3) to read and consider overnight. If the patient agreed to take part in the trial he was requested to sign a written consent form that was countersigned by the admitting nurse or researcher (see Appendix 7). After the consent form was signed the researcher/attending nurse phoned the secretary holding the allocation envelopes at the allocation centre a site away from the research sites without knowledge of the trial, patients and the trial team except the researcher. The trial secretary opened the next available numbered envelope taking into account the categories, chronic (leg ulcers or pressure ulcers) or acute (traumatic wounds and non-healing surgical wounds), small to medium (5 to 19.9 cm^2) and medium to large (20 to 40 cm^2). Thus both patient and nurse were blind to allocation prior to consent being obtained.

Implementation

Once patients were allocated a treatment, they were assessed as per study protocol. For complete patient flow through the study se**e Figure 5.1.**

5.6. Statistical methods

Baseline measurements for each group were compared, to ensure that any differences between the groups were not attributable to a difference in the case mix. Mann-Whitney tests were used for continuous variables, and Fisher's exact tests for categorical variables (Huck and Cormier, 1996).

The primary outcome was considered to be the debridement rates at week 4 and was intended to be compared between the two treatment groups using survival analysis techniques. Kaplan-Meier curves would be produced to show how the rates of patients achieving debridement changed over 4 weeks, and a Log-Rank test was used to compare the two treatment groups. For secondary outcomes, the difference between the initial measurement, and the final available measurement was calculated for each patient and compared between the treatment groups. Comparisons were made using Mann-Whitney tests, and the results reported as medians and quartiles.

For the analysis of the "Health Today" EQ-5D questionnaire (see Appendix 13), Mann-Whitney tests were used to compare the initial measurements, and the changes from the start of the study to the end of follow-up between the two groups. The data were then summarised using medians and quartiles. The individual domains of the EQ-5D questionnaire were then analysed separately. For each patient, the difference between the score for each domain at baseline, and at 4 weeks was first calculated. Since the score was only a 3 point scale, and

few patients registered more than a 1 point difference, the changes in the scores were grouped into three categories: increases, reductions and no change. Since this could not be treated as a continuous variable, the data were analysed using Kendall's tau-b test for ordinal categorical variables.

The data was analysed on an intention to treat basis (Hollis and Campbell, 1999). Where data was not available for week four of the study, the most recent measurements were used instead. All analyses were performed using IBM SPSS 19, with $p<0.05$ deemed to be indicative of statistical significance.

5.7. Adverse events

Adverse events were classified as serious or non-serious. Some events were always classified as serious (death, life threatening event, admission to hospital in case of out-patient and home treatment, persistent or significant disability or incapacity). The seriousness of other events like infection and deterioration of wound, was judged by the treating nurse. Nurses and doctors indicated whether or not they believed the event was related to trial treatment.

5.8. Results

5.8.1. Change to Protocol

After finalising the protocol, due to financial and logistical issues, it was not possible to assess patients daily as initially planned. As a result of this, the exact dates of debridement (primary outcome) would not be known, making survival analysis impossible. Instead, the primary outcome was taken to be the debridement rates at week 4 in the two groups. In addition to this, the target sample size was not attainable, and so the study was performed with the maximum achievable number of 41 patients. Based on these two points, the sample

size calculation for the primary outcome was repeated. Assuming a 30% debridement rate at 4 weeks in the control group, a rate of 78% in the sugar group would give 80% power at 5% alpha (Lenth, 2012).

5.8.2. Patients Lost to Follow Up.

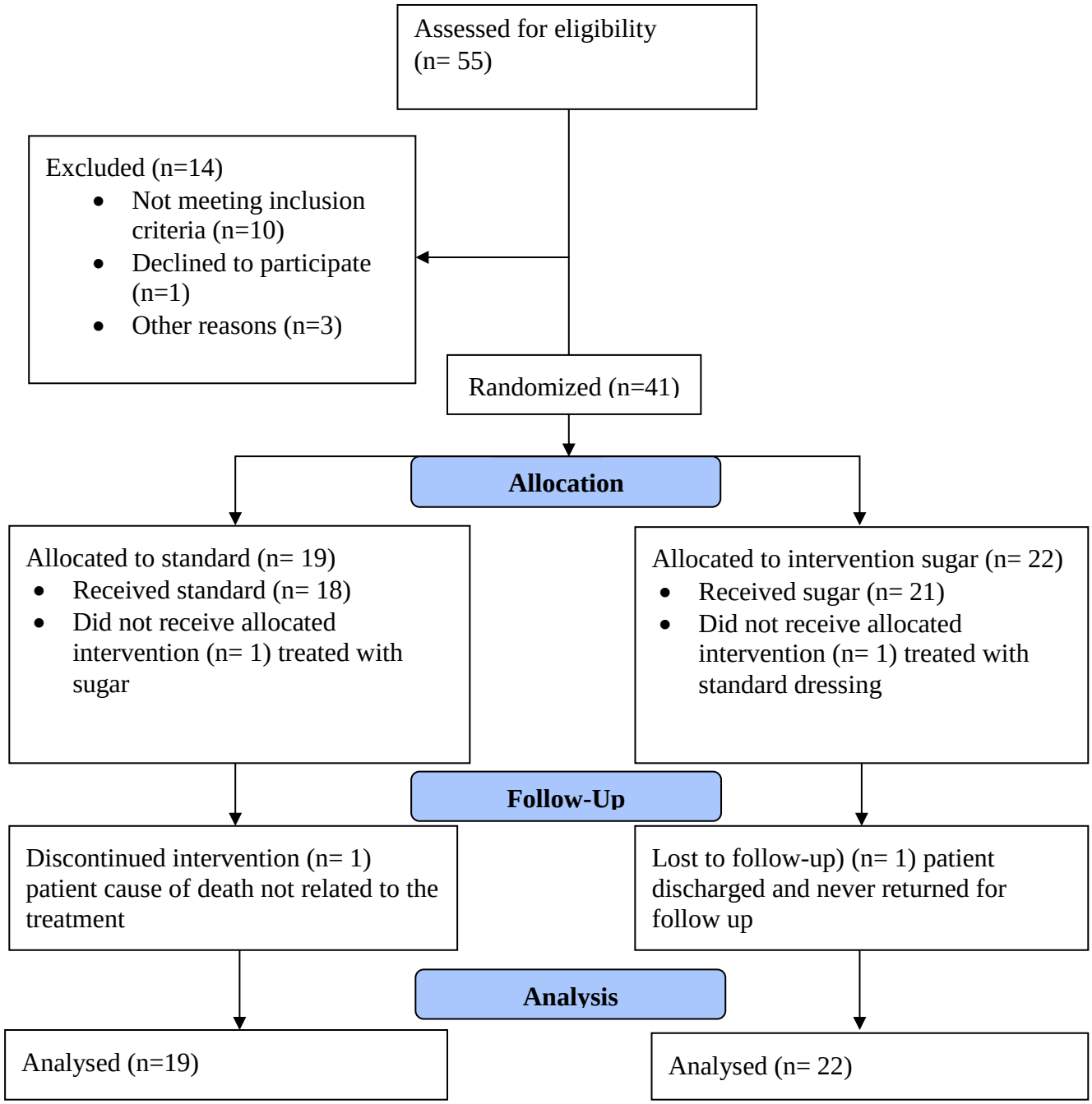
Patients lost to follow up were analysed using a Last Observation Carried Forward (LOCF) approach, i.e. the last available measurement was used in the (endpoint) analysis (Pledger, 1992).

5.8.3. Participant flow

Between June 2011 and June 2013, 55 patients were assessed for eligibility 41 (75%) met the inclusion criteria and were randomised. Ten (10) did not meet the inclusion criteria, one (1) declined and three (3) were seriously ill. Twenty two (22) were allocated to sugar dressings and 19 to standard dressings.

Of the 22 that were allocated to receive sugar treatment, one (1) did not receive the allocated treatment because of a misunderstanding by the clinical team, but remained in the group, due to the intention to treat methodology. The remaining 21 (95.5%) patients received sugar treatment and one (1) was lost to follow up as the home address was of no fixed abode. Of the 19 patients allocated to receive standard treatment, one (1) did not receive allocated treatment instead received sugar treatment, due to mix up of the clinical staff receiving the allocation number. One patient died a week into the study, and the cause of death was unrelated to wound treatment (see **Figure 5.1** flow diagram of the study).

Figure 5.1: The study flow



5.8.4. Demographic and other baseline characteristics

The distributions of baseline demographics were similar in the two interventions. The median age in the sugar dressing group was 66 years (quartiles: 60 – 77), and in the standard dressing group 67 years (quartiles: 58 – 78). Similarly, 64% of the sugar dressing group were male, compared to 47% in the standard treatment. Rates of diabetes and the modes of injury were also similar in the two groups see **Table 5.2**. There were fairly distributed wound aetiologies between groups; with the majority of the patients presenting with chronic wounds of medium to large size see **Table 5.2**. There were no patients presenting with acute small-medium wounds in the intervention group; with only 1 patient in the control group.

Baseline wound characteristics were evenly matched between the treatment arms as reported in **Table 5.2**. In addition, the quality of life measurements from the visual analogue scale question of the EQ-5D did not differ significantly between the groups at baseline with medians of 51 points in the sugar dressings group and 51 points in the standard dressings.

Table 5.2: Baseline characteristics

Characteristics	**Intervention (n = 22)**	**Control (n = 19)**
Wounds 20 cm^2 to 40 cm^2 (%)	16 (73%)	14 (74%)
Chronic/Acute wounds (%)	19 (86%)	15 (79%)
Males (%)	14 (64%)	9 (47%)
Age[#](Interquartile range) (IQR)	66 (60, 77)	67 (58, 78)
Diabetics (%)	6 (27%)	3 (16%)
Surgical wounds (%)	6 (27%)	4 (21%)
Leg ulcer (%)	7 (32%)	5 (26%)
Pressure ulcer (%)	2 (9%)	0 (0%)
Renal disease (%)	0 (0%)	0 (0%)
Trauma (%)	1 (6%)	0 (0%)
HRQOL – EQ5D IQR)	51 (40, 60)	50 (30, 60)
Wound Area (cm^2, IQR)	35.9 (21.2, 90.2)	32 (24.8, 45.0)
Slough (TELER, IQR)	10 (89, 100)	10 (80, 100)
Wound Healing (TELER, IQR)	2 (2, 2)	2 (1, 2)
Exudate Leakage (TELER, IQR)	2 (1, 3)	2 (1, 3)
Exudate Appearance TELER, IQR)	2 (2, 3)	2 (2, 3)
Odour (TLER, IQR)	3 (2, 5)	3 (2, 4)
Pain – Component (TELER, IQR)	3 (2, 4)	3 (3, 4)
Pain – Sleep (TELER, IQR)	2 (2, 4)	3 (2, 4)

Data reported as "N (%)", with p-value from Fisher's Exact test
[#]Data reported as "Median (Quartiles)", with p-value from Mann-Whitney test
Wound characteristics at baseline

Table 5.3: Sites of recruitment to the study

Site of recruitment	**Participant numbers**	**Wound type**
University Hospital Birmingham Queen Elizabeth	**32**	**28** - Non-healing post-surgical wounds **4** -Leg ulcers
Moseley Community Hospital (in patients and community home visits)	**6**	All Leg ulcers
Walsall Manor Hospital	**3**	All Leg ulcer

Primary Outcome

In the sugar group 19 (86%) achieved debridement at 4 weeks compared to 6 (32%) in the standard care group. This difference was statistically significant (Fisher's exact test: $p<0.001$).

Secondary outcomes

Table 5.4: EQ-5D HRQoL secondary outcomes; change from baseline to end of study: IQ range

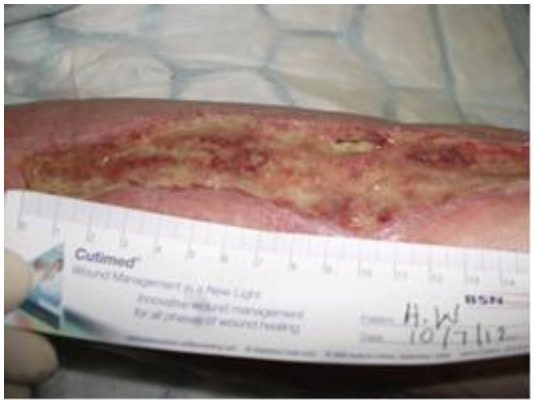
Secondary outcomes - TELER indicators	Sugar Dressing N=22	Standard Dressing N=19	p-Value
Wound Area (cm^2)	-10.7 (-28.7, -1.1)	-1.8 (-9.7, 0.6)	0.024*
Slough (% of surface area)	-83 (-91, -39)	-20 (-40, 0)	0.001*
Wound Healing (TELER Score)	1 (1, 2)	1 (0, 2)	0.393
Exudate Leakage (TELER Score)	2 (1, 3)	1 (0, 2)	0.124
Exudate Appearance (TELER Score)	2 (1, 2)	1 (0, 2)	0.005*
Odour (TELER Score)	2 (0, 3)	0 (0, 2)	0.059
Pain - Interference (TELER)	2 (0, 2)	0 (0, 1)	0.009*
Pain - Sleep (TELER)	2 (0, 2)	0 (0, 1)	0.020*
HRQOL (EQ-5D) Change after 4 weeks	30 (5, 40)	0 (-2, 15)	0.005*

Data reported as "Median (Quartiles)", with p-value from Mann-Whitney test
**Significant at p<0.05*

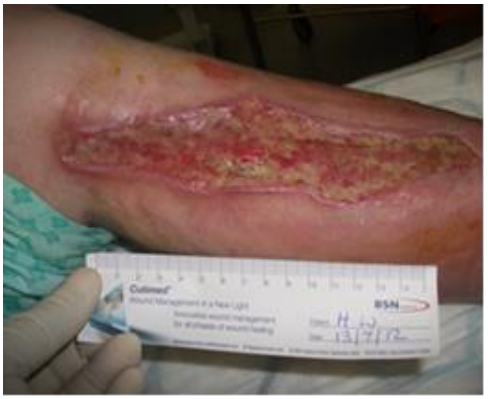
In patients treated with sugar, the median change in wound area from baseline to week 4 was -10.7 cm^2 (quartiles -28.7, -1.1). This was a statistically significantly larger improvement than in the standard care group -1.8 (-9.7, 0.6) cm^2 (*p=0.024).* Furthermore, the median change in wound surface area of slough from baseline to 4 weeks was -83% (quartiles -91, -39) in the sugar group. This was a statistically significantly larger improvement than in the standard care group -20 (-40, 0) % *(p=0.001).* This was further supported with digital

photographic evidence that was independently assessed and coded (**see Figure 5.2**). There is evidence of debridement on both wounds within the range of 3-12 days.

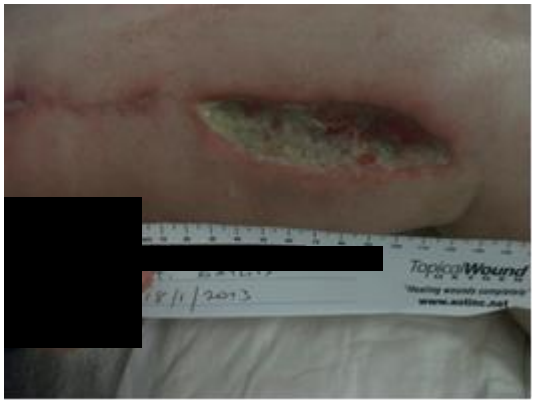
Figure 5.2: Sugar effect (estimate %) on slough at baseline, during and end of trial



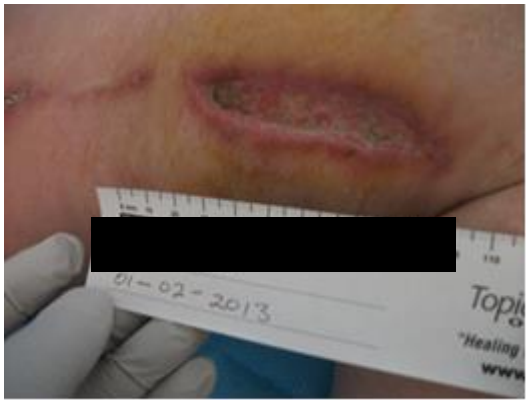
A – baseline (97%) slough



A – follow up 3 days (10%)

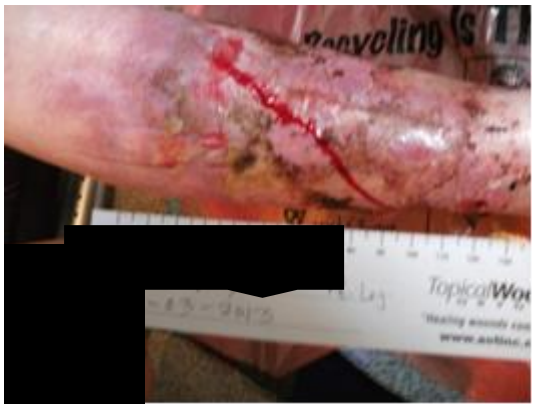


B - baseline (99%)

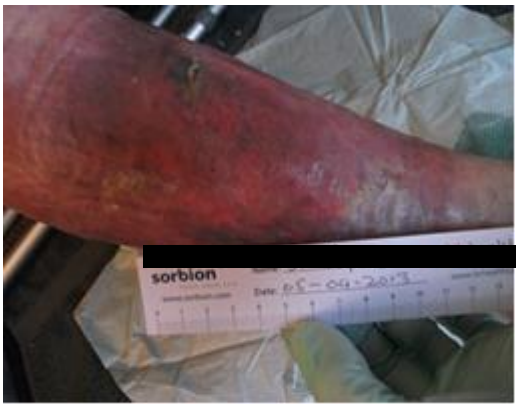


B1 – follow up 12 days (3%)

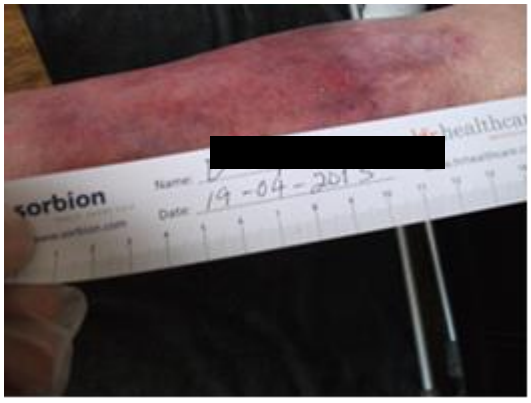
Figure 5.2 C 1-C4 illustrates the effective of sugar as a debriding agent. There was evidence of total healing at week 4 (see **Figure 5.2**).



C - baseline (95%)



C1 – follow up 12 days



C2 – 4 weeks (0%)

Of the TELER scores, exudate appearance showed a significantly greater improvement in sugar dressing patients (median 2 points) than the standard dressing group (median 1 point), (p=0.005). In the sugar dressing group, pain scores for the interference with daily life (p=0.009) and whilst sleeping (p=0.020) both showed statistically significantly greater improvements in the sugar dressing group (median 2 points), compared to no change in the median in the standard dressing group.

Although the sugar treated group saw the largest median improvements in all three of these measures, there was no statistically significant difference between the two groups was detected in the TELER scores for wound healing (p=0.393), exudate leakage (p=0.124) or

odour (p=0.059). All patients' wounds treated with sugar either had complete or partial debridement at the end of four weeks (see **Figure 5.2).** It must be made clear that patients whose wounds were debridement stopped using sugar and were prescribed other appropriate wound dressing products according to local trust protocol.

Health related quality of life HRQOL (EQ-5D)

By the end of the study, the sugar dressing group showed a median improvement of 30 points compared to no change in the standard dressing group (**Table 5.4** p=0.005).

EQ-5D HRQoL domains

For each patient, the difference between the baseline and final score was calculated for each EQ-5D domain and compared between the sugar and standard dressing groups. Very few patients showed 2 point changes from baseline final score and Kendall's tau-b tests were used to make the comparisons between the groups. For simplicity, the data was summarised as the number of patients who had improved scores at the end of follow-up (i.e. the change was -2 or -1), the number with worse scores (i.e. the change was +1 or +2) and the number with no change (see **Table 5.5**).

It is important to report that, the change in mobility, self-care usual activities and anxiety/depression from the start of the study to the end of follow-up did not differ significantly between the two groups (p=1.000, 0.098, 0.060, 0.432 respectively). However, the responses relating to the levels of pain/discomfort did differ significantly between the groups (p=0.012). In the patients treated with the sugar dressing, 13 (59.1%) reported an improvement in symptoms, compared to only 5 (21.1%) in the standard dressing group. No patients in the sugar dressing group reported a worsening of pain/discomfort, compared to 2 (10.5%) in the control group.

Table 5.5: Summary of EQ-%D HRQoL patients' responses

Individual health domains		**Sugar Dressing N = 22**	**Standard Dressing N = 19**	***p-Value***
Mobility	*Improvement*	3 (13.6%)	2 (10.5%)	*1.000*
	No Change	19 (86.4%)	17 (89.5%)	
	Worsening	0 (0.0%)	0 (0.0%)	
Self-Care	*Improvement*	6 (27.3%)	4 (10.5%)	*0.098*
	No Change	16 (72.7%)	15 (78.9%)	
	Worsening	0 (0.0%)	2 (10.5%)	
Usual Activities	*Improvement*	6 (27.3%)	2 (5.3%)	*0.060*
	No Change	16 (72.7%)	17 (89.5%)	
	Worsening	0 (0.0%)	1 (5.3%)	
Pain/ Discomfort	*Improvement*	15 (59.1%)	6 (21.1%)	*0.012**
	No Change	7 (40.9%)	13 (68.4%)	
	Worsening	0 (0.0%)	2 (10.5%)	
Anxiety/ Depression	*Improvement*	10 (45.5%)	9 (36.8%)	*0.432*
	No Change	12 (54.5%)	10 (52.6%)	
	Worsening	0 (0.0%)	2 (10.5%)	

P-value from Kendall's Tau-b test on 5 categories
**Significant at p<0.05*

5.9. Adverse events

In this study, no adverse events were reported from any patients in the sugar or standard dressing groups.

