Comparison of healing rates in diabetes-related foot ulcers with low frequency ultrasonic debridement.

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ABSTRACT

Diabetes is one of the most prevalent non-communicable diseases globally and the associated complications of the condition are responsible for major causes of early death in most countries. Foot ulceration is one such complication that is complex and multifactorial and can lead to hospital admission and amputation. Debridement is considered fundamental in managing diabetes-related foot ulcers. This treatment is required to remove non-viable tissue from the ulcer and its surrounds to reduce the chance of infection developing and to stimulate new tissue growth, which promotes healing. Different methods of debridement are available however there is limited evidence around the efficacy and cost effectiveness of each technique. This study aimed to investigate non-surgical sharps debridement, which is considered to be standard practice due to its ease of use and low cost, and low frequency ultrasonic debridement a newer treatment that is more expensive and requires more time and a specialised skill set to perform.

Research aims:

The aim of this research is to determine the clinical efficacy, cost effectiveness and infection control impacts of using low frequency ultrasonic debridement in the treatment of diabetes-related foot ulcers.

Research overview:

This thesis reports the findings from two research projects that were undertaken to address the research aim.

PROJECT ONE

The primary aim of the first project was to establish the degree and extent of microbial spread during the use of low frequency ultrasonic debridement and to determine what infection control risks this technology poses to the clinical environment.

PROJECT TWO

The primary aim of the second project was to determine if there is a difference in healing rates of diabetes-related foot ulcers using non-surgical sharps debridement compared with low frequency ultrasonic debridement. Secondary aims of this research included:

- To determine if there is a difference in pain during and after treatment between low frequency ultrasonic debridement and non-surgical sharps debridement
- To determine if there is a difference between the quality of life of people receiving treatment with low frequency ultrasonic debridement or non-surgical sharps debridement
- To determine if there is an overall cost difference between low frequency ultrasonic debridement and non-surgical sharps debridement

This was a randomised clinical efficacy trial undertaken in a metropolitan health service, primarily the acute care setting including inpatient and ambulatory care services. Participants in this research were people with a chronic diabetes-related foot ulcer, being treated by a podiatrist and who met the study criteria.

OVERVIEW OF THESIS CHAPTERS

This thesis is presented as a series of manuscripts that have been published or submitted to peer reviewed journals for publication. Additional information has been provided in the form of introductory and supplementary chapters to allow for a cohesive explanation of the study. The first chapter begins with an explanation of the global burden of diabetes leading into further details outlining diabetes-related foot disease, its aetiology and management.

Chapter 2 presents a systematic review that was published in Journal of Ostomy Wound Management.

Chapter 3 presents an overview of project one and includes the research paper published in The American Journal of Infection Control.

Chapter 4 presents an overview of the study protocol for project two and includes the research paper published in The Journal of Foot and Ankle Research.

Chapter 5 presents a summary of the main findings from this research and the implications of these findings. This chapter includes a discussion around strength and weaknesses of the thesis and recommendations for future research and includes the research paper published in BMC Research Notes.

Chapter 6 presents the economic evaluation undertaken as part of project two with a discussion around the impacts on clinical practice when utilising these therapies. The research paper that is currently under submission in Diabetes Care, has also been included.

The final chapter presents an overview of this thesis summarising and integrating the results of both studies with previous literature and proposes a treatment philosophy for clinicians managing diabetes-related foot ulcers.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the published thesis.

Name: Lucia Michailidis

Date: 30/01/2019

ABBREVIATIONS

CFU	Colony forming unit
CHS	Community Health Service
CW	Cylie Williams
DK	Despina Kotsanas
DFU	Diabetes-related foot ulcer
DRFU	Diabetes-related foot ulcer
DRG	Diagnoses Related Group Code
EO	Elizabeth Orr
GC	Georgia Coombes
HBA	Horse Blood Agar
LFUD	Low Frequency Ultrasonic Debridement
LM	Lucia Michailidis
MBS	Medicare Benefits Scheme
mmHg	Millimetres of mercury
NSSD	Non-Surgical Sharps Debridement
PBS	Pharmaceutical Benefits Scheme
PPE	Personal Protective Equipment
OP	Outpatient
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
SB	Shan Bergin
TBSD	Theatre-Based Sharps Debridement
TH	Terry Haines
VAS	Visual Analogue Scale