5.10. Discussion

5.10.1. Summary of findings

In this randomised controlled trial, sugar debrided exuding necrotic, infected or sloughy wounds of acute or chronic aetiology within 1 week up to 4 weeks. Debridement is the removal of non-viable tissues from the wound bed. This according to Falanga (2001), EWMA (2004), Wolcott et al (2009) and Strohal et al (2013) is essential component if ever wound care practitioners are to achieve wound healing goals. Strohal and colleagues (2013) further consider debridement as a global approach with a universal goal of not only focusing

on debriding the wound bed but accounts for the preparation of the wound edges and peri-wound skin. It is important to understand that chronic wounds often contain necrotic or sloughy tissue, which can harbour bacteria and act as a barrier to wound healing. In their study of wound and bacteria, White and Cutting (2008) comments that, in sloughy, necrotic wounds, the availability of nutrients as well as oxygen and the presence of ischaemic tissue make the wound bed an ideal environment for both aerobic and anaerobic bacterial proliferation. The same authors (White and Cutting, 2008) pointed out that, this proliferation of bacteria results in malodorous and infected wounds. Therefore, debridement of sloughy, necrotic tissue is one of the key component of good wound care practices that reduces bacterial burden within the wound bed (Vowden and Vowden, 1999a; Vowden and Vowden, 1999b). The ability of granulated sugar to debride wounds observed within this study as well as its ability to stop bacterial proliferation Murandu et al (2011) makes this wound care product a potential effective method of treating sloughy, necrotic and infected wounds.

Patients' wound pain and odour was improved. Furthermore, there were statistically significant changes in pain and discomfort (p=0.012); and improvements in mobility, self-care, usual activities and anxiety and depression which did not achieve statistical significance.

Under the current focus of wound care and that of the present study (including wounds of mixed aetiology), sugar treatment as shown in this trial facilitated reduction in wound odour. Wound aetiology distribution was fairly similar (see **Table 5.2**), with less patients in the acute wound category. This finding is similar to the findings of Tophan (2000) and Chiwenga and colleagues (2009) who observed that patients treated with sugar had their wound odour reduced or removed. In Murandu and colleagues' study of 22 patients' odour was reported to have been removed within 24 hours or up to 3 days (Murandu et al., 2011). It is important to recognise that patients assigned to this sugar arm had already been on other forms of

standard/conventional methods of dressing products; and sugar treatment was used as an alternative to these products other than as an initial dressing, so odour was an indication of failed management from these standard dressing products. It is therefore apparent that effects observed from the sugar arm would have been that of sugar. Others may argue that it might have been the residual effect of the standard treatment observed, but the fairly normal baseline characteristics distribution and comparable wound aetiology as well as consistence with other previous research results demonstrates the effectiveness of the sugar treatment on odour management.

In this study, the overall self-reported quality of life scores using the EQ-5D questionnaire were improved. There were changes in mobility, self-care usual activities and anxiety/depression at the end of the study. Usually in studies like these as acknowledged by Persoon et al (2004) which are new in clinical areas patients will at times report intolerable side-effects that result from receiving the treatment and at times complicate their lives too. Often it is thought that most patients especially elderly suffering from chronic wounds would rather keep quiet and not report pain (Hofman et al., 1997); therefore this result is encouraging.

Of note the TELER pain indicator median score of 2(0, 2) in the patients receiving sugar supports the belief that patients with poorly managed pain do at times live with feelings of depression and QoL deficits. An improved pain control conversely affects the quality of life of the patients; a scenario observed in this study. Most patients with wounds, be it acute or chronic, do suffer from severe to moderate pain sensation. Pain can arise from different wound care products, such as inappropriate dressing choice, mechanical debridement of devitalised tissue, wound cleansing and dressing change observations highlighted by Richardson and Upton, (2011). Soloweij et al (2009) go on to postulate that pain and stress play fundamental roles in wound care whether in acute or primary care setting and such pain

or anticipation of pain does have detrimental effect on the physical functioning of patients. It causes psychological distress as well as reduced quality of life as observed in this study.

Although this study did not set to explore in-depth reported qualitative experiences of patients, it was important to communicate some of the reports as they formed core findings to this research. The researcher concluded that, patients' wounds, if treated with sugar improves the overall health related quality of life of patients. Several patients reported pain reduction as suggested from this quote extracted from several of anecdotal evidence reported by patients during clinical visits:

> The pain was unbearable, I could not sleep, and all I could do was glare at the ulcer and rub my leg, hoping that the pain would go away. I took strong painkillers; tramadol, morphine but they had no effect. I would doze a bit but afterwards I would wake up in agony. A few days of using sugar brought relief. I could sleep and the pain was less and was able to manage the pain with only paracetamol. (Quote from patient No. 38)

The use of TELER indicator scoring assessments of wound during every dressing change including weekly evaluations enabled a more rigorous approach to understanding patients' pain in contrast to that reported by earlier researchers (Toba et al., 1999; Mphande et al., 2007; Biswas et al., 2010). These previous studies did not explicitly monitor vigorously the pain in relation to sugar treatment but just commented on pain in general a point reported in the QoL review by Persoon and colleagues (2004) that nurses' did not monitor and manage patients' pain appropriately. Mphande and colleagues (2007) asserted that patients in their sugar group reported more pain than those in the honey arm a result contrary to our findings or other findings. Of note is the insufficient information of baseline pain scores recorded in Mphande and colleagues (2007) study that makes it difficult for readers to establish and conclude the pain score differences. Contrary to Mphande and colleagues' findings is the study by Jull et al (2008) who noticed that patients treated with honey reported increased pain sensation. These findings concur with the earlier findings by Dunford and Hanano (2004)

who reported relieved symptoms on patients receiving sugar treatment. Arguably in Mphande and colleagues' (2007) study the base-line pain score was not similar as mentioned earlier and there were discrepancies on their conclusions of the pain difference in the two arms to suggest that this was the true effect of sugar or honey. In hindsight Molan and Betts (2004) attributed honey pain to its acidity and production of hydrogen peroxide a reaction not experienced in sugar treatment. With this explanation, it can be argued that patients treated with honey may tend to suffer more pain than those treated with sugar conclusions made in this study.

An earlier study by Roe and colleagues (1993) had found out that 55% of nurses did not report patients 'pain experiences as part of their assessment Four years later there was still no change as, Hofman and colleagues (1997) reported that pain was not adequately reported during assessment by nurses or medical teams even though pain is viewed as one of the most debilitating symptom of wound sufferers. It was acknowledged in this sugar study that pain needed special attention if it was seen as part of the domain in wound care. It is was also important to assess pain adequately because dressing changes were carried out every 2-3 days and if pain is not fully understood and managed appropriately then patients will suffer unnecessarily.

It is essential in this regard to note that in addition to the more frequent changing of dressings, the participants had an opportunity to discuss their wound progress with the nurse attending to their wound dressing. Unlike having to wait for either 2 or 3 days for a dressing change sugar treatment allowed dressing changes to be more frequent depending on the wound exudate. The patients had better opportunity to meet the nurse and discuss their wound progress. This is an important factor if patient concordance with adjuvant care is to be achieved. It must be added that an individual patient centred wound care management is paramount, as it plays a major role in each aspect of patient including that of good nutritional

intake. Providing a patient centred approach to care will cultivate concordance with adjuvant treatment including that of nutrition, this inversely increases the chances of improved healing rates (Dealey, 2005).

This sugar trial was also associated with good treatment adherence as well as easy dressing changes. The therapy was relatively painless to most patients. Dressings were changed easily because sugar is a water soluble substance and does not adhere to wounds. Dressings were easily removed by soaking in tap water or moistening with normal saline. Sometimes secondary dressing would easily be removed by cutting off the bandages. Additionally, sugar's hygroscopic effect helps reduce oedema in wounds (Yedkin et al 1971), thereby minimising inflammation and pain, allowing easy removal during dressing change. On very few occasions 2 patients complained of mild pain due to the granularity of sugar on initial application, however subsequently they found the dressing changes to be non-painful and soothing, a scenario reported by Chiwenga and colleagues (2009). Analgesics requirements were therefore minimal even to those who had been requiring opiates regularly prior to entering into the study.

It must be pointed out that not all the EQ-5D domains were statistically significant. The change in mobility, self-care and usual activities and anxiety/depression from before and after the study was not statistically significant as previously reported. There are two possible explanations; firstly, Brooks et al (2003) recommended the use of EQ-5D tool when incorporating economic evaluations into the trial, and the limited information on the utilisation of this instrument into leg ulcers, given that most of our wounds were leg ulcers. Probably the use of Price and Harding (2004) Cardiff Wound Impact Questionnaire, Short Form 36, generic and wound specific would have yielded a more specific result or the use of Palfreyman (2008) Sheffield tool, Ulcer 5-D, venous and healed Euro QoL SF-6 Generic and Ulcer specific. However, the reported information does point to the fact that granulated sugar

dressing has a potential to improve the quality of life. The second explanation can be that of Schrag et al (2000) and Marra and colleagues (2005) whose trials concluded that the EQ-5D needed a longer period of more than 12 weeks to be responsive to changes.

This was further supported by Jull and colleagues (2008) who surmised that the EQ-5D was not responsive to short-term changes. However, Iglesias and colleagues (2009) found the tool to be effective over three months (shorter-term) supporting the results of this sugar study. In addition, Persoon et al's (2004) review identified four themes related to quality of life on wounds or leg ulcers; these are pain, impaired mobility, sleep disturbances and problems related to wound characteristics such as odour and wound discharge. Soon and Action (2006) and Soloweij et al (2010) pointed out that there is a link between pain and the development of stress and if wound pain is well managed a large proportion of stress may disappear. Importantly, the use of the TELER indicator system allowed the clinicians to change or adjust analgesics in order to combat pain. Therefore the patient's quality of life must be seen as directly related to the comfort and experience of pain or no pain; or wound discharge leakage or persistent wound odour.

5.10.2. Strengths of the study

To date this is the first randomised controlled trial of sugar dressing that used a specifically calculated sugar dose for different wound categories. Sugar doses varied from 15g up to 90g in divided doses of 30g in each aliquot. This helped indicate specific doses of sugar required for different wound categories as well monitoring the amount of sugar administered to each patient wound. It would have been problematic to monitor the sugar dose had patients' wounds not been categorised prior to commencing the study. Thus, patients' wounds were stratified according to wound aetiology and size a method not previously reported. This stratification assisted with balancing the baseline characteristics and aided minimisation of confounding prognostic indicators amongst the researched sample.

Allocation was concealed up to the point of randomisation by using an out of research sites central telephone service. Furthermore this trial included a multicentre approach and this was not mentioned in any of the reviewed literature. However, the participants were not equally distributed from the three centres. Most patients (n=32) were recruited from the leading site see **Table 5.3**. In addition an independent assessor (A Tissue viability nurse specialist) autonomously and randomly reviewed the digital wound photographs from each arm and reported on their percentage of slough see **Figure 5.2** and

Appendix 15: . The tissue viability findings were compared to those reported by the nurses on the TELER indicator score assessment form Appendix 8. The findings were in agreement with the nurses' entries on the case report forms. This may have been enhanced by the fact that, the nurses decision to record debridement or not debridement that were disputed amongst themselves were reviewed by the clinical team during ward rounds as previously explained. The outcome was 95-99% slough reduction with visible granulation tissue within 3-12 days of sugar treatment. This is possibly the first RCT to have managed to have reported this form of comparative independent wound assessment. All the RCT literature reviewed did not mention this type of independent comparative assessment. Therefore it can be argued that in terms of assessor bias, the trial employed an appropriate method that reduced researcher bias related to outcome assessments and increased the reliability of the results. Intention to treat analysis was undertaken with the inclusion of all participants randomized, and follow-up was virtually complete with only one (n=1) participant lost.

5.10.3. Limitations/weaknesses of the study

This study like any other research study had limitations and weaknesses. Firstly, the trial recruited fewer participants than anticipated, 41 patients instead of the powered 108. Despite increasing the sites and extending the recruitment period the study failed to meet the targeted sample size. It did not recruit enough participants to retain 90 percent power, although the anticipated loss to follow-up did not occur. Secondly, funding limitations precluded longer follow-up. It meant no research nurses were employed to help with data collection. Most data collection and dressing changes were carried out by the research coordinator, a task that limited the recruitment process. Although there was minimal support from the ward and community nurses on data collection and dressing changes, it was not enough to enable constant flow of participants into the study. In addition, some potential participants were not approached and considered for the study due to clinical staff scepticism. At times the clinical

staff only considered the patients when they found it difficult to manage with standard treatment; a process that led to missed recruitment opportunities.

The two arms were balanced at baseline this allowed consistency between study groups. However, there was very little difference in wound aetiology and size from the two categories acute or chronic. Therefore, it was impossible due to the small sample size to analyse the data in four strata as initially proposed. The analysis was therefore done after combining each arm according to one size (Medium – large) and aetiology strands.

It was the intention of this study to compare differences after adjustment for baseline (ANOVA) and not to just compare differences from baseline to follow up (Huck and Cormer, 1996; Scott and Mazhindu, 2007; and Brysbaert, 2011). The researcher was aware that measurements that are most extreme (farthest from the mean) at the start of the study will always seem to improve more because everything which is an extreme values tends to be closer to the mean with repeated measurements i.e. regression to the mean. However, the limited funds and subsequently the nursing staff to carry out the frequent assessments as previously envisaged meant the above was not possible. Additionally, the data were not normally distributed due to the skew (wound area/slough/exudate) or discreteness (Likert scales), so the data did not meet the assumptions of ANOVA. If this assumption of ANOVA was to be carried out it would have resulted in an unreliable model. In addition, since the patients were randomised, it was expected that participants were reasonably well matched at baseline as mentioned earlier. Therefore, the testing was done using comparisons of the baseline levels of the outcomes between the two groups, none of which found any significant differences. As for the regression to the mean, since the groups were matched at baseline, this was expected to occur equally in the two treatment groups. Therefore it was not expected to bias the comparison between groups.

This combination could have not by any means influenced the outcome of the results in favour of the intervention arm as the baseline characteristics were comparable. An independent assessor was employed to minimise the possibility of bias on reporting the percentage of wound slough a plausible process, however human subjectivity on measurements and judgement cannot completely be discounted. This study was not blinded – that is also a weakness

5.11. Risk of Type 11 error

There is a potential for type 11 error in the repeated unadjusted analysis for a similar size, e.g. reduction with a small sample size of 42. However, this is unlikely to be the case, as the alpha was set to a significance level of 0.05 prior to commencing the study. Furthermore, Re Loux (1995) reckons a change in TELER indicator points denotes a clinically significant level either positively or negatively. Therefore, the change observed on the TELER indicators is considered clinically significant, rejecting the possibility of type 11 error mistakes. The change in the method of analysis following the low recruitment rate could be a source of type 11 error. To overcome this problem a repeated power calculation was undertaken (see chapter five results section).

5.12. Comparison to existing literature

Importantly, the results from this randomised study for sugar treatment are consistent with the findings from the previous RCTs (Dawson, 1996; Toba et al., 1997; Mphande et al., 2007; Bajaj et al., 2009 and Ruhullah et al 2013) and observational studies (Chirife et al., 1982 and 1983; De Feo et al., 2000; De Feo et al., 2003; Chiwenga et al., 2009) that concluded that sugar treatment was effective for wound cleansing and promotion of granulation tissue. In

another non comparative observational study undertaken in Italy by De Feo and colleagues (2000) and De Feo et al (2003) granulated sugar was observed to be effective in debriding post open heart surgery with mediastinitis. All patients survived the treatment and their wounds were reported to have been sterile after 11.22+/- 1.6 days of receiving the sugar treatment. They further reported that within 4.3 +/- 1.3 days temperature had normalised. From this study as well as other previous studies reported earlier, there is potential for sugar becoming a wound care dressing product. But it must clearly be pointed out that sugar in itself does not affect healing but creates a wound bed environment appropriate for wound healing. A moist environment also helps with easy removal of dressings during dressing change. Persoon and colleagues (2004) concluded that factors influencing QoL were not clearly distinguished and advised of further research in the area of QoL related to patients suffering from wounds or ulcers.

In this study, patients treated with sugar reported greater improvement in wound malodour and exudate leakage than those treated with standard dressings see **Table 5.5**. Walshe, (1995) and Hyde et al. (1999) believe leakage and odour are at times accepted as a sign of having wounds or ulcers. But these signs and symptoms can lead to embarrassment and difficulties in maintaining dignity and outward appearance. In this sugar trial clinicians observed that wound malodour can affect patients both socially and psychologically and this was also reported by Benbow (1999). In other reports assert that noxious odour is sometimes misinterpreted as poor hygiene leading patients to feel embarrassed (Van-Toller, 1995; Haughton and Young, 1995; Hack, 2003). The odour at times is constant stimulating nausea and vomiting that will eventually lead to lack of appetite and poor wound healing (Flanagan, 1997; Benbow, 1999). It is understood that chronic and infected wounds particularly venous leg ulcers, diabetic foot ulcers, pressure ulcers and fungating malignant lesions are the most common wounds associated with malodour (Lee et al., 2006) a trend observed in this study.

The later can be a justification for the difference in health related quality of life in favour of sugar. It can be argued that, the presence of infected or non-infected necrotic tissue within a wound bed acts as a focus for infection, encouraging multiplication of anaerobic bacteria, which causes wound malodour (O'Brien, 2002), in return this can be a burden to patients and relatives and clinical staff who have to live and interact with such odorous wounds. Therefore, removal of malodour and necrotic tissue can be a relieving factor to patients and their quality of life. The study findings supported Armstrong, et al. (2002); Sherman et al., (2002) and O'Brien (2002) who believed that, removing devitalised tissue from the wound surface is an important factor if healing is to be achieved and can encourage patient concordance to the treatment given. In this study, clinical observations showed patients whose wounds were no-longer odorous had their appetite improved. They were also more receptive of visitors than previously observed.

This can be asserted by one reported case in the sugar arm that of a patient who had suffered from bilateral leg ulcers for several years and stated:

> My wounds smelt that my daughter's dogs tended to smell my legs every time I and my wife were dog sitting. It was such an embarrassment that I did not want to look after the dogs whenever they went away. I was so embarrassed that I did not go out on family meals or visiting friends.
>
> After one day of sugar treatment the wounds were odourless:
> I noticed that the first thing the dogs did when my daughter visited was to jump on my chest, they did not smell my legs; it was such a relief. (Patient No. 37)

These comments highlighted that odorous wounds can lead patients into isolation a factor reported in (2002) by Holloway and colleagues. Further reports by Bale et al. (2004) acknowledged that malodorous wounds does pause social isolation, depression, shame, embarrassment and poor appetite, resulting in a negative impact on QOL. It is without doubt that odorous wounds are a burden that can affect patients' QOL and that if this symptom is eradicated patients can have an improved quality of life.

Following the improvement in mobility, pain, sleep patterns and removal of malodour, appetite was reported to have improved too. The improvement in appetite can be seen as a positive effect towards wound healing and recovery; especially that many patients with chronic wounds are elderly and susceptible to malnutrition.

Overall, this study recognised that patients with wounds of either acute or chronic have significant poor quality of life (QoL) affecting their ability to mobilise, and disturbing their sleep. The study employed the TELER indicator system to enable an understanding of the pain associated to specific pain domains such as sleep, mobility and wound dressing. In that way pain was reported according to each domain and the clinician was able to quantify and understand how pain was affecting each patient's quality of life. The treating clinician was then able to prescribe an appropriate plan of care and monitor accurately the pain progress and patient's QoL. It was also valuable to observe the treatment effect of sugar on an individual patient rather than as a group as patient experiences of pain sensations are different. This method of assessment (TELER) supported by the use of EQ-5D questionnaire enabled clear understanding of the effect on the intervention on each individual treatment arm. The mobility was improved (see table 4) this can arguably be seen as the effect of sugar since sugar reduces oedema, cleanses wounds of microorganism and dead tissues lessening pain and malodour. The clean wound with visible granulating tissues allows wound epithelialisation and wound healing a positive process towards wound healing. In support, Strohal et al (2013) sees debridement (removal of devitalised tissue) as an integrated part of the wound management plan that focuses on patients' attending to the wound with the aim of creating a healthy wound bed as well as healthy wound edges and peri-wound skin. In this positive framework, patients will show signs of improved mobility; less frustrations and improved self-esteem which are a positive a factor in wound healing. Strohal and colleagues (2013) further disputes Gethin and colleagues' (2010) view of debridement as a wound bed

preparation. Strohal and colleagues argued that debridement is a universal wound bed preparation that accounts not only wound bed but wound edges as well as the peri-wound skin (Strohal et al 2013). They further posit that if this global approach is successful clinical benefits such as wound healing and improved quality of life can be achieved a scenario experienced in this study. Patients on the sugar treatment had several clinical benefits such as pain reduction, odour removal, reduction in wound leakage. These clinical attributes are associated with increased quality of life in wound care.

5.13. Conclusions / Research & Policy implications

The data from this RCT though small in sampled patient numbers showed that granulated sugar applied topically is an effective debriding agent and well tolerated treatment option in patients with exuding necrotic or sloughy wounds. The wounds rapidly debrided, with normal granulation formation observed. This treatment effect may be the result of impetuous removal of microorganisms colonising the wound. Because the wounds were rapidly removed of slough which usually harbour bacterial contamination they became clean, enabling new tissue development an experience reported in earlier studies (Knutson et al., 1981; Tophan, 2000, Mphande et al., 2007 and Chiwenga et al., 2009). The effectiveness of sugar depends upon its antimicrobial high osmolar effect. Experiments performed both previously at Delta Medical Centre concluded that sugar is effective inhibiting growth of both gram-positive and negative bacteria (Kunutson et al., 1981) and currently as described in chapter two of this work; sugar inhibits microbial proliferation at a solution of 25% sugar concentration (Murandu et al., 2011). Similarly, sugar works in the same way when applied topically on wounds surfaces competing with microorganisms for water causing osmotic shock to bacterial survival (Chirife et al., 1983). As a result of these factors there is decreased bacterial colonisation as

bacterial eradication increases from the wound. Of note, sugar dressing is a moist absorbing wound care dressing that does not have any specific indications therefore it can be used to treat either acute or chronic wounds of various aetiologies. Therefore, on this aspect the results should be considered as generalizable to various wounds regardless of their clinical aetiology until further evidence suggests otherwise. Similarly, the results should be considered as applying to both sugar of cane and beet origin.

The dose (carefully measured quantity) of sugar in this present study merit comment, in particular the dose in different wound categories. The study also explored the securing mechanism of each type of wound and identified the practical mechanisms that are possibly appropriate to each given wound with a reproducible protocol.

It is important in this regard to keep in mind that in addition to the randomisation and allocation concealment nature of the study, the current sugar trial had several important additional design features that may have contributed to the positive observed outcome. The protocol required daily or alternate dressing change, with daily wound assessments as well as weekly evaluation starting from week 1 ending at week 4 of the study. This also included washing of wound and surrounding area with tap lukewarm water. Thus, the particular attention on wound washing/thorough cleaning within this study provided a situation rather different from what can often be achieved in clinical practice and may have significantly contributed to the acceptability of the study in both arms.

It is important that future studies allow sufficient time to provide training on the dressing technique on both intervention and control even if nurses were already trained and were competent. This will minimise the one sided enthusiasm of nurses and patients. If this is effected nurses will feel motivated to undertake dressing changes for both intervention and control probably avoiding the Hawthorne effect.

This study as well as the previous RCTs lacked sufficient powering a factor that needs to be affected in future planned sugar studies. There is also need to include clinical trials units to enabled planning of more effective statistical test that will be factored into the study.

5.14. Ethics and good clinical practice

Following the feasibility study it was principle that further ethical approval of the RCT was attained. Therefore, all necessary permission was obtained from North Birmingham and Solihull Local Research and Ethics Committee as well as permission from the three Trusts' Research and Development Departments. The researcher had honorary contracts with all designated trusts. MHRA permissions previously discussed in chapter 4 applied to this study as this was a continuation of the same work. Participation was entirely voluntary, and patient care was not affected in any way by their decision to participate or not to participate. Patients were explained of the study and given an information leaflet to read over-night at their own time. Having read the information and those who were happy to partake into the study were requested to sign a full written informed consent form that was counter-signed by the admitting nurse or researcher prior to joining the study. The trusts had robust and effective interpretation services that the researchers were to use if there was language barrier. All patients understood English and the use of interpreting services were not needed.

The following chapter will summary up the processes and stages of this thesis. Challenges will be identified and explored. The researcher will conclude with lessons learnt and proposals for the way forward for future research.

6. Chapter: Overall discussion and conclusion

6.1. Introduction

The overall aim of this work has been to explore whether that it is possible to use sugar as a dressing in a modern NHS hospital and explore its potential as an effective debridement agent. The purpose of this chapter is to summarise both the outcomes and the challenges that have arisen during the course of the work.

6.2. Preparing sugar as a dressing \and MHRA issues

6.2.1. Sugar the origin and its development into a wound care product.

Sugar is known to have been used in the treatment of infected wounds (Herszage et al., 1980). It is believed to be easy and painless to apply (Tanner, 1998). But there is a need to explore how sugar sterility can be maintained from the manufacturer to the consumer. During production sugar has gone through a highly tested process that involving burning the cane/beet with high furnace temperatures where microorganisms will not survive. It is then processed to produce the white crystal anhydrous disaccharide 99.9% material sugar (glucose and fructose). A certificate of conformity is produced (see Appendix 5) for each 25kg bag of sugar. Serial numbers are printed on the bags and they fall into different categories depending on the date and year of manufacturing.

The sugar is purchased from the manufacturer and delivered to a recognised pharmaceutical production centre for re-packaging of the 25kg bag of sugar into small 30g aliquots with serial numbers, each with a certificate of conformity. This will allow easy follow up if there are any adverse effects that require tracing back to the manufacturer. The 30g aliquots are distributed to the different hospitals. The sugar is now ready to be used on wounds and can be monitored for its effects and side-effects.

6.2.2. Medicine and Health Regulatory Authority issues –

The study in chapter 2 highlighted the effectiveness of sugar on microorganisms and its potential for use on treating sloughy, necrotic and infected exuding wounds. Having established the microbial effect an application was made to the Medicine and Health Regulatory Authority (MHRA) for the sucrose to be tested as a dressing product. At first the MHRA classified sugar (sucrose) when used on wounds as a dressing of medicinal product. This affected categorisation of the sugar feasibility study as a clinical trial of a medicinal product (CTMP) that requires a fee to register. This was negotiated by the researcher. The researcher explained to the MHRA, that the research was not for commercial and profit generation but for patient benefit, financed privately by the researcher. After negotiation the MHRA categorised the study as clinical trial of non-medicinal product. Having been granted MHRA permission, applications were made to the local Research Ethics Committee and the NHS hospital trust Research and Development committee for their approval. The two committees both granted authorisation and the small feasibility study commenced in 2009.

6.3. Potential for use on infected wounds

6.3.1. Laboratory studies and the rationale for frequency of dressing changes

By definition sugar is not an antibiotic. According to Oxford dictionary for nurses (2003) supported by Simonsen et al (2006) an antibiotic is a substance produced by or derived from a microorganism that destroys or inhibits the growth of other microorganisms. In order to understand the possibility of the effects of sugar on microorganisms' laboratory tests were carried out to identify the susceptibility of microorganisms to different types of sugars and

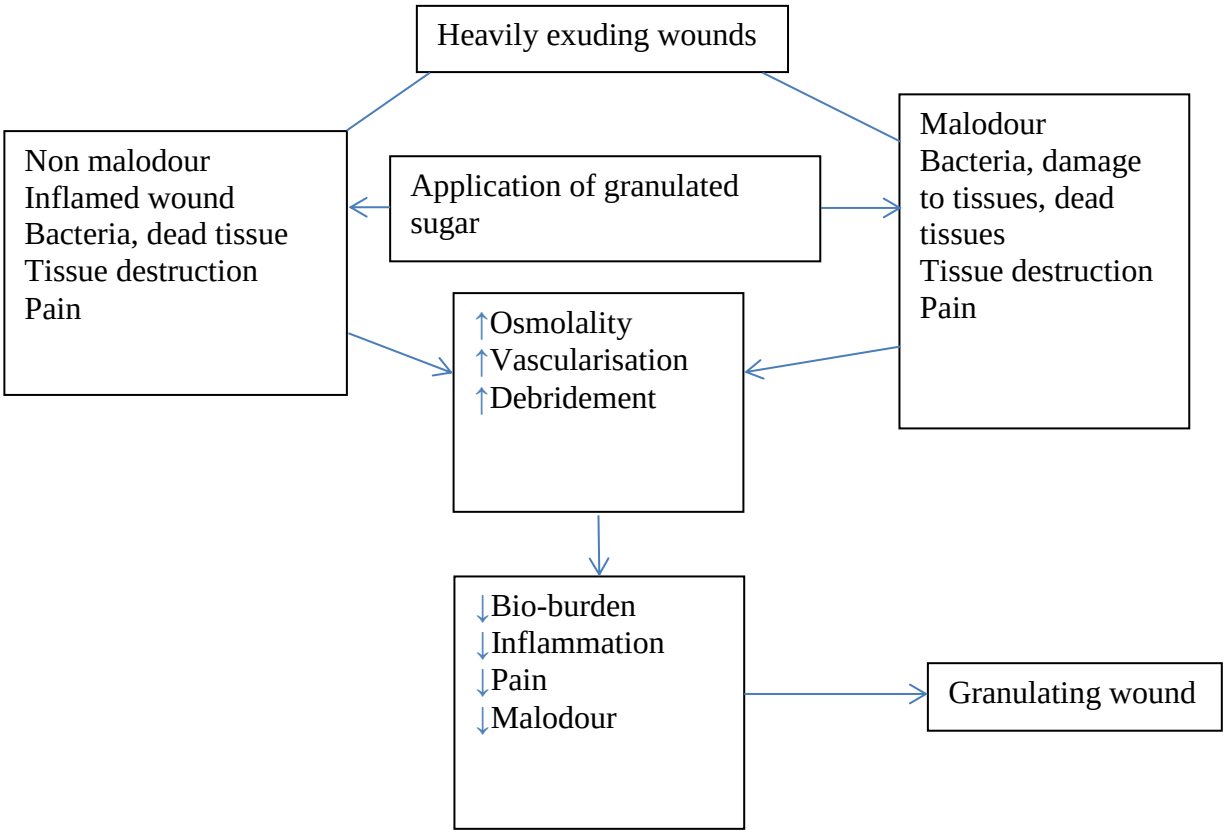
help with the planning phase of "the feasibility study" (chapter 4). It was important to establish how the sugar affected microorganism in order to decide on whether to use the sugar as a wound care product, if and also determine the frequency of application. Previous laboratory explorations of sucrose (Chirife et al., 1983) established that sugar prevented microorganism proliferating but did not identify how specific types of sugars affected various microbiological species. The current laboratory examination explored these areas and concluded that both refined and un-refined sucrose affected microorganisms' ability to proliferate. The un-refined (Demerara/brown) sugar required a solution of slightly higher concentration than that of white sugar. Overall, sucrose prevented microbial proliferation by osmolality; the higher the sucrose osmolality the more effective the sucrose was in preventing the growth. The researcher became aware that if the level of high osmolality of sucrose is achieved, then sucrose would probably act as a local universal antimicrobial agent that can affect healing process positively. This formed the basis of planning the frequency of dressing changes because it highlighted that dressing changes needed to be frequented to enable retention of high sucrose content on the wound bed. It was agreed that dressings changes were to be undertaken daily or every other day, depending on the level of exudate for each given wound. It also agreed that treatment was to be individualised to cater for wound aetiology and size.

6.4. Infected wounds

It is generally agreed that sugar is effective in inhibiting microbial proliferation (Knutson et al., 1981; Chirife et al., 1983; Trouillet et al., 1985; Toba et al., 1997; Mphande et al., 2007; Chiwenga et al., 2009; Murandu et al., 2011; Ruhulla et al., 2013); this is supported by this current work.

The sugar effect can possibly be explained in the context of *hyper tonicity* environment created on the wound-bed (see **Figure 6.1**) when sugar is applied on the wound. It manifests as suggested by Chang (2006) *osmotic pressure* phenomenon; that body fluid as well as water from bacterial cytoplasm is drawn into sugar granules. As a result the sugar granules liquefy thereby creating *hypotonic* area within the wound-bed. In response the heart increases, the blood flow to the wound-bed to create an equilibrium *isotonic* wound-bed environment. This process will possibly allow an increased flow of blood with it oxygen, nutrients and leukocytes all important components for tissue regeneration.

Figure 6.1: Granulated sugar action on wounds and microorganism



Clearly, the antimicrobial activity in sugar dressing that prevents and treats infections is fundamental to its wound healing properties (osmotic shock or osmotic vacuum). The emerging evidence points to a more diverse role (Tophan, 2000; Knutson et al., 1981; DeFeo 2000; De Feo et al., 2003) including debridement. Observed therapeutic effects attributed to using sugar include rapid healing (Mphande et al., 2007; De Feo 2003; Ruhullah et al., 2013), stimulation of the healing process (Murandu et al., 2011) clearance of infection (De Feo et al., 2003; Murandu et al., 2011). Wound healing is a complex dynamic process that involves several systems and cell types. Molecular and cellular components are responsible for the degradation and repair of tissue that occur during healing (Cooper, 2001). While the exact mechanisms for all the observed effects of sugar when applied to wounds are yet to be defined, the earlier explored in vitro studies (chapter 2) supported by Chirife and colleagues

(1983) point to water activity (Aw). Table 6.1 provides a summary of possible properties of sugar as observed from this study and reviewed literature. As a medical treatment, sugar is innocuous. Other than occasional stinging when applied to wounds no adverse effects have been reported. In addition, allergy to sugar is rare.

6.5. Protocol for the use of sugar

6.5.1. Treatment protocol and use of sugar in the NHS hospital

One of the weaknesses of previously reviewed sugar studies was the lack of clear guidelines on how to apply and the frequency of application of the sugar on wounds. The sugar wound dressing protocol. It became obvious that there was a need to develop a clear and publishable sugar protocol.

Applying sugar treatment to leg ulcers, and other complex superficial wounds, such as toe and below knee amputees without cavities can be challenging. A special technique to enable retention of sugar on the wound was developed. In RCT study 29 (70%) patients' leg ulcers and 8 (20%) patients toe and below and above knee amputees were involved and these wounds required special sugar application such as; the surrounding skin area of the wound was ridged with yellow paraffin to allow stability and retention of sugar. In other cases yellow paraffin was applied on the gauze and sugar was damp dusted over the Vaseline until completely covered in a thick layer. The gauze and the sugar were gently lifted and placed onto the wound, slowly covering the whole wound with sugar, before securing with an absorbent wound dressing pad. The cavity wounds were easier to apply the sugar as opposed to those of superficial wounds. It can be argued that superficial wounds may at times have failed to retain enough sugar as opposed to cavity wounds a scenario that could have been

viewed as advantaging the cavity wounds. This factor needs consideration when planning further sugar studies.

The follow-up time frame chosen (4 weeks) might have been limited for monitoring wound debridement, but given the previous studies (Trouillet et al., 1985; De Feo et al 2003; Mphande et al., 2007; Murandu et al., 2011), it was within an acceptable time period to enable evaluation of effects of granulated sugar on wound debridement. There are reported evidences that if the wound is completely debrided (wound bed preparation) that wound will progress to healing (Falanga, 2000; O'Brien, 2003). In the feasibility study (Murandu et al., 2011) concluded that, sugar debrided wounds within a minimum period of 5-14 days supporting previously reported findings of Dawson, (1996), De Feo, (2000), and De Feo, (2003).

Previous studies (Debure et al., 1987; Beading, 1997) had both reported that diabetic patients who had been treated with sugar had slightly raised blood sugars. However, these studies did not contradict the use of sugar on diabetic patients. Although the knowledge of treating wounds has been cascaded from generation to generation, there are no clear guidelines set on the effects on blood sugar levels and how to manage this side-effect if ever it was to be reported. The feasibility trial results did not report any increased blood sugar level in any of the treated diabetic patients. It must be added that none of these patients required supplementing insulin above the prescribed dosage, or changing the route of treatment from oral tablets to insulin injections. This effect supported the conclusion of Yudkin and colleagues (1971) that sugar to be absorbed requires enzyme sucrase situated in the brush border of the small intestine. These facts were crucial in persuading the clinical staff to support the sugar study. It must be added that, during the RCT running, there were diabetic patients who were treated with sugar, though not specifically monitored as part of the study;

they kept checking their blood sugar levels and did not report any increase in their blood sugar level.

6.6. Challenge of staff scepticism to sugar

6.6.1. Attitudes to use of sugar

The initial thought of using sugar was received with scepticism and doubts from different clinical staff. Initially, vascular consultants from different NHS trusts were approached and declined to work with the researcher. Some cited difficulties in obtaining ethical approval and others just felt sugar would cause more harm than good. Following discussions between the supervisory team and the researcher, the lead supervisor helped to secure the cooperation of a vascular consultant surgeon who had previously worked in Kenya and seen sugar being used in wound care. A meeting and presentation to the vascular medical team was arranged, questions were raised and answered accordingly. After the meeting, most of the medical staff agreed to support the study. Many clinicians felt sugar would encourage proliferation of microorganisms on the wound bed, a scenario they were not prepared to risk. The researcher used the *in vitro* study results as evidence of the potential for sugar as a wound care product. This information helped to convince the doctors to support the feasibility and the RCT studies.

An additional question and answer meeting was arranged between the senior nurses, researcher and the supervisor to discuss the study. Although the senior nurses were sceptical at the start of the meeting they agreed to support the study. A further meeting, including all nurses and the lead PhD research supervisor, led to a provisional date being arranged for commencing the study. During these meetings several questions were asked and the

researcher explained to the best of the available evidence. The questions helped in the formulation and designing of the research methodology.

Following the results of the feasibility study, an interest arose from two top surgeons of the British military medical team. The interest resulted in several strategic meetings organised between the researcher and the military medical team. The researcher presented the work with the support of the lead supervisor. Several questions were asked and answered to the best knowledge available at the time. After the meeting it was agreed that the military would like to be involved. This meant amending the protocol and seeking further permission from the Local Research Ethics Committee (LREC) and the Ministry of Defence Research Ethics Committee (MODREC). This was pursued by the researcher and the lead supervisor and permission was granted by the LREC (see Appendix 1). The researcher and the lead supervisor were invited to present the protocol and the planned RCT study at the MODREC meeting. The MODREC, agreed that there was a potential, but wanted the researcher to undertake a systematic review and meta-analysis in order for the committee members to assess whether it will benefit the injured soldiers. One particular comment from one of the ministry of defence chiefs to his colleagues was, “imagine if the public was to hear that the military is using sugar to treat our injured soldiers? It will make newspaper headlines”. The researcher did not have much time and resources to follow up on the MODREC request, however it is still the wish of the researcher to explore this effect as most soldiers die or loose limbs due to infection. If sugar can be of use to the injured soldiers, it is worth researching. May be the simplicity of the method makes many people doubt or overlook its potential. The researcher hopes that, in the future with research grants available and involvement of lead researchers into wound care, clinical trials team, microbiologists and infection control nurses, some of these myths and doubts can be resolved.

6.7. Challenge of world-wide interest before study completed

6.7.1. World-wide media interest

During the trial running there were visible and commendable results. Some of the patients approached the media reporting on the relief of their suffering (

Appendix 16). This media interest continued throughout the whole research period up to the present date. The researcher appeared on the BBC West Midlands six o'clock news as well as the BBC One Show. In Zimbabwe several newspapers reported on the study, as well as other countries like Canada, Russia, and Greece. Enquiries were made on a regular basis that led to more newspaper publications Pouring granulated sugar on wounds 'can heal them faster than antibiotics' The Daily Mail 15th February 2013.

There were numerous emails and phone calls that only limited number are included see (

Appendix 16). The amount of enquiries is a reminder that people suffering from non-healing wounds are looking for every opportunity to find a cure. The wide geographical enquiries also suggest that non-healing wound problem is not only confined in the UK, but it is world-wide problem that needs collaborative research in order to increase chances of finding research funding and be able to generalise the findings. Of positive note is the awareness of the sugar as a potential dressing product whereby several vascular surgeons from the UK and abroad are willing to engage in the sugar research. Although the world-wide media interest can be viewed as a positive way forward in this research area, it can be a hindrance in terms of recruitment. Patients were contacting the researcher, to be included into the study. What they really wanted was to be tried on sugar. They had been on different types of dressings and had failed to heal, so sugar was an alternative they wanted to be tried. Randomising would not have been an option to them. The dilemma to the researcher would be to balance patients interested in the treatment and the need to fulfil the criteria for a RCT, i.e. to randomise the potential patients who are to enter into the study. For treatment to be accepted there is need for large a RCT confirming its effectiveness. In previously published non-randomised sugar studies, there is a possibility that researchers felt compelled by the duty of care to provide the treatment (sugar treatment) that they thought was effective at the time. Patients may have wanted to be considered into the sugar because other treatments have failed (Herszage et al., 1983; De Feo et al., 2003) and researcher would have considered them for sugar. This was experienced by the researcher, during the feasibility trial.

6.8. Outcome of failing to recruit desired numbers

6.8.1. Limited sample size and recruitment issues

The number of patients suffering from chronic wounds is at an increase and the cost of treating these wounds is also high (Holloway et al., 2002; Hampton, 2007; Hampton, 2009). If this is correct, then the number presumably reported for consideration (55 patients) is not a reflection of the literature statistics. It can be argued that less than potentially eligible patients for the study were randomised to the intervention and control. Because it is known that NHS spends billions of pounds treating patients affected with chronic wounds (Posnett and Franks, 2007), there could have been more patients who were overlooked. If this is the case, then nurses needed more education on RCTs and the need for identification and invitation of potential patients to be considered for the study.

It might be possible that nurses and doctors did not fully understand the purpose of the trial which conversely led to the inadequate recruitment of patients. It is most reported that non entry into the RCT studies is due to staff preferences (McCulloch et al., 2002; Abraham, et al 2006; Cadwell et al., 2010), and some dislike the idea of randomisation. This can be a possibility and was never teased out. Another reason may be that of scepticism of the product by clinical staff. If staff are not familiar with a dressing product there would be difficulties of knowing whether patients are refusing to be in the study or it is just the clinician who was ignorant of the study. To combat this phenomenon, training was continued.

Training for the use of sugar and TELER system indicators took place during the initial feasibility trial period and continued into the RCT study. There were series of drop in training sessions that allowed clinical staff to attend without prior appointment. This was to suit the busy activities and routines of the wards and help nurses understand the study. It was hoped

that this process will keep the nurses focused on the progress of the study and also help with identification and recruitment of potential participants.

It would also have been advantageous to train the trainers. The researcher would have trained one or two nurses on each site to deliver training to other nurses on how to deliver the intervention. This method was not chosen for two main reasons: firstly, had one or two nurses been responsible for the training, it was much less likely that the intervention would have been the same for each individual in the study; secondly and more pragmatically, it was felt that using clinical nurses might have led to practical problems in finding free time that they would devote to the study, let alone training other nurses. Furthermore, as a senior lecturer and specialist nurse with high workload, the researcher was aware that utilisation of clinical nurses' time in a study might not have been particularly popular with the hospital trust management. This had been the experience observed during the running of the feasibility study.

The researcher assumed that all nurses undertaking wound dressing procedures were aware of the trust policy on dressing change and type. It must be added that, initially nurses were applying the sugar treatment with hesitancy, but with continued exposure and support from the researcher there were better understanding on the application and the effects of sugar. It will be unfounded to suggest that diminished staff morale led to under-recruitment. Most of the nurses trained to use sugar, wanted to apply sugar to every patient who fitted the inclusion criteria, throughout the study and even after the study. The researcher kept reminding the nurses that it was a study, not a licensed product and there was need for randomisation to all patients entering into the study.

With respect to the study settings, poor recruitment may have simply been due to lack of information, clinical staff commitments and forgetting/overlooking to recruit, which is not necessarily an absolute barrier to sugar treatment in this context. There is increasingly

staffing issues in NHS hospitals that patient care takes precedence for the nurses. The staff morale is at a low level due to limited staffing levels and this could have affected staff morale, thereby lacking motivation. The sugar study would have been seen as an added burden to the already stretched staff as described earlier. In a trial like this, it is difficult to tease out the real problem of low recruitment, but the most likely issue is the poor funding received for this study. There were no dedicated research nurses for this study and this contributed immensely to the low recruitment levels. This would suggest that recruitment to RCT in sugar studies needs to be effected by more in-house education of the role of clinical trials on enhancing evidence based practice and providing the most reliable evidence for evaluating the effects of health care interventions (Sackett et al 2000; Barton, 2000), such as sugar. The acceptability of the sugar as a wound care product in NHS hospitals, depend upon successful large clinical trials. This study, like many preceding sugar trials failed to recruit sufficient sample sizes. This reduces the power to detect significant intervention effects (Swanson and Ward, 1995). This inversely affects generalizability of the study findings and can incur increased trial costs. Some nurses may have felt less supportive of the study because they did not see any incentive in participating. In this study, there was a general willingness to support the study however the nurses were stretched in numbers, relying on the researcher to randomise the patients.

It is worth mentioning that at times clinical staff felt the intervention was an alternative to the failed standard treatment and it was constantly re-emphasised that this was a trial running and there was need for randomisation and to abide by the protocol guidelines. Also, patients were made aware of the type of dressings they were having and none reported a change of the randomised treatment after commencement.