THESIS INCLUDING PUBLISHED WORKS DECLARATION

I hereby declare this this thesis contains no material which has been accepted for the awarded of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes four original papers published in peer reviewed journals and one submitted publication. The core theme of the thesis is the evaluation of low frequency ultrasonic debridement on chronic diabetes-related foot ulcers. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Faculty of Medicine, Nursing and Health Sciences under the supervision of Professor Terry Haines, Doctor Shan Bergin and Doctor Cylie Williams.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research. In the case of Chapters 2-6 my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Student contribution	Co-authors	Contribution
2	A Systematic Review to Compare the Effect of Low-frequency Ultrasonic Versus Nonsurgical Sharp Debridement on the Healing Rate of Chronic Diabetes-related Foot Ulcers.	Published	70%	Dr. Shan Bergin Prof. Terry Haines Dr. Cylie Williams	10% 10% 10%
3	Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment?	Published	70%	Dr. Despina Kotsanas Ms. Elizabeth Orr Ms. Georgia Coombes Dr. Shan Bergin Prof. Terry Haines Dr. Cylie Williams	5% 5% 5% 5% 5% 5%
4	Comparison of healing rates in diabetes-related foor ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial protocol.	Published	70%	Dr. Cylie Williams Dr. Shan Bergin Prof. Terry Haines	10% 10% 10%
5	Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial.	Published	70%	Dr. Shan Bergin Prof. Terry Haines Dr. Cylie Williams	10% 10% 10%

6	Clinical and cost effectiveness of two debridement methods for management of diabetes-related foot ulcers.	Submitted	70%	Dr. Cylie Williams Dr. Shan Bergin Prof. Terry Haines	10% 10% 10%

Chapter 2

LM, TH, SB & CW conceived and contributed to the study design. LM & SB contributed to the critical review of the literature. LM, CW & TH interpreted the results. LM drafted the manuscript. LM, TH, SB & CW revised the manuscript for important intellectual content. All authors approved current version of the manuscript that has been published.

Chapter 3

LM, TH, SB, CW, DK & EO conceived and contributed to the study design. LM, GC & DK were responsible for data collection. LM, CW, TH & DK interpreted the results. LM drafted the manuscript. LM, TH, SB, CW, DK, EO & GC revised the manuscript for important intellectual content. All authors approved current version of the manuscript that has been published.

Chapter 4

LM, TH, SB & CW conceived and contributed to the study design. LM & CW drafted the manuscript with revision and support from TH & SB. The final manuscript was revised by LM, TH, SB & CW for intellectual content. All authors approved the current version of the manuscript that has been published.

Chapter 5

LM, TH, SB & CW conceived and contributed to the study design. LM was responsible for data collection. LM, CW, TH & SB interpreted the results. LM drafted the manuscript. LM, TH, SB & CW revised the manuscript for important intellectual content. All authors approved current version of the manuscript that has been published.

Chapter 6

LM, TH & CW conceived and contributed to the study design. LM & CW contributed to the data collection. LM, CW & TH interpreted the results. LM drafted the manuscript. LM, TH, SB & CW revised the manuscript for important intellectual content. All authors approved current version of the manuscript that is under review for publication.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

LIST OF PUBLICATIONS

Publications by candidate incorporated into thesis:

PUBLISHED

Michailidis, L., Kotsanas, D., Orr, E., Williams, C., Coombes, G., Haines, T., Bergin, S. Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment? American Journal of Infection Control, 2016, 44(12): 1656-1659.

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Michailidis, L., Bergin, S.M., Haines, T.P., Williams, C.M. A Systematic Review to Compare the Effect of Low-frequency Ultrasonic Versus Nonsurgical Sharp Debridement on the Healing Rate of Chronic Diabetes-related Foot Ulcers. *Journal of Ostomy Wound Management, 2018, 64(9): 39-46.*

Michailidis, L. Bergin, S., Haines, T., Williams, C. Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial. *BMC Research Notes, (2018) 11:732*

UNDER REVIEW

Michailidis, L. Williams, C., Bergin, S., Haines, T. (under review) The minimum economically important difference: Application to comparative effectiveness of different debridement approaches for diabetes-related foot ulcers. (Diabetes Care)

ORAL AND POSTER PRESENTATIONS BY CANDIDATE

ORAL PRESENTATIONS

Michailidis, L., Bergin, S., Williams, C., Haines, T. Low frequency ultrasonic debridement for diabetes-related foot ulcers in the acute hospital, but at what cost? Paper presented at the Diabetes Foot Australia Conference, Gold Coast, Australia September 4 2017.