6.9. Lack of cost-effectiveness data

6.9.1. Cost-effectiveness of granulated sugar use

This sugar study initially included cost-effectiveness analysis in the planning stage, but this was impossible due to financial constraints. In this study, we concluded that granulated sugar is a simple dressing that is cheap, costing £1.49 per dressing change, compared to charcoal 7.5x 10cm dressing for odour reduction, £2.7 which might need an additional debriding agent. Other comparative is vacuum assisted closure costing £20.00 per canister £19.43 total £39.43 per treatment. Sugar does control odour as well as debriding the wound at a cost of £1.49 a reasonable saving, if the products were to be compared. However, it is not just the unit cost but time to debridement that needs to be considered when measuring cost-effectiveness. Though, this can be viewed as supporting earlier studies by Knutson and colleagues' (1981) conclusions that sugar is readily available and cheap (Knutson et al., 1981; Tophan, 2002; Bajaj et al., 2009). In a more recent study by Ruhullah and colleagues (2013), exploring use of sugar on 25 patients suffering from pressure ulcers, similar findings were reported that sugar is relatively cheap and can be used without difficulties. They also report quicker granulation results that led to early skin graft and discharge.

However, this notion was based on the fact that previous researchers used ordinary sugar from the shops or supermarkets. In this study sugar was specifically prepared and was tested in a controlled environment and given a certificate of conformity with a serial number for the purpose of quality control. This has never been done before and the process allowed effective monitoring of the sugar products used on each wound. Given this process; it was observed that the sugar was costing extra per container than if we had to get a bag from the shop. Although there is an increased cost following the extra test and packaging, if this product were to be adopted and produced in bulk the cost per product, as compared to standard

treatment, can still be cheap. The £1.49 was costed using single request; it may be cheaper if the production is undertaken on a large scale. But it goes without saying that sugar treatment requires frequent dressing changes that may increase the nursing time per dressing management. Even though, sugar can crudely be seen to be cheaper, there is need for in-depth understanding of the real unit cost as well as total wound care cost including staff time and hospital costs. Future research must include cost-effectiveness in their bid for research grants.

6.10. Need for more research

6.10.1. Randomised controlled trials of sugar in the UK and funding issues

Lack of awareness of the potential of sugar treatment can be viewed as the reason why there are no relevant RCTs registered or published in UK. Hence, in making generalisations beyond the settings of this work, it is important, from an NHS perspective that such evaluation of relatively simple and possible cheap interventions with potential to make a difference to daily wound care practice takes place in UK hospitals and abroad. Surprisingly, there is not much funding available for research in wound care, although of late there has been an increase in government grants such as National Institute for Health Research for Patient Benefit (NIHRfPB). It is with regret that sugar research has not been fully explored of its potential in wound care, and this may remain the same if private/business enterprises or charity organisations are not involved. It is most likely that sugar research is overlooked due to its status as a food product and chances of development are limited. In addition, the difficulty in obtaining patents means that if private pharmaceuticals fund the research there will be enough research nurses to recruit participants increasing the chances of meeting the required powered sample size. However, the funding into sugar trial is up to now a problem as identified in this work. One problem identified is the inability to have a sufficiently

powered study that can convince the reviewers and funders into believing the worthiness of this product. The small sporadic RCT studies to date, though reporting encouraging outcomes, are not very convincing and lack quality and sufficient power. It is therefore important that future proposals for sugar research are well powered. It is hoped that this work and the knowledge gained undertaking this RCT can help in future designing and planning of high quality rigorous sugar research studies. Government grants are the best possible source of funding to take this work forward if there is to be any properly powered and funded RCTs. However it must be acknowledged that competition is fierce for limited funds.

6.11. Conclusions and researcher's musings

This study demonstrated that it is possible to prepare granulated sugar for single use on wounds. It was also feasible to use the sugar on sloughy, necrotic and infected exuding wounds in a modern NHS hospital. Participating nurses and doctors eventually accepted the treatment and now are hoping this method can be explored further so that it can be used more frequently. There is a sugar dressing protocol available. The protocol was used successfully to undertake a RCT. There was evidence of effective debridement of sloughy, necrotic and infected exuding wounds of various aetiologies. This rapid debridement and granulation has been supported by *in vitro* studies on animal models (Eto et al., 1989; Shi et al., 2007) and by Anania et al (1985). Also, the role of debridement in wound bed preparation has been well documented (EWMA, 2004; Wolcott et al., 2009; Falanga, 2000; Strohal et al, 2013).Patients felt the treatment was friendly and did not cause any extra pain when removing wound dressings. When a wound care product is effective it is associated with reduction in exudate, odour and the appearance of granulation tissue in the wound (Vowden and Vowden, 2011). Moreover, the formation of granulation tissue can only take place in a moist wound environment (Winter, 1962; Winter, 1965). This effect was observed during the 4 week trial

of this study. Figure 2.2 illustrates observed sugar effects during this current study as well as of those already reported (Pieper and Caliri, 2003; Mphande et al., 2007; Murandu et al., 2011; Ruhullah et al., 2013).

Although the results were plausible, the sample size of 41 subjects was small. There is a need to conduct a fully funded and well powered study in the future. The methodology used in this sugar study is reproducible in practically every practice in the country and internationally and utilises skills already held by trained and semi-trained nurses in both acute and primary care health services. This developed sugar dressing protocol can be easily being reproduced in any country.

Table 6.1: Summary of findings observed from this current work and reported by previous researchers possible wound healing capabilities of sugar

Property	**Anticipated Clinical Outcomes**	**Suspected Mode of Action**
Antimicrobial activity	Sterilization of wound Inhibition of potential wound pathogens that destroy tissues Deodorization of malodorous wounds Protective barrier to prevent cross-contamination Increased self esteem Improved social interactions	Acidity Action of non-peroxide components (phytochemicals) Stimulation of immune system multiplication of β-lymphocytes and T-lymphocytes; activation of neutrophils; release of cytokines by monocytes; supply of glucose for "respiratory burst" and for energy production in macrophages Glucose metabolism by the infecting bacteria to lactic acid instead of metabolism of amino acids from serum and dead cells to malodorous ammonia, amines and sulphur compounds High viscosity (when sugar dissolves when in contact with body fluids) creates physical barrier that limits exposure to environmental pathogens
Anti-inflammatory activity	Resolution of oedema and exudates Reduction of pain Reduction in keloids and scarring Increased limb mobility Less sleep disturbance	High osmolality leading to fluid outflow to create layer of dilute solution of sucrose in plasma or lymph, resulting in moist conditions necessary for healing and no adhesion to the skin surface of the wound Decrease in leucocytes associated with inflammation Inhibition of reactive oxygen intermediates (ROI) production as a result of antioxidant activity Suppression of the inflammatory process through the scavenging of free radicals by antioxidants.
Stimulation of rapid healing	Increased phagocytosis Increased autolytic debridement Increased angiogenesis Promotion of granulation tissue Cell proliferation Collagen synthesis	Stimulatory effects of glycosylated sucrose protein or other components on macrophages Clearing of debris with moist dressing Increased nutrification of tissue secondary to the outflow of lymph and the liquification of sucrose Increased oxygen supply secondary to the outflow of lymph and the acidity of sucrose Controlled low hydrogen peroxide production with antioxidant protection that modifies proteins important to cell growth and debridement.

6.11.1. Unanswered questions and future research

Sugar allows retention of wound moisture and facilitates healing (Chirife et al., 1983). Whether my father knew this principle or not, I never had a chance to ask him and now he is old and has dementia and can hardly remember anything he did in the community in terms of managing wounds. This is how most of African traditional treatment was lost. This failure to document has prevented the use of this information by the new generation. Today many useful treatments lie in the grave because of this tradition. Part of the knowledge gained from working on this thesis is the importance of documentation, a tradition emphasised in the developed countries and not so much in the developing countries. This knowledge of using sugar was not documented; it was just cascaded down the generations.

The present study supports the view that sugar therapy is an antimicrobial agent as discussed in chapter 2 and it is effective in inhibiting microbial growth by high osmolality depleting water activity. However, there is need to explore at what level does the sugar effect wound healing is it at molecular/cellular or tissue level?

Another area to explore is the cost-effectiveness of sugar therapy. Whilst bulk purchased sugar is inexpensive, it is impractical for clinical usage. In this study, additional costs were incurred to repackage the sugar into single use containers. This cost could be reduced if a single use product was mass produced. Further studies are warranted to test whether the additional cost of the sugar product would be sufficiently offset by the improvement in outcomes of the treated patients.

Maybe other area of research is to explore how much do African elders know about wound care treatment? If any; can that knowledge be translated into the western health care system research topics as suggested below?

- Is sucrose an antibiotic or antibacterial?

- What role does sucrose have on MMPs?
- Does sugar prevent fungi growth? If so how?
- Does sugar increase oxygen levels onto the wound-bed?
- The list goes on and the researcher is sure that with more interest the scientific world can establish more and solve more too.

6.11.2. Researcher's musings

In Africa like any other continents, there are many different ailments including wounds that require treatment; and receiving the best treatment in developing countries many a times depends on the ability of the family to pay for the private doctors. Because of poverty, these wounds will sometimes develop into chronic wounds and delay healing. They become a burden to communities who do not have enough proper resources to manage them. It was in these scenarios that my father used his knowledge of granulated sugar treatment to facilitate healing of these wounds; a treatment method he learnt from his forefathers. There were no documented protocols, or methods of using the sugar treatment, other than by word of mouth, a noted African tradition. The dose and type of sugar varied according to the availability of the sugar. This poses difficulties to the scientific world that requires evidence to support treatment. In the western world, a treatment without a protocol is not accepted. This is contrary to the delivery of healthcare in the developing countries, where every available treatment is valued as an effort towards alleviating suffering. Patients receive the treatment without questioning the evidence or effectiveness and safety of that treatment. Having worked and studied in the western world, I understood and valued the purpose of evidence and how each available treatment must be critiqued if patients' safety is to be maintained. This reflection led me to recall the sugar treatment that my father used when I was a child. I wanted to explore its applicability to modern western hospitals and help develop a sugar

treatment protocol (incorporating the dose and type of sugar) that will avail in developing and developed countries.

The researcher hopes you can agree that this was a worthy cause that requires doctoral recommendation and this work has carefully explored sucrose a food substance turned into a dressing product because of its osmotic effect and that the research has paved way for further research.

References

Abraham, Ned S., Young, J.M., Solomon, M.J (2006) A systematic review of reasons for nonentry of eligible patterns into randomised controlled trials. **Journal of Surgery.** Vol. 139: (4) 469-483

Adam, J. Singer, M.D. Steve, A., Mcclan, M.D (2002) Persistent wound infection delays epidermal maturation and increases scarring in thermal burns. **Wound repair and generation** Vol. 10 No.6 372-377

Addison, M.K., Walterspiel, J.N. (1985) Sugar and wound healing. **Lancet** ii:665-664

Ahsan, N., Palmer, B.F., Wheeler, D., Greenlee, R.G. jr., Toto, R.D. (1994) Intravenous immunoglobulin-induced osmotic nephrosis. **Arch Intern Med;** 154: 1985-1987

Allen, K., Molan, P., Reid, G. (1991) A survey of the antibacterial activity of some New Zealand honeys. **Journal of Tissue Viability** 43: 817-22

Altman, D. (1997) **Practical statistics for medical research**.1st edition. London. Chapman and Hall

Ambrose, U. (1986). An investigation into the role of action of Northwick Park Hospital sugar paste. ***Hatfield Polyethytechnic.*** **BSc Applied Biology Thesis**

Ambrose, U., Middleton, K., Seal, D. (1991) In vitro studies of water activity and bacterial growth inhibition of sucrose polyethylene glycol 400 (PEG 400) hydrogen peroxide pastes used to treat wounds **Antimicrobial Agents Chemotherapy** 35 (9): 1799-1803

Ammons, M.C., Ward, L.S., James, G.A (2011) Combined treatment of Pseudomonas aeruginosa biofilm with lactoferrin and xylitol inhibits the ability of bacteria to respond to damage resulting from lactoferrin iron chelation. **International Journal of Antimicrobial Agents,** Vol. 37 (4); 316-23

Anania, W.C., Rosen, R.C., Wallace, J.A., WEinblatt, M.A., Gerland, J.S., Castillo, J (1985) Treatment of diabetic skin ulcerations with povidone-iodine and sugar. **Journal American Podiatr Med Assoc**. 75: 472-474

Apqelvist, J., Larsson, J., Agardh, C. (1993) Long term prognosis for diabetic patients with foot ulcers. **Journal of International Medicine** 233: 485-91

Archer, H., Brnette, S., Irving, S., Middleton, K., and Seal, D. (1990) A controlled model of moist wound healing: comparison between semi-permeable film, antiseptics and sugar paste. **Journal of Experimental Pathology**. 71: 155-170

Archer, H., et al. (1990). A controlled model of moist wound healing: comparison between semi-permeable film, antiseptics and sugar paste. **Journal of experimental Pathology.**75: 155-170

Argen, M.S. Steenfos, HH, Dabelsteen, S. Hansen, JB. Dabelsteen, E (1999) Proliferation and mitogenic response to PDGF-BB of fibroblasts isolated from chronic leg ulcers is ulcer-dependent. **Journal of Investigative Dermatology** Vol. 112:463-9

Armstrong, D.G., et al (1997) Surgical morbidity and the risk of amputation due to infected puncture wounds in diabetic versus nondiabetic adults. **South Medical Journal**: 90: 4, 384-389

Assmann, S.F., Pocok, S.J., Enos, L.E., Kasten, L.E. (2000) Subgroup analysis and other (mis)uses of base-line data in clinical trial. **Lancet** 355:1064-1069

Bajaj, G., Karn, N.K., Shrestha, B.P., et al. (2009) A randomised controlled trial comparing eusol and sugar as dressing agents in the treatment of traumatic wounds. **Tropical Doctor**, 39: (1): 1 - 3.

Bale, S., Tebble, N., Price, P. (2004) A topical metronidazole gel used to treat malodorous wounds. **British Journal of Nursing** 13Sup2. 13233

Beading, L. (1997) A bag full of sugar, Surgeons find that ordinary table sugar is a sweet adjunct to conventional therapy of deep wound healing. **Today's Surgery Nurse** 19:28-30

Benbow, M. (1999) Malodorous wounds how to improve quality of life. **Community Nurse** 5: 1:43-46

Biswas, A., Bharara, M., Hurst, C., et al. (2010) Use of sugar on the healing of diabetic ulcers: a review. **Journal of Diabetes Science & Technology**, 4: (5): 1139-1145.

Booth, S. (2004) Are honey and sugar paste alternatives to topical antiseptics? **Journal of Wound care** Vol. 13: 1, 31-33.

Boulton, A., Connor, H., Cavannagh, P. (1995) **The foot in diabetes**. Chichester Wiley.

Bowling, A (2014) **Research Methods in Health Investigating health and health services.** 4th Edition Open University

Breasted, J.H (1930) **The Edwin Smith surgical papyrus**. Chicago. University of Chicago Press.

British Medical Journal (2007) Designing and evaluating complex intervention, pp 334:455

Brooks, R., Robin, R., de Charro, F (2003) **The measurement and Evaluation of health status using EQ-5D. A European perspective. Evidence from the EuroQoL BIOMED Research Programme**. Kluwer Academic Publishers

Browne, N., Grocott, P., Cowley, S., Cameron, J., Dealey, C., Keogh, A., Lovatt, A., Vowden, K., Vowden, P (2004b) Woundcare research for appropriate products (WRAP) validation of the TELER method involving users. **International Journal of Nursing Studies,** 41**:** 559-571

Brysbaert, M (2011) **Basic Statistics for Psychologists**. Palgrave Macmilllan.

Cadwell, P.H.Y., Hamilton, S., Ian, A., Craig, J.C (2010) Strategies for Increasing Recruitment to Randomised Controlled Trials: Systematic Review. **PLOSMED** 7(11): e1000368.do:10. 1371/**journal.pmed**.1000368

Calman, K.C (1984) Quality of life in cancer patients – an hypothesis. **Journal of Medical Ethics.** September 1;10 (3): 124-127

Chang, R. (2006) **General Chemistry** 4th edition McGraw-Hill International Edition

Charles, H. (1995) The impact of leg ulcers on patients' quality of life. **Professional Nurse** 10: 571-573

Chirife, J., Herszage, I., Joseph, A., Kohn, E.S. (1983) In *vitro* study of bacterial growth inhibition in concentrated sugar solutions: microbial basis for the use of sugar in treating infected wounds. **Antimicrobial Agents and Chemotherapy** 23(5) 776-783.

Chirife, J., Scarmato, G. and Herszage, L. (1982) Scientific basis for use of granulated sugar in treatment of infected wounds. **Lancet**, 1: (8271): 560-561.

Chiwenga, S., Dowlen, H. and Mannion, S. (2009) Audit of the use of sugar dressings for the control of wound odour at Lilongwe Central Hospital, Malawi. **Tropical Doctor**, 39: (1): 20-22.

Colagiuri, S., Marsden, L.L., Naidu, V., Taylor, L. (1995) The use of orthotic devices to correct plantar callus in people with diabetes. **Diabetes Research Clinical Practice** 28: 29-34

Cook, H., Davies, K.J., Harding, K.G., Thomas, D.W (2000) Defective extracellular matrix reorganisation by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2 activity. **Journal of Investigative Dermatology** Vol. 115:225-33

Cooper, R (2001) How does honey heal wounds? In "Honey and Healing" ed. P. Munn and R. Jones. **International Bee Research Association,** Cardiff, UK.

Cooper, R., Lawrence, J.C. (1996) The isolation and identification of bacteria from wounds. **Journal of Wound Care** 5: 335-40

Cooppan, R., Habershaw, G. (1995) Preventing leg and foot complications. **Patient Care** 29: 35-48

Creel, R.E. (2003) **Thinking Philosophy: An Introduction to Critical Reflection and Rational Dialogue**. Blackwell Publishing

Dawson, J.S. (1996) Preiskel Elective Prize. The role of sugar in wound healing. A comparative trial of the healing of infected wounds using traditional gauze/antiseptic packing, and granulated sugar, undertaken during an elective period at Kagando Hospital, Uganda. **Annals of the Royal College of Surgeons of England**, 78: (2 Suppl): 82-85.

De Feo, M., De Santo, L.S., Romano, G., Renzulli, A., Della Corte, A., Utili, R., Cotrufo, M (2003) Treatment of reccurent staphylococcal mediastinitis still a controversial issue. **The Annals of Thoracic Surgery**, 75: 538-542

De Feo, M., Gregorio, R., Renzulli, A., Ismenno, G., Romano, G.P., Cotrufo, M. (2000) Treatment of recurrent post-operative mediastinitis with granulated sugar. **Journal of Cardiovascular Surgery** 41: 715-719

Dealey, C. (1994) **The care of wounds**. Blackwell Scientific Publications

Debure, A., Gachot, B., Lacour, B., Kreis, H (1987) Acute renal failure after granulated sugar in deep infected wound. **The Lancet.** 5(2): 1034-5

Drouet, N. (1983) The use of sugar and honey for the treatment of infected wounds. **Presse Med.**, 12: (38): 2355-2356.

Drummond, M. (1994) **Economic analysis alongside controlled trials: an introduction for clinical researchers**. London: Department of Health

Duffet, A.M. and Viau, F. (1986) [Treatment of wounds and ulcers with crystallized sugar. Technical aspects and results]. **Revue de L'Infirmiere**, 36: (20): 37-38.

Dumville J.C., Worthy, G., Soares, M.O et al (2009) VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. **Heath technology Assessment,** 13 (55)

Dunford, C.E., Hanano, R. (2004) Acceptability to patients of a honey dressing for non-healing venous leg ulcers. **Journal of Wound Care.** 13: 193-197

Edmond, S.M. (1987) **Experience in a multidisciplinary diabetic foot clinic**. In: The foot in diabetes: Proceedings of the first National Conference on the Diabetic Foot. Chichester: Wiley.

Edwards, R., Harding, K.G (2004) Bacteria and wound healing.**Curr Opin Infect Dis**, 17: 91-96

Engelsen, S.B., Perez, S (1997) Internal motions and hydration of sucrose in a diluted water solution. **Journal of Molecular Graphic Model,** 15 (2) 122-131

Eto, Y., Matsumoto, J., Akiba, T., Wada, Y., Nagakura, M., Nakamura, M (1989) The healing effect of KT-36 on incised and open wounds in rats. **JPN Pharmcological Therapy** 17(Suppl 1):7-13 (in Japanese)

EWMA (2004) **Position Document. Wound bed preparation in practice** MEP Ltd. London

Falanga, V (2000) Classification for wound bed preparation and preparation and simualtion of chronic wounds. **Wound Repair Regeneration.** 8(5): 347-52

Falanga, V (2001) Position document. Wound bed preparation in practice. **MEP Ltd. London**.

Fay, B (1996) **Contemporary philosophy of social science: A multicultural approach**. Cambridge University Press.

Flanagan, M. (1997) **Wound Management.** Churchill Livingstone

Franks, P and Moffatt, C (2007) Leg Ulcers in Smith and Nephew Foundation (2007) **Skin breakdown The Silent epidemic.**

Friedman L.M., Furberg C.D., DeMets D.L (1998) **Fundamentals of Clinical Trials.** 3rd Edition Springer, NewYork

Gardner, G., Cook, R. (2004) Telling accounts of wound infections avoidance, anomaly and ambiguity. **Health (London)** 8:183-97

Gardner, S.E.; Frantz, R.A., Doebbbeling, B.N (2001) The validity of clinical signs and symptoms used to identify localised chronic wound infection. **Wound Repair Regeneration**, 9: 178-186

Gethin, G. Seamus, C. (2008) Manuka honey vs hydrogel – a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. **Journal of Clinical Nursing** Vol. 18: 466-474

Gethin, G., Seamus, C. (2008) Manuka honey vs hydrogel – a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. **Journal of Clinical Nursing Vol**. 18: 466-474

Gethin, G., Cowman, S., Kolbach, DN (2010) Debridement for venous leg ulcers. **Cochrane Database** Systematic Review. 7:CD008599

Glass, L.M. (1966) We use granulated sugar in the treatment of decubitus ulcers. **Geriatric Nursing** 2:44

Gordon, H., M.K., Seal, D., Sullen, K. (1985) Sugar and wound healing. **Lancet.**, 2: (8456): 663-664.

Gorin, D.R., Lamorte, W.W., Barry, M., Scott, T., Menzoian, J.O. (1997) Is complete wound healing a valid end point for clinical trials of venous stasis ulcer treatment? **Vascular Surgery** 31: 163-69

Gotzsche, P., Liberati, A., Torri, V., Rossetti, L. (1996) Beware of surrogate outcome measures. **International Journal of Technology Assessment Health Care** 12: 238-46.

Grauwin, M.Y., Cartel, J.L., Lepers, J.P (1999) How does one treat the osteítis and ostearthritis of the extremities in older leprosy patients using granulated table sugar? **Acta Leprol**. 11: 147-52

Great Britain Parliament (1998) **Data Protection Act 1998.** London: HMSO

Griffiths, G., Wieman, T. (1990) Metatarsal head resection for diabetic foot ulcers. **Archives of Surgery** 125: 832-5

Grocott, P. Cowley, S. (2001) The palliative management of fungating malignant wounds--generalising from multiple-case study data using a system of reasoning. **International Journal of Nursing Studies**. 38(5):533-45

Hack, A. (2003) Malodorous wounds –taking the patient's perspective into account **Journal of Wound Care** 12: 8; 319-321

Haddad, M.C., Vannuchi, M.T., Chenso, M.Z., et al. (1983) [The use of sugar in infected wounds]. **Revista Brasileira de Enfermagem**, 36: (2): 152-154.

Haddad, M.d.C., Bruschi, L.C. and Martins, E.A. (2000) [The effect of sugar on the process of cicatrization of infected surgical incisions]. **Revista Latino-Americana de Enfermagem**, 8: (1): 57-65.

Hampton S (2009) Recognizing and treating colonized wounds. *Nursing & Residential Care* Vol. 4:177-181

Hampton, S (2007) Bacteria and wound healing. **Journal of Community Nursing** Vol.21, 10:32-40

Hasan, A., Murata, H., Falabella, A., Ochoa, S., Zhou, L., Badiava, E., Falanga, V (1997) Dermal fibroblasts from venous ulcers are unresponsive to action of transforming growth factor-beta. **International Journal of Dermatology Science**Vol. 16:59-66

Haughton, W., Young, T. (1995) Common problems in wound care: malodorous wounds. **British Journal of Nursing** 4:16; 959-963

Hayland, M.F., Ley, A., Thomson, B. (1994) Quality of life of leg ulcer patients: questionnaire and preliminary findings. **Journal of Wound Care** 3: 294-298

Herszage, L. et al (1980) Tratamiento de las heridas supuradas con azucar granulado commercial, **Biol Trab Soc Argent**. Vol. 41; 315-330

Hofman, D., Ryan, T.J, Arnold, F., Nerry, G.W., Lindholm, C., Bjell-erup, M., Glynn, C. (1997) Research, Pain in venous leg ulcers. **Journal of Wound Care.** 6: 222-224

Hollis, S and Campbell, F (1999) What is meant by intention to treat analysis? Survey of published randomised controlled trials *BMJ 319: 670-674*

Holloway, S., Bale, S., Harding, K., Robinson, B., Ballard, K. (2002) Evaluating the effectiveness of a dressing for use in a malodorous exuding wounds. **Ostomy/Wound management** 48(5):22-28

http://www.dailymail.co.uk/health/article-2278942/Pouring-granulated-sugar-wounds-heal-faster-antibiotics.html|following

Hyde, C., Ward, B., Horsfall, J., Winder, G (1999) Older women's experience of living with chronic leg ulceration. **International Journal of Nursing Practice**, 5: 189-198

Huedo-Medina, Tania, B., Sanchez-Meca, J., Marin-Martinez, Fulgencio, Btella, Juan (2006) **Psychological Methods**, Vol. 11(2): 193-206

Iglesias, C., Mitchell, J.L., Nelson, E.A., Soares, M.O., Torgerson, D.J (2009) Larval therapy for leg ulcers (VenUS 11): randomised controlled trial**. BMJ** 2009;338:b773

Ivers, N.M., Taljaard, M., Dixon, S., et al. (2011) Impact of CONSORT extension for cluster randomised trials on quality of reporting and study methodology: review of random sample of 300 trials, 2000-8. **BMJ (Clinical research ed.)**, 343: d5886.

Jacobsen, C.N., Rosenfeldt-Nielsen, V., Hayford, A.E, Moller, P.L., Tvede, M., Jackobsen, M. (1999) Screening of Probiotic activities of forty-seven strains of lactobacillus spp. By In vitro Techniques and Evaluation of the colonisation ability of five selected strains in humans**. Applied and Environmental Microbiology** vol. 65 (11): 4949-4956

Jadad, A.R., Enkin, M.W (2007) **Randomized Controlled Trials, Questions, Answers and Musings.** second editionBMJI Books; Blackwell Publishing

Jadad, A.R., Moore, R.A., Caroll, D., Jenkinson, C., Reynolds, D.J.M., Gavaghan, D.J., McQuay, H.J (1996) Assessing the quality of of reports of randomised clinical trials: is blinding necessary? **Control Clinical** Trial. 17: 1-12

Jadad, A.R., Rennie, D (1998) The randomised controlled trial gets a middle-aged checkup. **Journal of American Medical Association 279(4):319-320**

Jones, M.A., Song, B., Thomas, D.M (2004) Controlling Wound Healing through Debridement **Elsevier Science Direct** Vol. 40:1057-1064

Jull, A., Parag, V., Rogers, A. (2010) Responsiveness of generic and disease-specific health-related quality of life instruments to venous ulcer healing. **Wound Repair and Regeneration** Vol. 18: 1: 26-30

Jull, A., Walker, N., Parag, V., Molan, P. and Rogers, A. (2008) Randomised clinical trial of honey-impregnated dressings for the venous leg ulcers. **British Journal of Surgery.** 95: 175-182

Keith, JF, Knodel, L (1988) Sugar in wound healing. **Drug Intell Clinical Pharmacology 22:409-411**

Kilic, A. (2001) Healing of diabetic ulcers with granulated sugar. **Plastic Reconstructive Surgery**, 108: (2): 585.

Kilkenny, C., Browne, W.J., Cuthill, I.C., et al. (2010) Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. **PLoS biology**, 8: (6): e1000412.

Kirketorp-Moller, K., Jensen, P.O., Fazil, M. et al (2008) The distribution, organisation and ecology of bacteria in chronic wounds. **Journal of Clinical Microbiology** 46(8): 2717-22

Knuston, R.A., Merbitz, L.A., Creekmore, M.A., Snipes, H.G (1981) Use of sugar and povidone-iodine to enhance wound healing: five years experience **South Medical Journal** 74: 1329-1335

Kveclar, J.C., Edwards, R.A, Menn, E.R., Maofid, M., Gonnzalez, F., Dover, J., et al. (1997) The substitution of digital images for dermatologic physical examination. **Archives of Dermatology** 133:161-7

Larsson, J. (1994) **Lower extremity amputation in diabetic patients**. Lund:Lund

Lazarus, G.S., Cooper, D.M., Knighton, D.R (1994) Definitions and guidelines for assessment of wounds and evaluation of healing. **Archives of Dermatology** Vol. 130:489-493

Le Roux, A A (1995) " TELER: The Concept" **Physiotherapy**, 79, 11, pp 755-58

Lee, G., Anand, S.C., Rajendran, S., Walker, I. (2006) Overview of current practice and future trends in the evaluation of dressings for malodourous wounds **Journal of Wound Care** Vol. 15.8:344-346

Levin, M., O'Neal, L. (1983) **Peripheral vascular disease.** In: Ellenberg B, Rifkin H, editors. Diabetes mellitus**.** New York: Medical Examination 803-28

Lombardo, Y.B., Drago, S., Chicco, A., Fainstein-Day, P., Gutman, R., Gagliardino, J., Gomez, Dumm, C (1996) Long-term administration of a sucrose-rich diet to normal rats: relationship between metabolic and hormal profiles and morphological changes in the endocrine pancreas. **Metabolism** 45 (12) 1527-32

Madeo, M. (2001) Understanding the MRSa experience. **Nursing Times** 97:36-7

Majno, G. (1975) **The healing Hand: Man and wound in the Ancient World**. Harvard University Press, USA.

Marcan, S (2003) Test-retest performance of EQ-5D. In: Brooks R, Rabin R, de Chario F, editors. **The measurement and valuation of health status using EQ-5D: a European perspective**, Dordrecht: Kluwer Academic Publishing Publishing. 43-54

Marra, C.A., Woolcott, J.C., KOpec, J.A., Shojania< K., Offer, R., Brazier, J.E., Esdaile, J.M., Anis, A.H (2005) A comparison of generic, indirect utility measures (the HU12, HU13, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and HAQ) in rheumatoid arthritis, **Social science and medicine**, vol. 60 (7): 1571-1582

Matthews, K.A and Binnington, A.G (2002) Wound management using sugar. **In Compedium for Continuing Education.** Vol. 24: (1) 41-50

McCulloch, P., Taylor, I., Sasako, M., Lovetl, B., Griffin, D (2002) Randomised trials in surgery; problems and possible solutions. **BMJ**: 324:1448

Meakins, J. L. (1976) Pathophysiologic determinants and prediction of sepsis,. **Surgical Clinical Nursing America** 56:847-857

Metcalfe A, Dealey C, Hallowell T, Stubbs R (2008) Validating a new instrument to improve wound measurement. **Nursing Times,** 104 (16) 30-31

Middleton KR (1985) **The Pharmaceutical Journal**. December 7: 757-758

Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF (1998) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. **Lancet.** 354:1896-900

Molan, P.C, Betts, J.A. (2004) Clinical usage of of honey as a wound dressing: an update. **Journal of Wound Care.** 13: 353-356

Molan, P.C. (2006) The evidence supporting the use of honey as a wound dressing. **International Journal of Lower Extremity Wounds** 5(1) 40-54

Molan, P.C. and Cooper, R.A. (2000) Honey and sugar as a dressing for wounds and ulcers. **Tropical Doctor**, 30: (4): 249-250.

Morgan, D. (1993) Is there still a role for antiseptics? **Journal of Tissue Viability** 3: 80-4

Mphande, A.N., Killowe, C., Phalira, S., et al. (2007) Effects of honey and sugar dressings on wound healing. **Journal of Wound Care**, 16: (7): 317-319.

Mudge, E., Price, P., Neal, W., Harding, K.G. (2014) A randomized controlled trial of larval therapy for the debridement of leg ulcers: Results of a multicenter, randomized, controlled, open, observer blind, parallel group study. **Wound Repair Regeneration** 22 43-51

Mueller, M.J, Diamond, J.E, Delitto, A. (1989) Insensitivity, limited joint mobility and plantar ulcers in patients with diabetes mellitus. **Physiotherapy Therapy** 69: 453-62

Murandu, M., Webber, M.A., Simms, M.H and Dealey, C (2011) Use of granulated sugar therapy in the management of sloughy or necrotic wounds: a pilot study. **Journal of wound care** Vol. 20 206-216

Nakao, H., Yamazaki, M., Tsuboi, R., et al. (2006) Mixture of sugar and povidone--iodine stimulates wound healing by activating keratinocytes and fibroblast functions. **Archives of Dermatological Research**, 298: (4): 175-182

Naylor, W (2002) Malignant wounds: aetiology and principles of management. **Nursing Standard**. Vol. 16: (52) 45-54,56

O'Brien, J.F. et al (2002) Leg ulcers: a cross-sectional survey of management practices and treatment costs in Ireland. **Phlebology;** 17: 98–102.

PC Webopaedia (online). Available from: www.pcwebopedia.com/JPEG.htm/2013,Sep.13

Pecoraro, R. (1991) **The nonhealing diabetic ulcer- a major cause for limb loss**. In: Barbul A, Caldwell M, Eaglstein W, (eds.) Clinical and experimental approaches to dermal and epidermal repair: normal and chronic wounds. New York: Wiley-Liss 27-43.

Pecoraro, R., Reiber, G., Burgess, E. (1990) Pathways to diabetic limb amputation: basis for prevention. **Diabetes Care.** 13: 513-21

Percival, S., Dowd, S. (2010) The microbiology of wounds. **In Microbiology of Wounds**. S Percival and K Cutting (eds). CRC Press: London: 187-219

Persoon, A., Heinen, M.M., van der Vleuten, C.J.M., de Rooij, M.J.M., van de Kerkof, P.C.M., van Achterberg, T. (2004) Leg ulcers: a review of their impact on daily life Blackwell Publishing Ltd **Journal of Clinical Nursing** 13:341-354

Phillips, T.J. (1996) Cost-effectiveness in wound care. **Ostomy/Wound Management** 42: 56-60

Pieper, B. and Caliri, M.H. (2003) Nontraditional wound care: A review of the evidence for the use of sugar, papaya/papain, and fatty acids. **Journal of Wound, Ostomy, & Continence Nursing**, 30: (4): 175-183.

Pledger, GW (1992) Basic statistics: Importance of adherence. **Journal of Clinical Research Pharmacoepidemiology** 6: 77-81

Plowman, R., Graves, N., Griffin, M.A., Roberts, J.A., Swan, A.V., Cookson, B., et al. (2001) The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialities of district general hospital in England and the national burden imposed. **Journal of Hospital Infection.**47: 198-209

Pojman, L (2002) **Philosophy: The Quest for the Truth**. Oxford University Press

RD., F. (1982) Early history of wound treatment. **Journal of Royal Society of Medicine**, 75: (3): 198-205.

Review Manager (RevMan) (2008) [Computer program].Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration008)

Reyes-Gibby, CC, Aday L, Cleeland, C (2002) Impact of pain on self-rated health in the community-dwelling older adults **International Association for the study of Pain 95:75-82 Elsevier Scince**

Roe, B.H., Luker, K.A., Cullum, N.A., Griffiths, J.M., Kendrick, M. (1993) Assessment, prevention and monitoring of chronic leg ulcers in the community report of a survey. **Journal of Clinical Nursing.** 2: 299-206

Root, M (1999) **Philosophy of social science. The Methods, Ideals, Politics of Social Inquiry**. Blackwell. Oxford & Cambridge USA

Rostenberg, A Jr., W.F., Medansky, R.S. (1958) Sugar paste in the treatment of leg ulcers. **AMA Arch Dermatology**, 78: (1): 94.

Ruhullah, M., Sanjay, S., Singh, HR., Sinha, KD., Irshad, M., Abhishek, B., Kaushad, S., Shambhu, SK (2013) **Academic Journals. Vol. 4(4): 27-32**

Sackett, D.L., Straus, S.E., Richardson, W.S., Rosenberg, W., Haynes, R.B (20000 **Evidenced-based Medicine: How to Practice and Teach EBM** 2nded Edinburgh, Scotland: Curchill Livingston

Schillinger, U. and Lucke, F.K. (1989) Antibacterial activity of lactobacillus sake isolated from meat. **Applied Environmental Microbiology** 55:1901-1906

Schrag, A., Jahanshahi, M., Quinn, N (2000) What contributes to quality of life in patients with Parkinson's disease? **Journal of Neurology, Neurosurgery and Psychiatry,** 69: 308-312

Schultz, G.S., Barillo, D.J., Mozingo, D.W., Chin, G.A. (2004) Wound bed prepation and a brief history of TIME. **International Wound Journal** Vol. 1:1:19-32

Schultz, G.S., Sibbald, R.G., Falanga, V., Ayello, E.A., Dowsett, C., Harding, K., Romanelli, M., Stacey, M.C., Teot, L., Vanscheidt, W (2003) Wound bed preparation: a systematic approach to wound management. **Wound repair Regeneration** Vol. 11:1-28

Schultz, K.F., Chalmers, I., Hayes, R.J., Altman, D. G (1995) Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. **JAMA**, 273: 408-12

Schulz, K.F, Grimes, D.A. (2002) Generation of allocation sequences in randomised trials; chance, not choice. **Lancet** 359: 515-519

Schulz, K.F., Altman, D.G., Moher, D., et al. (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. **BMJ (Clinical research ed.)**, 340: c332.

Scott, I., Mazhindu, D (2007) **Statistics for health care professionals an introduction**. Sage Publications

Scotts, N.A (2004) Wound infection; diagnosis and management. In Morrison MJ, Ovington LG, Wlkie K, eds (2004) **Chronic Wound Care. Aproblem-Based Learning Approach.** Mosby, Elsevier Limited, London: 101-16

Seal, D.V, Middleton K (1991) Healing of cavity wounds with sugar. The **Lancet**. 338:8766, 571-572.

Selwyn, D.; Durodie, J (1985) The antimicrobial activity of sugar against pathogens of wounds and other infections of man. *In*: Simatos, D.; Multon, J.; Dordrech, (eds). **Properties of Water in Foods in relation to Quality and Stability**. The Netherlands, Martinus Nijhoff Pub. p.293-307.

Shi, C.M., Nakao, H., Yamazaki, M., et al. (2007) Mixture of sugar and povidone-iodine stimulates healing of MRSA-infected skin ulcers on db/db mice. **Archives of Dermatological Research**, 299: (9): 449-456.

Sibbald, R.G., Williamson, D., Orsted, H.L., Campbell, K., Keast, D., Krasner, D., Sibbald, D (2000) Preparing the wound bed – debridement, bacterial balance and moisture balance. **Ostomy Wound Manage.** Vol. 46:14-35Silverman, W.A., Chalmers, I (1992) Sir Austin Bradford Hill: an appreciation. **Controlled Clinical Trials.** 13:100-105

Silvetti, A. (1981) An effective method of treating long-enduring wounds and ulcers by topical applications of solutions of nutrients. **Journal of Dermatological Surgery Oncology**, 7: (6): 501-508.

Simonsen, T., Aarbakke, J., Kay, I., Coleman, I., Sinnott, P., Lysaa, R. (2006) **Illustrated Pharmacology for Nurses.** Hodder Arnold.

Soloweij, K., Mason, V., Upton, D (2009) Review of the relationship between stress and wound healing: part 1. **Journal of Wound Care** 18 (9): 357-66

Solweij, K., Mason, V., Upton (2010) Psychological Stress and pain in wound care. part 3: management. **Journal of Wound Care** 19 (4): 153-5

Soon, K., Action, C (2006) Pain induced stress: a barrier to wound healing. **Wounds UK** 2(4): 92-101

Stacey, M.C., Burnand, R.G., Layer, G.T., Pattison, M., Browse, N.L. (1991) Measurement of the healing venous ulcers. **Australian New Zealand Journal of Surgery** 61: 844-8

Steenvoorde, P., Jacobi, C., Van Doorn, L., Oskam, J (2007) Maggot debridement therapy of infected ulcers: Patient and wound factors influencing outcome- A study on 101 patients with 117 wounds. **Annals The Royal College of Surgeons of England** Vol. 89:6:596-602

Strohal, R., Apelqvist, J., Dissemond, J., et al (2013) EWMA Document: Debridement. **Journal of Wound Care**, 22 (Suppl. 1): S1-S52.

Subrahamanyam M (1991) Topical applications of honey in treatment of burns. **British Journal of Surgery** 78: 497-8

Sussman G (2001) How To Treat Australian Wound management Part 11 **Doctor Pull-Out Section** 1-V111

Szerafin, T., Vaszily, M., Peterffy, A., (1991) Granulated sugar treatment of severe mediastinitis after open-heart surgery. **Scandinavian Journal Thoracic Cardiovascular Surgery**, 25:77-80

Tanner, A.G (1998) Successful treatment of chronically infected wounds with sugar paste. **European Journal of Cilinical Microbiology and Infectious Diseases** 7: 524-5

The Daily Mail 15th February 2013

The EuroQol Group (1990) EuroQol – a new facility for the measurement of health-related quality of life. **Health Policy,** 16 (3) 199-208

Thomas, A.C., Wysocki, A.B. (1990) The healing wound: a comparison of three clinically useful methods of measurement. **Decubitus** 3: 18-25

Toba, K., Sudoh, N., Nagano, K., Eto, M., Mizuno, Y., Nakagawa, H., Kawabata, N., Yamami, M. and Fukushima, Y. (1997) Randomized prospective trial of gentian violet with dibutylryl cAMP and povidone-iodine with sugar as treatment for pressure sores infectected with methicillin-resistant staphylococcus aureus in elderly patients. **Japanese Journal of Geriatrics** 34:577-82

Topham, J. (2002) Why do some cavity wounds treated with honey or sugar paste heal without scarring? **Journal of Wound Care**, 11: (2): 53-55.

Tophan, J (2000) Sugar for wounds. **Journal of Tissue Viability** Vol. 10:3: 86-89

Tovey, F. (1991) Honey and healing. **Journal of Royal Society of Medicine**, 84: (7): 447.

Trouillet,

Trouillet, J.L., Chastre, J., Fagan, J.Y., Pierre, J., Domart, Y., Gibert, C. (1985) Use of granulated in treatment of open mediastinitis after cardiac surgery. **Lancet** 2(8448): 180-184

Valls LT, Altisen MT, Poblador RP, Alvarez AC, Biosca RG (1996) Sugar paste for treatment of decubitus ulcers. **Journal Pharmacological Technology** 12: 289-90

Van-Toller, S. (1995) Pyschological consequences arising from the malodorous produced by skin ulcers. In Harding, K.G., Cherry, G., Dealey, C., Turner, T. (1992) Proceeding of the 2nd European Conference on Advances in Wound Management. **Macmillan Magazines.** *(eds).*

Viau, F., et al (1986) Treatment of wounds, eschars, and leg ulcers with crystallized sugar. **Sem Hop Paris**, 62: (30): 2431-2435.

Viau, F., Mangenot, D., Boval, C., Perron, J. (1985) [Treatment of eschars with commercial granulated sugar]. **Presse Med.**, 14: (14): 792.

Vowden, K and Vowden, P (1999a) Wound debridement Part 1: non-sharp techniques. **Journal of Wound Care** 8(5): 237-40

Vowden, K and Vowden, P (1999b) Wound debridement Part 2: sharp techniques. **Journal of Wound Care** 8(6) 291-4

Vowden, K., Vowden, P (2011) Debrisoft: Revolutioninsing debridement. **British Journal of Nursing** Vol. 20: 20(Suppl.), S1-S16

Vuorisalo, S., Venermo, M., Lepantalo, M. (2009) Treatment of diabetic foot ulcers. **Journal of Cardiovascular Surgery.** (Torino) 50(3): 275-91

Walshe, C (1995) Living with a venous leg ulcer: a descriptive study of patients experiences. **Journal of Advanced Nursing** 22, 1092-1100

White, R.J., Cutting, K.F., Kingsley, A.R. (2006) Topical antimicrobials in the control of wound bioburden. **Ostomy Wound Management** 52 (8): 26-59

White, R and Cutting, C (2008) Critical colonisation of chronic wounds: microbial mechanisms. **Wounds UK** 4(1) 70-8

Wieman, T., Griffiths, G., Polk, H. (1992) Management of diabetic midfoot ulcers ulcers. **Annals of Surgery** 215: 627-32

Willix, D.J., Molan, P.C. and Harfoot, C.G. (1992) A comparison of the sensitivity of wound-infecting species of bacteria to the antibacterial activity of manuka honey and other honey. **Journal of Applied Bacteriol** 73: 388-394.

Winter GD (1965) A note on wound healing under dressing with special reference to perforated Film **Dressings.** Vol. 45:4;299-302

Winter, G.D (1962) Formation of scab and the rate of epithelisation of superficial wounds in the skin of a young domestic pig. **Nature** 193: 293-4

Wiseman, L.A (1989) Sugar as an aid to wound healing and the treatment of ulcers in leprosy. **Lepr Rev** 60(1): 67-8

Wolcott, R.D., Kennedy, J.P., Dowd, S.E (2009) Regular debridement is the main tool for maintaining a healthy wound bed in most chronic wounds. **Journal of Wound Care** 18(2): 54-6

World Health Organisation (1948). Constitution of WHO. **WHO Basic Documents Geneva**

www.mrc.ac.uk/complexinterventionsguidance

Yarkony, G.M. (1994) Pressure ulcers: a review. **Archives of Physiology Medical Rehabilitation** 75: 908-17

Yudkin, J., Edelman, J., Hough, L (1971) **SUGAR: Chemical Biological and Nutritional Aspects of sucrose**. London Butterworths

Appendices

Appendix 1: Ethical approval letters

Birmingham, East, North and Solihull Research Ethics Committee Approval Letter

Appendix 2: MHRA Correspondence and approval letter**.**

MHRA approval form

Appendix 3: Patient Information

Patient Information Sheet

Study Title: *A randomised controlled trial to investigate the clinical and cost-effectiveness of sugar dressing compared with standard treatment in the management of exudating wounds with parallel economic evaluation*

Study Number:

Patient Information Sheet

Part 1

1.1 Invitation paragraph

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. (Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study). Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

The research is an **experiment** investigating the clinical and cost-effectiveness of sugar dressing compared with standard treatment in the management of exudating wounds. Sugar has been used in the management of wounds in Argentina, Italy, Africa and the United Kingdom at Middleton Hospital in the 1980s. It is also recorded that sugar has been used for this purpose for many years during the earlier centuries and was particularly effective in managing exudating and odorous wounds. Sugar generally cleans wounds in less than two weeks. Sugar dressings are sterilised and provided in small individual packets for ease of application. The researchers are also interested into finding if there is any change in blood sugar levels to those suffering from diabetes. This is a pre-study to provide information for a larger study in the future. It is going to be used to develop a procedure that will be used in the main study and also to determine the number of patients required for the main study.

1.2 What is the purpose of the study?

The purpose of the study is to determine whether using granulated sugar on exudating wounds will have an effect compared to standard dressings on wound healing. We also want to know if there are any cost-effectiveness when using granulated sugar. The other reason for carrying out this study is to develop a standard protocol for use in different parts of the world.

1.3 Why have I been invited?

You are chosen to participate in this study because you have a heavily exuding chronic wound and you are a patient at Queen Elizabeth Hospital or Walsall Manor Hospital.

1.4 Do I have to take part?

It is up to you to decide. We will explain the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

1.5 What will happen to me if I take part?

You will be expected to be in the study for no more than three weeks.
The researcher will clean and dress your wound or supervise the team caring for you until you no longer require the sugar dressing. During this period your wound will be photographed using a digital camera prior to commencing the study and then weekly for up to three weeks. These photos will be compared to see if there is any change in the size of the wound and its appearance.
Wound swabs will be collected from your wound and sent to the laboratory for analysis of bacteria. Finally you will be asked to fill in a questionnaire that will enable the researcher to determine your satisfaction/dissatisfaction with the use of this product.

If you decide to take part in this experiment your wound will be treated with granulated sugar or standard dressings on a daily basis. It might be two-times a day to begin with depending on the amount of fluid your wound produces. This will slow down to daily, then once in two days until healing begins. If you suffer from diabetes your blood glucose level will be checked before putting granulated sugar on the wound throughout the study period (3 weeks). After the study your blood glucose level will be monitored for a period of three weeks. During the period of study you will be given some questionnaire asking you about the treatment. Your wound will be measured with a clinical ruler, photographs and wound swab taken.

1.6 What will I have to do?

You do not have to do anything in particular other than signing the consent form if you decide to take part and completing the questionnaire at the beginning and at the end of the study.

1.7 What is the device that is being tested?

Your wound will be treated with either granulated sugar specifically prepared for wound treatment only or with standard treatment that is normally used with wounds similar to yours. The granulated sugar comes in pre-packed single use packets. Your wound will be cleaned as normal then granulated sugar will be applied covering the whole wound. There are no known risks associated with using granulated sugar on exudating wounds. We also carried out a small study with 22 patients and we did

not encounter any problems. However, the team will keep a close monitoring of all those who are in the study to see if there is any problem arising from this method of wound management.

There are no known side effects reported in previous studies related to granulated sugar treatment. However to those who are Diabetic we would monitor blood glucose closely to exclude any change in blood sugar levels. We had no problems with blood sugar levels during the small study we undertake with 22 patients.

1.8 What are the alternatives for treatment?

This method of using granulated sugar is an experimental treatment compared with standard treatment that would otherwise be received. There are many different dressings that may be used if you wish not to take part or should you decide to withdraw at any point in the study. The clinical staff will inform you of the dressing they consider to be most suitable.

1.9 What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study will help improve the treatment of people with chronic exudating wounds.
If the trail is successful it will also help with the possible funding of the major study to follow. The product might become widely used in the United Kingdom and possibly other European and Developing countries.

1.10 What happens when the research study stops?

You will still be monitored as usual to determine the progress of your wound. If the ward staff consider that there is still benefit for you in continuing to use sugar dressing on your wound they will do so.

1.11 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

1.12 Will my taking part in the study be kept confidential?

Yes, We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.
This completes Part 1.
If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.
Patient Information Sheet

Part 2

2.1 What will happen if I don't want to carry on with the study?

If you decide to withdraw from the study, we will destroy all your identifiable samples, but we will need to use the data collected up to your withdrawal.

2.2 What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researcher/research team who will do their best to answer your questions If you remain unhappy and wish to complain formally, you can do this through the NHS complaints Procedure (or Private Institution). Details can be obtained from the hospital switchboard on 0121 627 1627 or Patient Advice Liaison Service on telephone 0121 627 8820, if you are a patient at Queen Elizabeth Hospital. If you are a Walsall Manor Hospital Patient details can be obtained from the hospital switchboard 01922721172.

Harm

There is no harm expected however should any harm occur you can contact Patient Advisory Liaison Services (PALS) on 0121 627 8820 or you can ask the hospital switch board on 0121 627 1627 to put you through to PALS office if you a Queen Elizabeth Hospital Patient. If you are Walsall Manor Hospital use the hospital switch board at 01922721172.

NHS Based Research

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against University Hospital Birmingham NHS Foundation Trust, or Walsall Manor Hospital NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (PALS).

2.3 Will my taking part in this study be kept confidential?

If you join the study, some parts of your medical records and the data collected for the study will be looked at University Hospital Birmingham NHS Foundation trust if you are a patient at Queen Elizabeth hospital. If you a Walsall Manor Hospital NHS Trust patient some parts of your records will be looked at Walsall Manor Hospital, by authorised persons only. The data may also be looked at by people from the Ward, by research supervisors of Birmingham University and by authorised people to check that the study is being carried out correctly. All people who will look at the data have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information, which is collected, about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital/ward will have your name and address removed so that you cannot be recognised.

2.4 What will happen to any samples I give?

Samples taken from your wound will be sent to the laboratory for the purpose of analyzing the bacteria in your wound only.

2.5 What will happen to the results of the research study?

The results of the study will be disseminated to the whole tissue viability nursing team within each trust. It is also hoped that the outcome of this study be shared with those with interest on wound management by publishing the results in professional journals and presentation of papers at conferences. During publication of results in professional journals all participants will remain anonymous.

2.6 Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Birmingham, East, North & Solihull Research Ethics Committee.

2.7 Further Information and Contact Details

The study is independent and aimed at finding ways of helping patients suffering from chronic exudating wounds. A PhD student from Birmingham University School of Health Science initiated this research project. He has used this method of wound treatment before in Lesotho, South Africa and Zimbabwe with favourable results. A small study was carried out from January 2009 to July 2009 to build on information that can help develop an appropriate protocol to be used with this major study. The Principal investigator has witnessed the use of this method whilst on sabbatical in East Africa.

If you require more information or talking through this treatment you can contact the researcher Moses Murandu

You are not obliged to take part, however should you decide to take part it might be of interest to you and might benefit your wound treatment.

If you are unhappy with the study inform any research team member who will consult your consultant for an alternative treatment.

Or you can contact the patient advisory liaison services at the contact details below:

The Manager

Patient Advice Liaison Services
University Hospital Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Vincent Drive
B15 2TH

Or
The Manger
Patient Advice Liaison Services
Walsall Manor Hospital NHS Trust
Walsall Manor
Moat Road
WS2 9PS

Thank you for taking time to read this information.

Appendix 4: Amended Ethical Authorisation 2012
Amended North Birmingham and Solihull Ethics authorisation form

Appendix 5: Tate & Lye Certificate of conformity
Certificate of conformity Tate & Lyle

Appendix 6: North Staffordshire Pharmaceuticals services Certificate of conformity
Certificate of conformity North Staffordshire Pharmaceutical services

Appendix 7: Patient Consent Form

CONSENT FORM

NHS Study Number:

Title of Project: A randomised controlled trial to investigate the clinical and cost-effectiveness of sugar dressing compared with standard treatment in the management of exudating wounds with parallel economic evaluation

Name of Researcher: Moses Murandu

Please initial box

1. I confirm that I have read and understand the information sheet dated 19/08/2010 (Version 1) for the above study: I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from [University of Birmingham], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to have a photograph taken of my wound ☐

5. I agree to have a wound swab taken from my wound ☐

6. I agree to take part in the above study ☐

_____	_____	_____
Name of Patient:	Date:	Signature:
_____	_____	_____
Name of Person taking consent:	Date:	Signature

Appendix 8: Case report form and TELER Indicators

University Hospital Birmingham NHS
NHS Trust

CONFIDENTIAL

R&D Study No:

PATIENT INITIALS _____

CONTACT DETAILS

Principle Investigator: **Mr Malcolm Simms Vascular**

Consultant

Selly Oak Hospital

Birmingham

INVESTIGATORS CHECKLIST

(PLE OMPLETE)

Patient fulfils criteria for study ☐

Study explained to patient	☐
Patient has read the information sheet	☐
Consent form completed and signed	☐
Copy of consent form placed in patient's notes	☐
Confirmation of consent form signed	☐
Baseline characteristics recorded and complete (Proforma 1)	☐
Photograph of wound taken on initial assessment	☐
Initial Wound Assessment (Proforma 1)	☐
Blood Glucose taken and recorded	☐
Follow up Assessments Completed (Proforma 2)	☐
Final Assessment (Proforma 3)	☐
End of Study form completed (Proforma 4)	☐
Serious Adverse Incident form completed (if appropriate) (Proforma 5)	☐

Clinical Investigators signature when complete _____

Date of Completion _____/_____/_____

CONFIRMATION OF PATIENT CONSENT

"A randomised controlled trial to investigate the clinical and cost-effectiveness of sugar dressing compared with standard treatment in the management of exudating wounds"

Patient initials _____

Date of Birth _____/_____/_____

Hospital Number _____

Study Number _____

Date consent obtained _____/_____/_____

I hereby confirm that informed consent has been given from the above patient to participate in this study.

The patient signed the consent form.

A copy of signed consent form will be retained in the patient's medical records

A copy has been given to the patient

The third copy has been retained with the study records

…… ……
____/__/____
Investigators signature Print Name Date

PROFORMA - END OF STUDY FORM

TO BE COMPLETED AT ANY STAGE WHEN THE PATIENT IS WITHDRAWN FROM THE STUDY

1. Patient study Number	_____
2. Date of Assessment	_____/_____/_____

3. Reason for withdrawal from study
(tick one box only)

- ☐ Study wound healed
- ☐ End of study period
- ☐ Patient withdrawn*

4. *If patient withdrawn, please give reason(s)

- ☐ #Adverse incident
- ☐ *Lack of response
- ☐ *Patients request
- ☐ *Patient lost to follow up
- ☐ *Other

*Please give details_____

#Adverse incident = complete adverse incident form - Proforma 5

1. Comments

_____
_____
_____
_____

_____ _____ _____/_____/_____
Clinical Investigator **Print Name** **Date**

PROFORMA -SERIOUS ADVERSE INCIDENT REPORT

Patient study Number _____

Date of assessment _____/_____/_____

The Clinical Investigator has determined that the patient has suffered a serious adverse incident. This is defined as any undesirable clinical occurrence in the patient that may be considered to be directly or indirectly related to the study treatment.

A description of the serious adverse event:

_____

_____

_____

_____

_____

The patient is therefore withdrawn from the study and the following personnel informed.

1. Patient's Consultant Diabetologist ☐

2. Principle Investigator ☐

3. Local Research Ethics Committee (via R&D) ☐

_____ _____ _____/_____/_____

Clinical Investigator **Print Name** **Date**

STUDY NUMBER:

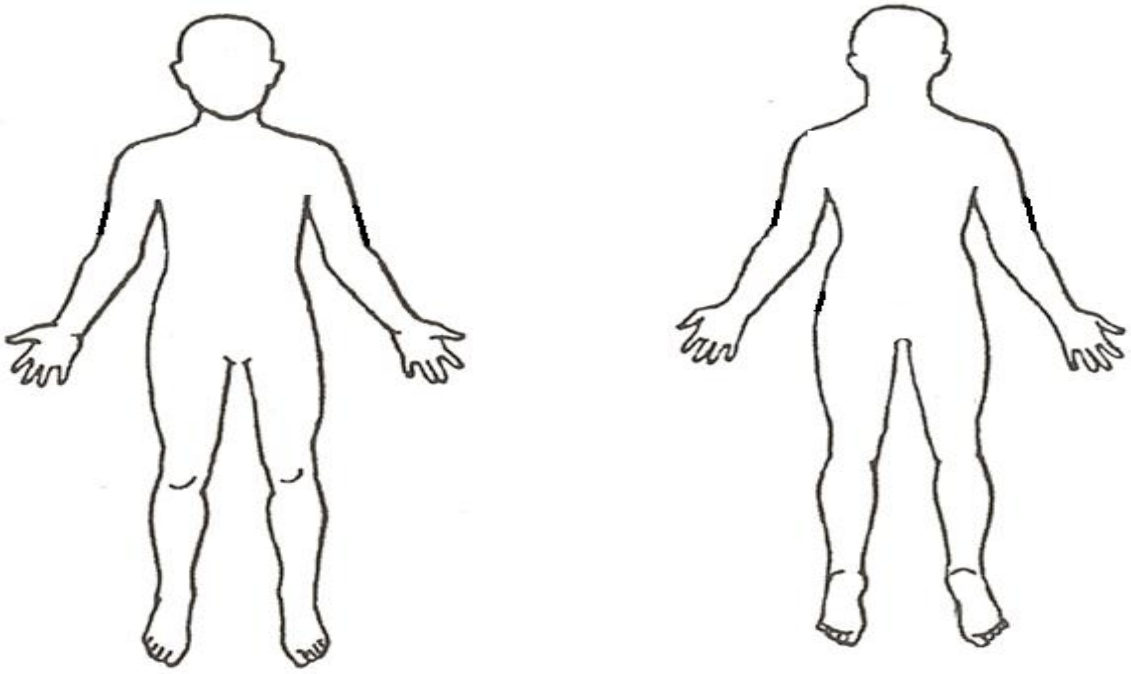
RECORD OF WOUND ASSESSMENT AND DRESSING PLAN USING TELER METHOD

Complete one form for each of the patient's wounds at initial assessment

Patient S/N:	**Wound site:**
Wound Size: small / medium / large **Length:** **Diameter:** **Depth:** **Area:**	**Type of wound:** **Acute: Y/N** **Chronic: Y/N**
Photographed/ traced	**Y / N**
Measured using clinical ruler	**Y / N**
Medical Condition:	

Mark on the body map position of wound

FRONT **BACK**



Dressings Selected - complete at initial assessment and following any dressing changes

Date and Time			
Skin Care/Cleansing			
Standard treatment **Y / N** Type:			
Granulated Sugar **Y / N** Amount:			
Securing Mechanism			
Frequency of dressing change			
Print Name			
Signature			
Designation			

UHB No:

WMH No:

Complete this section weekly for 1 month then monthly for 6 months or when healing is complete

Number of weeks	**Week….**	**Week ….**	**Week ….**	**Week ….**
Date and Time				
SIZE (in cms)				
Diameter				
Length				
Depth				
Area				
Photographed / traced Y/N				
BLOOD SUGAR LEVEL				
INFECTION				
Slough (in %)				
Swab sent? Y/N				
Swab results: MRSA Y / N				
1 Exudate Appearance				
0 Sanguineous, predominantly blood				
1 Serosanguineous, i.e. bloodstained but not bleeding frankly				
2 Odorous purulent, i.e. odour + cloudy, thick yellow/blue/green tinge				
3 Non-odorous purulent, i.e. cloudy, thick, yellow				
4 Serous, i.e. think, pale straw/clear				
5 No exudates to describe				
2. Exudate Leakage				
0 Dressing(s) and bed clothes are soiled				

1	Dressing(s) and bed clothes are wet				
2	Dressing(s) wet and bed clothes are damp				
3	Dressing(s) wet and bed clothes are soiled in patches, size of 50p piece				
4	Dressing(s) only is wet				
5	Dressing(s) only is soiled				
3. Odour					
0	Odour is obvious in the house/clinic/ward				
1	Odour is obvious at arms length from patient				
2	Odour is obvious at less than an arms length from patient				
3	Odour is detected at arms length				
4	Odour is detected by patient only				
5	No odour				
4. Uncomfortable Dressing					
0	Continuous discomfort from dressing sleeping and waking hours				
1	Occasional discomfort from dressing during sleeping hours and constant discomfort waking hours				
2	Regular discomfort from dressing				
3	Periodic discomfort now and then from dressings				
4	Discomfort now and then from dressings				
5	Aware of dressings but no discomfort				
5. Pain (component) Pain interferes with patient's ability to:					
0	Relax				
1	Mobilise				
2	Concentrate				
3	Socialize				
4	Sleep				
No pain at all					
6. Pain disturbing sleep					
0	Wakes frequently difficulty getting to sleep				

1	Wakes frequently (4 or more times a night)				
2	Wakes infrequently (3 or less times a night)				
3	Sleeps through 1-3 nights a week				
4	Sleeps through 4-6 nights a week				
5	Sleep undisturbed every night				
7. Impact of Dressing Change					
0.Unbearable dressing change, medication needed during pre and post change					
2.	Distressing dressing change, medication needed				
3.	Unpleasant dressing change, medication needed				
4.	Disagreeable dressing change, no medication				
5.	Some unpleasantness				
6.	Dressing change alright				
8. Pressure Sore					
0	Deep wound with infection and slough				
1	Deep wound with slough but no infection				
2	Deep wound without slough				
3	Evidence of granulation				
4	Healing from wound edges				
5	Healed				
9. Achieving Wound Healing					
0	Deep necrotic offensive, infected wound, down to bone				
1	Deep infected wound, heavy exudates, and damage to muscle				
2	Sloughy wound, infected and offensive, to subcutaneous fat				
3	No infection, no exudates, granulating, odour free				
4	Superficial damage, some inflammatory change, broken ‘healthy’ skin				
5	Healthy ‘pink’ unbroken skin. Healed wound.				
10. Wound Appearance					
0	Clinically Infected				

1	Hard Necrotic Eschar				
2	Necrotic/Sloughy				
3	Thin Layer of Slough				
4	Granulating				
5	Epithelialising				
6	Healed*				
PRINT NAME					
SIGNATURE					
DESIGNATION					

Appendix 9: RCT protocol

RCT Protocol final version

Granulated Sugar Dressing Protocol

Name of Student: Moses Murandu

Course: Doctor of Philosophy

Title of Research: ***A randomised controlled trial to investigate the clinical and cost-effectiveness of granulated sugar dressing compared with standard treatment in the management of exudating wounds with parallel economic evaluation.***

Supervisors: Professor Carol Dealey and Professor Tom Marshall

Background and justification of the two studies

A wound is a breach of the epidermis of the skin that can lead to infection and sepsis. However, the body has evolved well defined protective systems to counter this potential threat. It can be argued that, everyone has received minor wounds that were expected to heal in a reasonable amount of time, but for more serious scrapes, sores and cuts this may not happen, as different factors exacerbate wound healing to the extent some wounds slowly or never heal. A slow-healing wound tends to collect dead tissue or debris (slough). This process can lead to wound infection and delayed healing (Adam 2002, Jones et al 2004, Steenvoorde et al 2007). In order to facilitate wound-healing Sibbald et al (2000) advocated for wound bed preparation that entails debridement, wound-friendly moist interactive dressings and bacterial balance. Debridement is widely used to clear wounds of necrotic tissue and bacteria to leave a clean surface that will heal relatively easily. Debridement and appropriate dressings are often used to accelerate healing, although in the early stages of wound healing, debridement occurs autolytically through the action of neutrophil-derived enzymes including elastase, collagenase, myeloperoxidase, acid hydrolase and lysosomes (Schultz et al 2003). A study by Gethin and Cowan (2008) on 108 leg ulcer patients showed that after 4 weeks, 80% of all wounds had a reduction of less than 50% slough; although there was no statistically significant difference at week 4 between treatments. It is also worth noting that a slough reduction of at least 50% by week 4 was associated with a higher probability of healing at 12

weeks across all groups (p-0.029) i.e. at 12 weeks, 44% vs. 33% healed (p=0.037). Healing is defined by the Wound Healing Society as a "complex dynamic process that results in the restoration of continuity and function" (Lazarus et al 1994). To date most of the current understanding of wound healing management has been derived from studies of the healing process in acute wounds. These wounds, caused by trauma or through surgery generally follow a well-defined wound healing process that involves four main stages i.e. coagulopathy, inflammation, cell proliferation and repair of the matrix and epithelialization and remodelling of the scar tissue. While the chronic or non-healing ulcers are characterised by defective remodelling of the extracellular matrix (ECM) protein, a failure to reepithelialise and prolonged inflammation (Hasan et al 1997, Agren et al 1999, Cook et al 2000).
Sugar dressing has been used to debride heavily exudating wounds. However, current evidence shows that there is a limited literature relating to sugar dressing in the management of exudating wounds though extensive research has been done on honey dressing. While sugar dressing has been used over 50 years ago in the United States of America (Dressing Times 2006), and Matthews and Binnington (2002) reckoning its use dates back to 1879 and since been used by surgeons at Ontario University College in the aid of wound healing of contaminated wounds. Despite this occasional use it is yet to be considered an alternative agent for wound care. According to Matthews and Binnington (2002) sugar dressing has been used less extensively than other debridement agents in human medicine although it is well recognised as a suitable adjunct therapy for decontamination of wounds in veterinary medicine (Tophan 2000). It is believed that sugar therapy has been used in injuries such as degloving, infected surgical wounds, necrotizing fasciitis, decubitus ulcers, and self-mutilation, crush injuries, deep tissue infections, or other skin defects that need a healthy granulated bed (Matthews and Binnington 2002). In 1985 Trouillet et al described successfully treating 19 patients with acute mediastinitis following cardiac surgery. Earlier on in 1976 Herszage and Montenegro of Argentina had used ordinary sugar to treat the wounds of two patients with post-surgical necrotic cellulitis. Following his successes, he further reported another 120 patients going through a successful therapy (Herszage et al 1980). Sugar paste has been used on most wound types but it has been found to be particularly effective for treating infected and malodorous wounds (Gordon et al 1985). Mphande et al (2005) compared the effects of sugar and honey dressings on wound healing and concluded that honey was more superior to sugar in terms of healing times, reducing bacterial contamination and less painful though the later needs more scrutiny. Furthermore honey is more expensive and there is a probability of increased blood sugar levels when used on diabetic patients;

given that enzymatic action of bees on nectar changes it to glucose. It is also understood that both sugar and honey have natural antibacterial properties that facilitate healing by reducing bacterial colonisation (Knutston et al 1981; Willix, Molan and Hartfoot 1992, Tophan 2000 and Booth 2004).

It is well documented that wound healing is impaired in the presence of devitalised tissue (Sieggreen and Malkebust 1997, Baharestani 1999, NICE 2001, Gregory et al 2004). The removal of slough, when consistent with treatment goals is considered the first step in wound bed preparation of both acute and chronic wounds (Falanga 2002, Adam et al 2002, and Schultz et al 2004). This premise is supported by the Gethin and Cowan study (2008) which found that the removal of devitialised tissue promoted wound healing. Wound bed preparation varies from patient to patient and on the condition of the wound bed and resources available. Methods range from surgical to natural autolytic debridement and at times influenced by the clinician knowledge and treatment goals.

This research will evaluate the clinical efficacy and cost-effectiveness of sugar as a wound debriding product for managing sloughy, necrotic or infected exudating wounds. These are wounds which at times are odorous, leak fluid, sometimes in large quantities and pose a great difficulty in management. To patients, they are a source of poor quality of life. Therefore the provision of care for these acute and chronic wounds impacts heavily on the day-to day practice of health care professionals in both hospital and community settings and cost the NHS in excess of £2 billion each year (Posnett and Franks, 2007). Diseases associated with the ageing process such as diabetes and hypertension are a contributing factor to the problem of chronic wounds that often pose a health burden (Harding et al 2002) and health care professionals are left with a difficult challenge in managing these wounds. Therefore extensive research into the best methods/products of treatment is the way forward in order to provide quality of life assurances to patients. The method of sugar dressing has been used before in the United Kingdom around the 1980s at Northwick Park Hospital (Dealey 1994).

A small pilot study of 22 patients with various aetiologies (Murandu et al 2011) undertaken within an NHS acute hospital produced plausible results that facilitated further work into this sugar product. Murandu et al (2011) concluded that sugar was safe to use on diabetic patients. Within the same study a small patient quality of life survey indicated that, their quality of life was improved. There was also reduction in bacterial load and patient use of strong analgesics was reduced. The practical concerns were determined by the involvement of all nurses and

medical staffs in the vascular ward were the study took place. The proposed research will compare desloughing efficacy of sugar dressing within four weeks with current standard treatments used for the same purpose.

It is anticipated that the findings from this research will facilitate improvement of both patient reported and clinical outcomes. Overall the benefits include; an improvement in the patient experience and improvement in the experience of healthcare professionals who have to dress the wounds, shorter wound duration which benefits patients, healthcare professionals and the NHS as fewer dressings have to be used. It is also hoped that there will be reduction in the costs of dressings to the NHS as sugar dressings are cheaper unit for unit than many of the modern wound management products used in daily practice. Therefore the study outcomes could demonstrate considerable cost savings for the NHS, having clear potential impact on clinical practice and ultimately on policy-making in this area.

The proposed RCT will compare the debriding efficacy of sugar after four weeks in sloughy wounds of differing aetiologies with standard debriding treatments.

Purpose of the Research

The aim of this project is to investigate the effectiveness of sugar dressing as a wound debridement product on exudating sloughy, necrotic or infected wounds.

Primary Questions

How effective is sugar dressing in reducing the time to debridement of sloughy, necrotic or infected exudating wounds/ ulcers compared with standard treatment?

Secondary Questions

Does the use of sugar dressing reduce the bacterial load in a wound to a greater extent than standard treatment?

Does the use of sugar dressing improve the quality of life patients with sloughy, necrotic and/or infected wounds?

Is sugar a cost effective alternative to current treatment modalities?

Is patient satisfaction improved when using sugar dressing?

Potential Benefits Arising from the Study

This study will restore the use of sugar dressing in the management of exudating wounds/ulcers. The potential benefits are improvement of wound care management of exudating wounds and data collected can be directly costed and compared to a control sample

(standard treatment) to determine the cost-effectiveness. The quality of life related outcomes will be measured using patients' related outcomes on quality of life.

Research Design

The study will be a prospective pragmatic randomised controlled open trial of clinical outcomes comparing sugar dressing with standard debriding treatment. The methods used are based on those developed by Dumville et al (2009) for similar pragmatic randomised controlled trials of wound management products.

Population, Sample and Location

Definitions of the wound types and associated terminology can be found in Appendix 1.

Eligibility

Two hundred and thirty patients with sloughy, necrotic or infected heavily exudating, wounds will be recruited from in-patients at University Hospital Birmingham NHS Foundation Trust, Walsall Hospital NHS Trust and Moseley Hall Hospital by Research Nurses or suitably trained and designated hospital tissue viability nurses. The patients will be predominantly those with moderate-severe traumatic injury, non-healing surgical wounds or chronic wounds. It has been determined that it is reasonable to use this wide range of aetiologies because the treatment aims are the same at this stage in the healing process; namely control of exudate and debridement of sloughy necrotic or infected tissue (Schultz et al 2003, Schultz et al 2004). All patients should have ≥ 25% wound area covered in slough and able to provide written informed consent. The inclusion and exclusion criteria are listed in the table below.

Inclusion Criteria

Table: 1

Inclusion criteria	**Exclusion criteria**
Patients who can independently and willingly consent	Patients who are currently in a trial evaluating other therapies for their wound
Sufficient vascular supply (Ankle Brachial Pressure Index of greater than 0.6)	Patients who previously been in this trial
Exudating wounds between the sizes $5cm^2$ and $20cm^2$	Women who are pregnant or lactating
Wounds with a minimum of 25% slough with infected or necrotic tissue present	Patients who are not able to tolerate a daily dressing change
Wounds with no dry necrotic eschar present	Patients who have neuropathic component to the underlying aetiology and require callus removal

Patients who are over the age of 18 years	Less than 18 years
	*Wounds with fungal infection

***New *change applies to Military participants only*.**

Patients for whom English is not their first language are eligible to participate as long as they are able to give informed consent. The patient questionnaires used in this study are unlikely to have been validated in other languages, however, they are not self-administered and patients with some knowledge of English should be able to respond to the questions. Those unable to complete them will be followed up for wound data.

Interventions

All patients will receive relevant adjunctive therapies such as compression therapy or pressure relief as part of their treatment.

Debridement Period

Patients allocated to the sugar group will have daily dressings following the protocol developed during the pilot study. Sugar dressing will be discontinued once the wound bed is clean and granulating. The pilot study found the mean time to achieve debridement was 11.13 days. Patients in the control group will have standard treatment for debridement following current hospital policy. Debridement treatment will be discontinued once the wound bed is clean and granulating.

Follow Up Period

After debridement all patients will revert to standard care for the follow up period and will be assessed weekly. They will remain in the study for a total of 4 weeks. It is anticipated that the majority of these patients will be in-patients for most of the time. If they are discharged they will either be followed up in the community by a research nurse in collaboration with the community nurses or in the outpatient clinic, whichever is most appropriate in relation to timing of reviews.

Deterioration of Reference Wound

If there is deterioration of the reference wound; i.e. increased in the wound size and increased slough percentage over period of two dressing changes the wound will be reviewed by the ward team and treatment stopped and changed to other appropriate dressing product. Even if the treatment is changed, the patient will remain in the study and the outcomes monitored.
Withdrawal from the study

Patients will be withdrawn from the study if an allergic reaction occurs or if the patient request to withdraw from the study.

Sugar Dressing Group

Sugar dressing is supplied in single use sterilised containers of 15g and 30g. It will be applied to the wound and then covered with a sterile pad and secured firmly in place. Where there may be difficulty in applying and retaining the sugar in the wound, a thin layer of soft paraffin can be applied to the wound margins. The dressing should be applied daily. However, in the initial stages of treatment it may be necessary to change the dressing twice daily as there is often increased exudate as the wound starts to debride.

Control Group

A variety of wound management products may be used to debride wounds. Patients in the control group will be assessed and the most appropriate product will be selected according to patient need and current hospital policy and in collaboration with the ward team. Dressing change will be undertaken as required by the treatment in use.
In discussion with a member of the ward team, research nurses will use their clinical judgement as to when the debridement treatment is no longer required, i.e. *if the wound bed is clean and granulating, a wound photograph will be taken and recorded in the case report form (CRF).* Appropriate standard treatment will then be selected by the clinical team. Although this approach appears to move control of the outcome away from the research team, it was found not to affect the results in the Dumville et al (2009) study.

Adjunctive Therapies

The use of any adjunctive therapies depends on the wound aetiology and patient assessment. They will be prescribed by the ward team and recorded by the research nurse *in the case report form.*
Leg Ulcers: compression therapy may be prescribed for venous leg ulcers depending on the wound status, for example it is not current practice to use compression therapy on infected venous leg ulcers, but application of compression will recommence as the infection resolves.
Pressure Ulcers: support surface such as mattress and cushions will be determined by the clinical team.

Randomisation

Patients will be approached by one of the Tissue Viability Nurses or other members of the ward team. If they express a willingness to consider participation in the study a member of the research team will be notified and asked to visit the patient. All members of the research teams in both hospitals will receive standardised training on all aspects of the trial including informed consent. A research nurse will provide written and verbal information about the study to the patient and be available to answer any questions. Patients will have a minimum of 24 hours to decide whether to participate or not. Written consent will be obtained from all patients participating in the study and the clinical team informed of this decision (A copy of the patient information sheet and the consent form can be found in Appendix 2). Once a patient has signed the consent form and before randomisation, the following data will be collected:

Wound measurement; length, width and depth using wound measurement ruler. This will be recorded on the study wound assessment pro-forma and the approximate shape of the wound selected from a range of shapes. Wound size will be determined using the algorithm developed by Metcalfe et al (2008) to validate the use of the clinical ruler and then calculated using computer software.

Wound appearance the percentage of slough, infected tissue and necrotic tissue (a minimum of 25%) will be recorded on the wound assessment pro-forma and a digital photograph taken. A masked observer (Tissue Viability Nurse) will later record the percentage of slough, infected tissue or necrosis seen in the wound using digital analysis to confirm reported proportion of slough and/or necrosis.

Wound assessment exudate type and quantity, pain and odour will be undertaken using the Treatment Evaluation Wound indicators by Le Roux TELER (Le Roux, 1993). These indicators have been used in other studies (Grocott and Cowley, 2001); Browne et al, 2004a; Browne et al, 2004b) and also in the pilot study. They were found to provide objective measurements of exudate volume, odour and pain by using a series of indicator codes where 5 is the desired outcome and zero is the worst possible outcome. Each code from 0 to 5 indicates a clinically significant change that can be recorded as an ordinal measurement. The clinical indicators for odour are shown below to illustrate this.

Odour

Code	Description
5	No odour
4	Odour is detected on removal of the dressing
3	Odour evident on exposure of dressing
2	Odour evident at arms length from patient
1	Odour evident on entering room
0	Odour evident on entering ward

Wound infection: all wounds will be assessed against a check list for clinical indications of infection and a wound swab will be taken.

History: wound aetiology, longevity of the wound, Ankle Brachial Pressure Index (ABPI) for leg ulcers, nutritional status (BMI), mobility and antibiotic usage will be recorded.

Health Related Quality of Life (HRQL) will be measured using EQ-5D (The EuroQoL Group, 1990).

The research nurse/ward nursed trained to run the trial will then ring *the University of Wolverhampton for randomisation number*. Patients will be randomised to one of the two arms of the study. Allocation to treatment will be stratified by two variables, (wound type and wound size) to ensure equal balance between the two arms of the study for factors that may be prognostic for healing.

Wound type: wounds will be divided into acute and chronic depending upon the underlying aetiology as shown below:

Acute or Chronic	<u>Acute:</u> Traumatic Wound Non-healing surgical wound	<u>Chronic:</u> Leg ulcer Pressure ulcer

It is recognised that acute wounds, by their very nature heal faster than chronic wounds, although there is limited information about healing rates.

Wound size:

Size: either	<u>Small to Medium:</u>	<u>Medium to Large:</u>

	Minimum = 5cm^2 Maximum = 10cm^2	Minimum = 11cm^2 Maximum = 40cm^2

Wounds less than 5cm^2 and greater than 40cm^2 are not included as they are difficult to measure accurately.

Outcomes

Primary Outcome

The primary outcome measure will be time to complete debridement at 4 weeks and healing at 12 weeks. Complete debridement will be defined as a cosmetically clean wound (Dumville et al, 2009). Reference wounds will be photographed on entry to the study and then weekly. When the research nurse decides that the wound is debrided, she/he will ask a member of the ward team to confirm this. In the event of disagreement, the local Principal Investigator will be asked to review the wound status. The date of debridement will be recorded.

Secondary Outcomes

Reduction in Wound Size

Wounds will be measured at enrolment and then weekly for the study period. The surface area will be calculated using the methods previously described.

Reduction in Bacterial Load

Wound swabs will be taken at baseline and then weekly for 1 month. They will be cultured for Gram positive and negative aerobes, anaerobes and fungi.

Reduction in Pain and Odour

Levels of pain and odour will be recorded using the TELER system (previously described) at baseline and at each dressing change until debridement is complete.

Health-Related Quality of Life

The EQ-5D will be used to measure quality of life. Measurements will be taken at baseline, at end of debridement before reverting to the standard treatment.

The costs of using sugar dressing and standard treatment will be monitored by recording all the materials used at each dressing change until debridement is complete. The frequency of dressing change will also be recorded. Although sugar dressing is relatively cheap compared with other wound management products, it does require more frequent dressing changes than

some products. It is important therefore to monitor both the components of the dressings applied and the frequency of application and cost of deterioration

Statistical Considerations

The sample size for this randomised controlled trial has been calculated using the outcomes of the pilot study. An *a priori* calculation found that 200 patients will be required for this study, assuming that there will be a median debridement time of 12 days in the sugar group and 17 days in the control group and a 4 week follow-up period. Allowing for a 15% loss to follow up, a total of 230 patients will be recruited giving an 80% power at the 5% significance level. It should be noted that this calculation is based on limited information and therefore an interim analysis will be done by an independent Queen Elizabeth Hospital Birmingham NHS Foundation Trust Statistician after 75 patients have been recruited to review the study outcomes and confirm the numbers required in the study to achieve a significant result. Any alterations in the required numbers will be communicated to East Birmingham Ethics Committee and amendment approval sought if necessary.

Patients with heavily exuding wounds will be screened and those meeting the inclusion criteria will be randomised to either sugar dressing or standard treatment. The randomisation will be stratified both by acute or chronic wounds and by size as described previously.

Both patients and researcher will be blind to allocation until after consent has been given. If a patient has more than one wound the largest with a minimum of 25% slough, infected tissue or necrosis will be selected as the reference wound.

It is estimated that 3 patients per week will be recruited across the three centres and that recruitment will take a maximum of 24 months which allows for some under recruitment during holiday periods.

Data analysis

A range of parametric and non-parametric statistical tests will be undertaken as appropriate to determine the progression of the wound healing process. Data recorded during the study will be analysed using an 'intent to treat' analysis.

- Differences in the time to debridement will be analysed using Life Table Analysis
- Differences in the reduction of wound size in the two groups will be analysed using Mann-Whitney T-test
- Changes in respect of odour, pain and bacterial load from baseline to end of debridement and end of debridement to week 4 in the two arms of the study will be compared with a Mann-Whitney T- test. Unadjusted p values will be reported, but that

the effect of multiple comparisons will be considered in the interpretation of the results.

- Differences in the incidence of complications when using sugar dressing compared to that of current methods
- Cost of using the sugar dressing to that of current methods will be contrasted. This is an additional study to be undertaken by an student undertaking MSc in Health Economics
- The EQ-5D measurements will be used to facilitate the construction of QALYs.

Procedure

All patients in the study will be assessed on admission to the study, weekly until debridement is complete and monitored daily using TELER indicators. Thereafter participants will be followed weekly until 4 weeks is completed.

Initial assessment

- Assess wound bed and of surrounding skin
- Measure and record wound size using a disposable clinical ruler
- Record amount and type of exudate
- Complete EQ-5D Quality of Life Questionnaire
- Collect wound swabs for M C & S
- Take Photograph of wound
- Use TELER indicators to record odour, pain, and exudate

Weekly assessments

- Assess wound bed and status of surrounding skin
- Measure and record wound size
- Collect wound swabs for M C & S until debridement complete
- Take Photograph of wound
- Use TELER indicators to record odour, pain, and exudate

Final assessment at 4 weeks

- Assess wound bed and status of surrounding skin
- Measure and record wound size
- Take Photograph of wound
- Use TELER indicators to record odour, pain, and exudate

Dressing procedure: Table 2.

Experimental group	**Control group**
Assess wound and record on wound pro-forma	Assess wound and record on wound pro-forma
Take wound photograph	Take wound photograph
Collect wound swab	Collect wound swab
Measure wound with clinical ruler	Measure wound with clinical ruler
Use TELER indicators to record **Odour, Pain,** and **Exudate**	Use TELER indicators to record **Odour, Pain**, and **Exudate**
Clean wound with normal saline and dab dry with sterile gauze	Clean wound with normal saline and dab dry with sterile gauze
Apply granulated sugar on the wound covering all areas	Apply current product used according to dressing formulary and trust policy
Apply dressing pad and secure appropriately	Apply pad or alternatives and secure appropriately

Ethical issues

Ethical approval was granted from the North Birmingham and Solihull local research and ethics committee prior to commencing the study. Ethical principles laid down in the NHS Research Governance framework will be adhered to. The researcher has an honorary contract with the UHBNHSF trust. Full informed consent procedures will be followed. Prospective participants will be given time to read the information about the proposed trial prior to inviting them to take part. The researcher is aware of the diversity of the population to be studied and the need for an informed decision to take part in the study. The trust has a robust and effective interpretation services that the researcher will use if there is language barrier. All prospective participants will be asked to sign consent form.

Patients will be informed of their right to withdraw from the study at any time. Confidentiality of data, subjects and study settings will be maintained throughout this study in accordance with the Data Protection Act (Great Britain Parliament 1998). Anonymous data will be stored at the research centre (the University Hospital Birmingham NHS Foundation Trust (UHBNHSFT) Research and Development offices) on a computer with a protected password. Hard copies of data will be stored in a locked facility at the centre and the keys kept in a safe supplied by the Research and Development Supervisor. Following completion of the study all data will be kept securely according to the UHB NHS FT Research and Development protocol.

Reference List

Adam, J. Singer, MD. Steve, A. Mcclan, MD (2002) Persistent wound infection delays epidermal maturation and increases scarring in thermal burns. *Wound repair and generation Vol. 10 No.6 372-377*

Archer HG., Barnett S., Irving S., Middleton KR., Seal DV (1990) A controlled model of moist wound healing: comparison between semi-permeable film, antiseptic and sugar paste. *Journal of Experimental Pathology 75: 155-70*

Argen, MS. Steenfos, HH, Dabelsteen, S. Hansen, JB. Dabelsteen, E (1999) Proliferation and mitogenic response to PDGF-BB of fibroblasts isolated from chronic leg ulcers is ulcer-dependent. *Journal of Investigative Dermatology Vol. 112:463-9*

Booth, S. (2004) Are honey and sugar paste alternatives to topical antiseptics? *Journal of Wound care Vol. 13: 1, 31-33.*

Browne N, Grocott P, Cowley S, Cameron J, Dealey C, Keogh A, Lovatt A, Vowden K, Vowden P (2004b) Woundcare research for appropriate products (WRAP) validation of the TELER method involving users. *International Journal of Nursing Studies,* **41:** 559-571

Calman, K.C (1984) Quality of life in cancer patients – an hypothesis. Journal of Medical Ethics. September 1;10 (3): 124-127

Cook, H, Davies, KJ, Harding, KG, Thomas, DW (2000) Defective extracellular matrix reorganisation by chronic wound fibroblasts is associated with alterations in TIMP-1, TIMP-2 activity. *Journal of Investigative Dermatology Vol. 115:225-33*

Dealey, C. (1994) *The care of wounds*. Blackwell Scientific Publications

Dumville JC, Worthy G, Soares MO et al (2009) VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. Heath technology Assessment, 13 (55)

Franks, P and Moffatt, C (2007) Leg Ulcers in Smith and Nephew Foundation (2007) *Skin breakdown The Silent epidemic.*

Gethin, G. Seamus C. (2008) Manuka honey vs hydrogel – a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. *Journal of Clinical Nursing Vol. 18: 466-474*

Grocott P. Cowley S. (2001) The palliative management of fungating malignant wounds--generalising from multiple-case study data using a system of reasoning. International Journal of Nursing Studies. 38(5):533-45

Great Britain Parliament (1998) *Data Protection Act 1998. London:HMSO*

Hasan A, Murata H, Falabella A, Ochoa S, Zhou L, Badiava E, Falanga V. (1997) Dermal fibroblasts from venous ulcers are unresponsive to action of transforming growth factor-beta. *International Journal of Dermatology ScienceVol. 16:59-66*

Herszage, L. et al (1980) Tratamiento de las heridas su

Jones MA, Song B, Thomas DM. (2004) Controlling Wound Healing through Debridement Elsevier Science Direct Vol. 40:1057-1064

Lazarus GS, Cooper DM, Knighton DR (1994) Definitions and guidelines for assessment of wounds and evaluation of healing. *Archives of Dermatology Vol. 130:489-493*

Le Roux, A A (1993) " TELER: The Concept" *Physiotherapy*, 79, 11, pp 755-58

Marcan, S (2003) Test-retest performance of EQ-5D. In: Brooks R, Rabin R, de Chario F, editors. The measurement and valuation of health status using EQ-5D: a European perspective, Dordrecht: Kluwer Academic Publishing Publishing. 43-54

Matthews, K.A and Binnington, A.G (2002) Wound management using sugar. *In Compedium for Continuing Education. Vol. 24: (1) 41-50*

Mphande, A.N.G, Kilowe, C., Phalira, S., Jones, H.W. and Harrison, W.J. (2005) Effects of honey and sugar dressings on the wound healing.

Metcalfe A, Dealey C, Hallowell T, Stubbs R (2008) Validating a new instrument to improve wound measurement. *Nursing Times, 104 (16) 30-31*

Murandu, M, Webber, M.A, Simms, M.H and Dealey, C (2011) Use of granulated sugar therapy in the management of sloughy or necrotic wounds: a pilot study. *Journal of wound care Vol. 20 206-216*

Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K, Romanelli M, Stacey MC, Teot L, Vanscheidt W. (2003) Wound bed preparation: a systematic approach to wound management. *Wound repair Regeneration Vol. 11:1-28*

Schultz GS, Barillo DJ, Mozingo DW, Chin GA. (2004) Wound bed prepation and a brief history of TIME. *International Wound Journal Vol. 1:1:19-32*

Sibbald RG, Williamson D, Orsted HL, Campbell K, Keast D, Krasner D, Sibbald d. (2000) Preparing the wound bed – debridement, bacterial balance and moisture balance. *Ostomy Wound Manage. Vol. 46:14-35*

Steenvoorde P, Jacobi C, Van Doorn L, Oskam J. (2007) Maggot debridement therapy of infected ulcers: Patient and wound factors influencing outcome- A study on 101 patients with 117 wounds. *Annals The Royal College of Surgeons of England Vol. 89:6:596-602*

Tanner AG. (1998) Successful treatment of chronically infected wounds with sugar paste. *European Journal of Cilinical Microbiology and Infectious Diseases 7: 524-5*

Tophan J (2000) Sugar for wounds. Journal of Tissue Viability Vol. 10:3: 86-89

Trouillet, J.L. et al (1985) Use of granulated sugar in treatment of open mediastinitis after cardiac surgery, *Lancet; 2, 180-183.*

Willix, D.J., Molan, P.C. and Harfoot, C.G. (1992) A comparison of the sensitivity of wound-infecting species of bacteria to the antibacterial activity of manuka honey and other honey. *Journal of Applied Bacteriol 73: 388-394.*

The EuroQol Group (1990) EuroQol – a new facility for the measurement of health-related quality of life. Health Policy, 16 (3) 199-208

Appendix 10: Patient' Questionnaire

Patient Name: _____

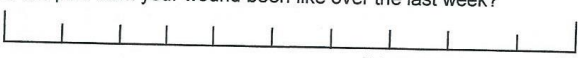
Hospital Number: _____

Ward: _____
(or affix Patient Label)

Wound Symptoms Self-Assessment Chart

1.

- What has the pain from your wound been like over the last week?



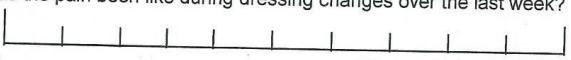
No pain — Worst pain I can imagine

- How much has pain from your wound interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

2.

- What has the pain been like during dressing changes over the last week?



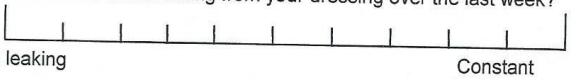
No pain — Worst pain I can imagine

- How much has pain during dressing changes interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

3.

- How often has fluid been leaking from your dressing over the last week?



No fluid leaking — Constant leaking

- How much has fluid leaking from your dressing interfered with your life over the last week?

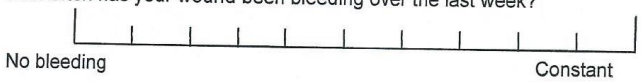
1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

(Adapted from Wayne Naylor 2000)

Page 1 of 4

4.

- How often has your wound been bleeding over the last week?



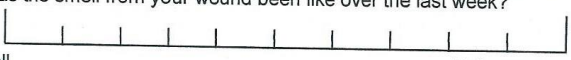
No bleeding — Constant bleeding

- How much has bleeding from your wound interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

5.

- What has the smell from your wound been like over the last week?



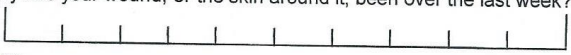
No smell — Unbearable smell

- How much has the smell from your wound interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

6.

- How itchy has your wound, or the skin around it, been over the last week?



No itching — Unbearable itching

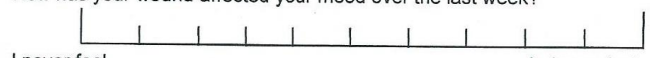
- How much has fluid leaking from your dressing interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

(Adapted from Wayne Naylor 2000)

13.

- How has your wound affected your mood over the last week?



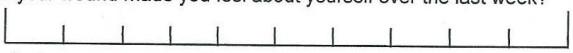
I never feel Depressed — I always feel Depressed

- How much has your wound interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

14.

- How has your wound made you feel about yourself over the last week?



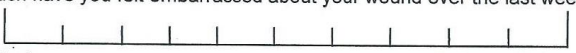
I always feel happy with myself — I always feel unhappy with myself

- How much have your feelings about yourself interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

15.

- How much have you felt embarrassed about your wound over the last week?



I never feel embarrassed — I always feel embarrassed

- How much has feeling embarrassed about your wound interfered with your life over the last week?

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

(Adapted from Wayne Naylor 2000)

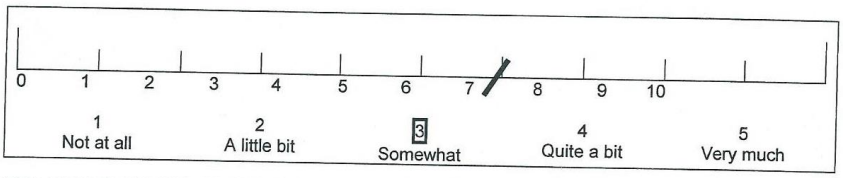
Appendix B: Sample of the Symptom Evaluation Grid

WoSSAC Symptom Evaluation Grid

INSTRUCTIONS FOR USE
Fill in the Grid for each symptom once the patient has completed the self-assessment chart. For severity record the level by counting the number of lines from left (0) to the patient's mark and then colour in an equal number of blocks. Record the level of interference (circled number) in the box below the severity scale (see example)

Patient Name: _____
Hospital Number: _____
Ward: _____
(or affix Patient Label)

Example



EXAMPLE	DATE	0/00
	Severity	
	Interference	3

	DATE	
1. PAIN FROM WOUND	Severity	
	Interference	
2. PAIN DURING DRESSING CHANGE	Severity	
	Interference	
3. LEAKAGE OF EXUDATE	Severity	
	Interference	
4. BLEEDING FROM WOUND	Severity	
	Interference	
5. SMELL FROM WOUND	Severity	
	Interference	
6. ITCHING RELATED TO WOUND	Severity	
	Interference	

(Adapted from Wayne Naylor 2000)

Appendix 11: Nurses Questionnaire**.**

Healthcare Professional Satisfaction Questionnaire

Please help us improve our product by answering some questions about the use of granulated sugar on exudating wounds you have been using for the past three weeks.
We are interested in your honest opinion, whether they are positive or negative. Please answer all of the questions. We also welcome your comments and suggestions.
Thank you very much we really appreciate your help.

Circle Your Answer

1 How many years of nursing experience do you have?

5	4	3	2	1
Less than a year	2-5 years	5-10 years	10-20 years	More than 20 years

2 How would you rate the usefulness of granulated sugar on exudating wounds?

4	3	2	1
Excellent	Good	Fair	Poor

3. Did you find it easy to use granulated sugar on exudating wounds?

1	2	3	4
No, definitely not	No, not really	Yes, generally	Yes, definitely

4 To what extent has our training and support met your needs?

4	3	2	1
Almost all of my needs have been met	Most of my needs needs have been met	Only a few of my needs have been met	None of my needs have been met

5 If a ward were in need of similar product, would you recommend this product to that ward?

1	2	3	4
No, definitely not	No, not really	Yes, generally	Yes, definitely

6 How satisfied are you with the use of granulated sugar on exudating wounds?

1	2	3	4
Quite dissatisfied	Indifferent or mildly Dissatisfied	Mostly satisfied	Very satisfied

7. Have granulated sugar helped you deal with exudating wounds more effectively?

4	3	2	1
Yes, it helped a great deal	Yes, it helped somewhat	No, it really didn't help	No, it seemed to make things worse

8. In an overall, general sense, how satisfied are you with the use of granulated sugar on exudating wounds?

4	3	2	1
Very satisfied	Mostly satisfied	Indifferently or mildly dissatisfied	Quite dissatisfied

9. If you were to have chronic exudating wounds would you use granulated sugar again as your choice of treatment?

1	2	3	4
No, definitely	No, I don't think so	Yes, I think so	Yes, definitely

Any comments or suggestions?

Appendix 12: Operational definitions

Operational Definitions for Wound Types and Associated Terminology

Wound

Is defined by Schultz (1999) as a disturbance in the normal anatomy and function; tissue injury resulting in the loss of continuity of epithelium with or without the loss of underlying connective tissue.

Acute Wounds

Acute wounds can be defined as wounds of sudden onset and of short duration

Dehiscent surgical wounds

Dehiscence means the breaking down, or splitting open, of all or part of a wound

Chronic Wounds

Chronic wounds are defined as wounds, which have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity over a period of 3 months (Mustoe et al, 2006).

Pressure Ulcers

A pressure ulcer is localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers; the significance of these factors is yet to be elucidated (NPUAP/EPUAP, 2009)

Leg Ulcers

An ulcer on the leg and below the knee which has been present more than 8 weeks

Diabetic Foot Ulcers

Ulceration of the foot as a complication of diabetes mellitus

Granulation

A transitional substance that replaces the fibrin/fibronectin matrix, that begins to appear after about 4 days following injury.

Debridement

The process of clearing wound, of necrotic tissue and bacteria leaving it with a clean surface that will heal relatively easy.

Wound Healing

Is defined by the Wound Healing Society as a “complex dynamic process that results in the restoration of continuity and function” (Lazarus et al 1994).

Appendix 13: EQ-5D Questionnaire

Quality of Life Health Questionnaire: EQ-5D

Health Questionnaire

English version for the UK

Title of the Study: *A randomised controlled trial to investigate the clinical and cost-effectiveness of sugar dressing with standard treatment in the management of exudating(Weeping) wounds.*

Thank you for agreeing to take part in this Health Questionnaire today. Please kindly answer the questions as requested below, **By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.**

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

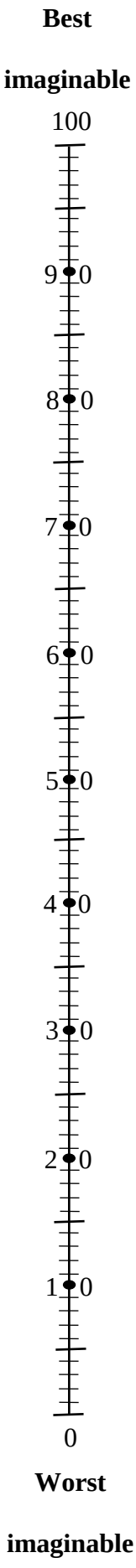
I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own

health state

Thank You for completing this Health Questionnaire today.

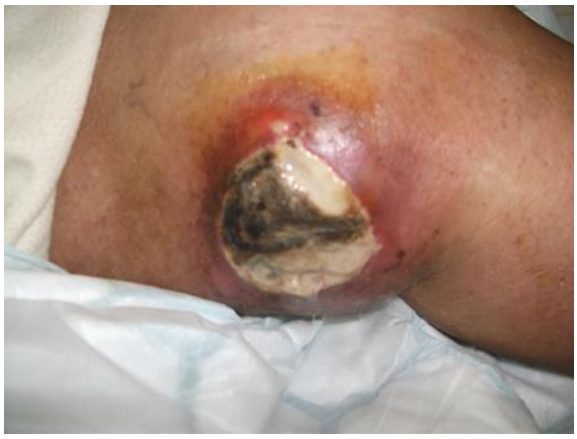
Appendix 14: Wound dressing procedure

Wound dressing procedure:

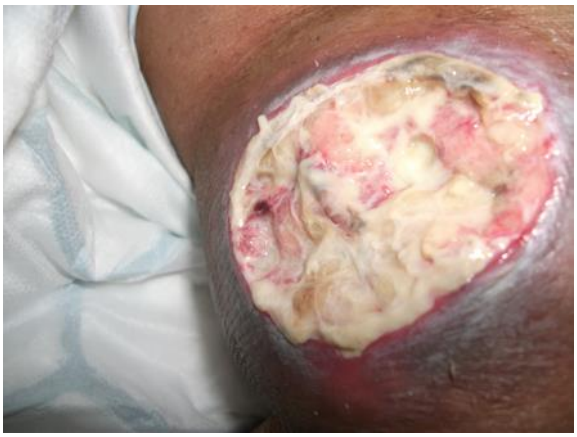
- *Half-filled bowl with lukewarm water*
- *Soaked wound in the water if wound was on the foot and washed surrounding area*
- *Washed the wound and surrounding area if unable to soak; wounds such as sacral pressure ulcers*
- *After soaking and washing; rinsed all wounds with normal saline or clean tap water*
- *Dabbed dry the wound with sterile gauze and surrounding area with a clean towel*
- *Applied yellow paraffin or ordinary Vaseline around the wound area to hold the excess sugar*
- *Dust gently the granulated sugar on the wound until the wound is fully covered with no visible open area (approximately 0.1-0.2cm thickness of granulated sugar)*
- *Applied gently a dressing pad over the sugar*
- *Secured the pad and sugar with surgical tape and bandage*

Appendix 15: Wound images treated with sugar

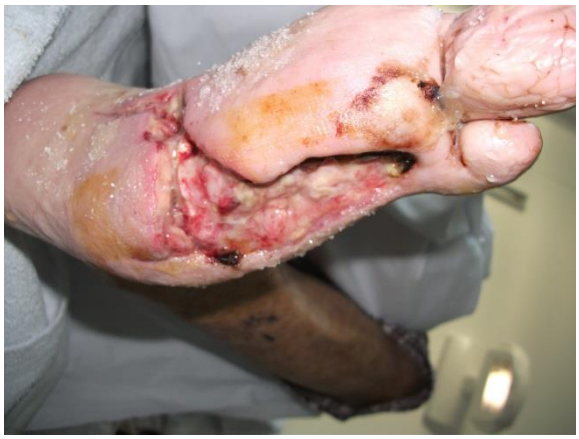
FIGURE(S) – A SELECTION OF RCT WOUND SAMPLES TREATED WITH SUGAR



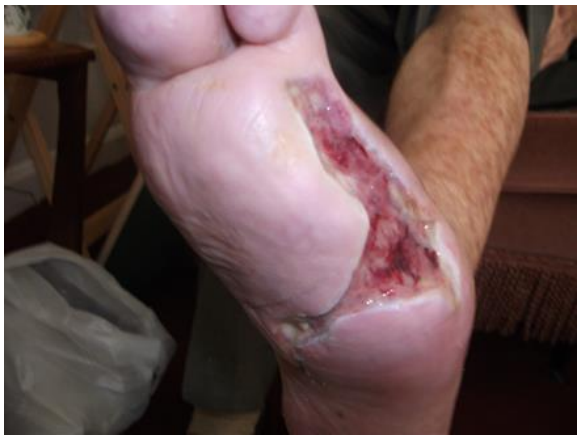
A1- Abcess (before treatment)



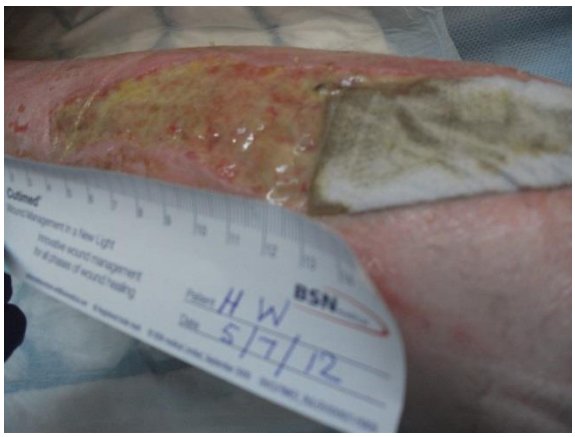
A1 – (after 14 days of sugar treatment)



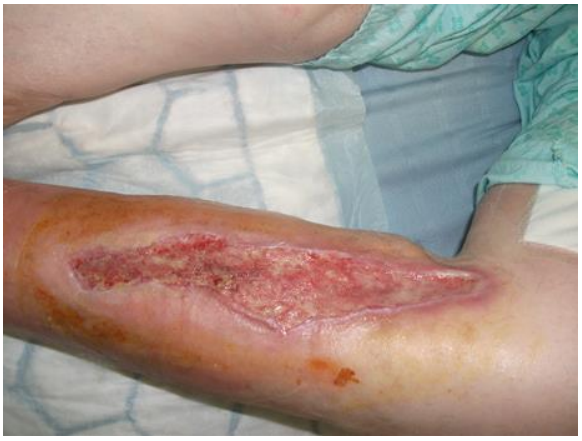
B1- Toe amputee (before treatment)



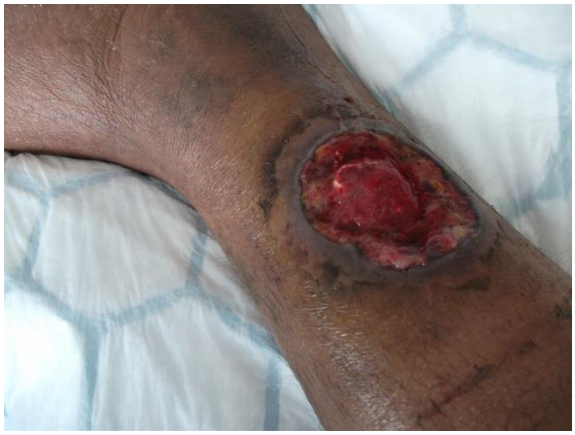
B1- (after 14 days of sugar treatment)



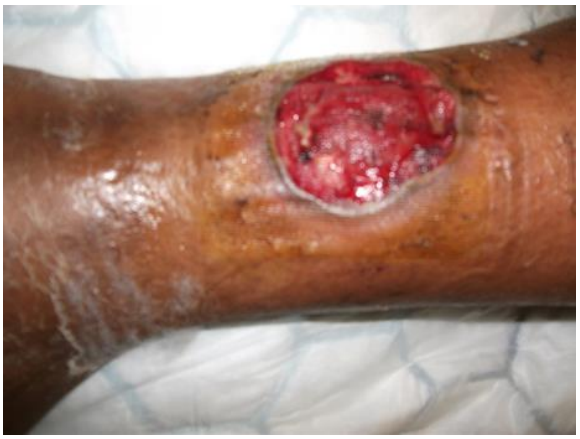
C1 – Surgical wound (before treatment)



C1- (after seven days of sugar treatment)



D1 – Ulcer (before treatment)



D1- (after seven days of sugar treatment)

Appendix 16: Media publications

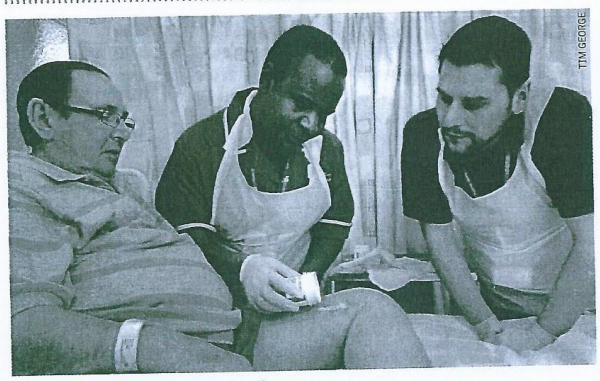
What's on

News in brief

The sweetest healing

Picture: Jacqui Fletcher, Herve Le Lous Board Member, Senior Lecturer at the University of Wolverhampton Moses Murandu and cricketer Darren Gough.

Pioneering lecturer wins £25,000 grant



TIM GEORGE

Early success for sugar treatment

Granulated sugar may be effective in healing wounds quickly and relieving pain, according to a nurse leading a study at the University of Wolverhampton.

Senior lecturer in adult nursing Moses Murandu (pictured, centre, with Charlie Moss, right, and patient Alan Bayliss) is researching the effects of sugar in treating patients' wounds such as pressure ulcers, leg ulcers and amputation sites.

Appendix 17: Academic publications

practice

Use of granulated sugar therapy in the management of sloughy or necrotic wounds: a pilot study

• **Objective:** To determine the *in vitro* antimicrobial efficacy of three types of sugar and conduct a pilot clinical study with a view to developing a protocol for a randomised controlled trial (RCT).
• **Method:** In the *in vitro* studies three types of granulated sugar (Demerara, granulated beet sugar and granulated cane sugar) were tested to determine their minimum inhibitory concentrations (MICs) against 18 Gram-negative and Gram-positive bacteria in a micro-titre broth dilution assay; growth inhibition of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* in different concentrations of sugar (0.38–25%) was also tested over 12-hours in an agar diffusion assay. The pilot clinical study selected patients from a vascular surgical ward and a vascular outpatient department. All had acute or chronic exuding wounds, some of which were infected. White granulated sugar was applied to the wounds. The following parameters were assessed: surface area; wound characteristics including pain, malodour, appearance (slough/granulation); exudate level; pain level and bacterial load. Patients with diabetes had their blood sugar levels checked daily. All patients completed a short health questionnaire at the start and end of the study. Staff completed a satisfaction questionnaire at the end of the study. The study period was 21 days.
• **Results:** *In vitro* tests demonstrated that sugar inhibits bacterial growth. All three types of sugars had MICs ranging from 6–25% in the bacterial strains tested. The diffusion tests showed that strains were able to grow well in low concentrations of sugar but were completely inhibited in higher concentrations. The two granulated sugars were found to be slightly more effective than Demerara sugar, so the latter was excluded from the clinical pilot study. Twenty-two patients (20 inpatients and two outpatients) with sloughy or necrotic wounds were recruited into the clinical study. Two patients had MRSA and two had *Staphylococcus* colonisation at baseline. Blood sugar levels remained stable in the seven patients with insulin-dependent diabetes mellitus. All wounds were clean/debrided in a mean of 11.13 days. Pain and malodour reduced markedly. Patient and staff surveys revealed overwhelming support for the sugar therapy.
• **Conclusion:** The pilot study achieved its aim of developing a protocol for a RCT. Preliminary data suggest that sugar is an effective wound cleansing and is safe to use in patients with insulin-dependent diabetes. *In vitro* studies demonstrate that sugar inhibits bacterial growth.
• **Conflict of interest:** None.

sugar; wound cleansing; patient and staff perceptions

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M.H. Simms,[3] MBBS, FRCS Consultant Vascular Surgeon;
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continued on page 208

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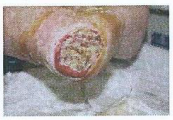
The use of granulated sugar to treat two pressure ulcers. A case report

09/11/09 | Pressure ulcers | Moses Murandu, Carol Dealey



This case reports presents the management of a patient with two infected pressure ulcers, one on the heel and one on the sacrum, using a granulated sugar dressing.