Michailidis, L., Kotsanas, D., Orr, E., Williams, C., Coombes, G., Haines, T., Bergin, S. Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment? Paper presented at the Wounds Australia National Conference 2016, Melbourne, Australia, 11 November 2016.

Michailidis, L., Kotsanas, D., Orr, E., Williams, C., Coombes, G., Haines, T., Bergin, S. Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment? Paper presented at the European Wound Management Associated Conference 2016, Bremen, Germany, 13 May 2016.

Michailidis, L., Kotsanas, D., Orr, E., Williams, C., Coombes, G., Haines, T., Bergin, S. Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment? Paper presented at the Victorian Allied Health Research Conference 2019, Melbourne, Australia, 22 March 2019.

Michailidis, L., Williams, C., Bergin, S., Haines, T. Investigating the use of low frequency ultrasonic debridement in the treatment of diabetic foot ulcers. Paper presented at the Victorian Allied Health Research Conference 2019, Melbourne, Australia, 22 March 2019.

POSTER PRESENTATIONS

Michailidis, L., Williams, C., Bergin, S., Haines, T. Investigating the use of low frequency ultrasonic debridement in the treatment of diabetic foot ulcers. International Diabetes Federation Diabetes Complications Congress, Hyderabad, India, 25th October 2018.

Michailidis, L., Williams, C., Bergin, S., Haines, T. Comparison of healing rates in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial protocol. Victorian Allied Health Research Conference, Melbourne, Australia, 28 March 2014.

AWARDS

Winner – Innovative Technology and Therapies, Peninsula Health Research Week 2017 "Low frequency ultrasonic debridement for diabetes-related foot ulcers in the acute hospital, but at what cost?"

Winner – Interprofessional Research, Peninsula Health Research Week 2015, “Does the use of low frequency ultrasonic debridement pose and infection control risk to the patient, clinician and environment?”

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On a personal note, I thank my mum, SM, for your inspiration, patience and willingness to help in so many ways. Without your continual support I would not have become the woman I am today, nor had the self-confidence to venture down this path.

To my closest friends, DVC, RB, EH and NP, thank you for listening to me talk about the highs and lows of this journey, for letting me hide away to sneak in those extra few hours of writing and for your constant reminders that I was crazy enough to have started this journey and that I was definitely going to make it to the finish line. Without all of your positivity and encouragement, homemade crepes and indoor picnic sessions it would have been a far more difficult journey.

Finally, this thesis is dedicated to all the participants who agreed to be involved in this project and to the patients who are treated by podiatrists with chronic diabetes-related foot ulcers. I hope this work contributes to further improving the treatment and outcomes of people suffering from this long-term complication of diabetes.

CHAPTER 1 – DIABETES-RELATED FOOT DISEASE

SUMMARY OF CHAPTER

This chapter summarises the global impact of diabetes and then follows with a detailed exploration of diabetes-related foot disease and the complexity of this condition. This chapter also summarises the treatment approach for diabetes-related foot ulcers with a particular focus on debridement, the most commonly provided treatment approach for diabetes-related foot ulceration. Finally, the chapter concludes with a statement of thesis aims and an overview of subsequent thesis chapters.

1.1 BACKGROUND

1.1.1 THE GLOBAL BURDEN OF DIABETES

Diabetes and its complications are rapidly becoming the world's most significant cause of morbidity and mortality. In 2015, there were 415 million adults [1], or one in eleven adults, diagnosed with diabetes globally. It is also thought that in the same year an additional one in two adults was likely to have undiagnosed diabetes [1]. These statistics have superseded predications of prevalence set by The International Diabetes Federation in 2009. It was estimated that the current adult prevalence with diabetes would not be reached until 2030 [2]. It is anticipated over the next 20 years this will rise by more than 50% and that by 2040 over 642 million people will be living with diabetes [1].

Complications associated with diabetes develop gradually and often insidiously and are associated with a duration of diabetes and poor glycaemic control. In almost every high-income country diabetes is ranked among the leading causes of lower limb amputations, renal failure, cardiovascular disease and blindness [1]. In 2015, 14.5% of global mortality was directly related to diabetes-related complications for people aged between 20 and 79 years old [1]. This is equivalent to one death every six seconds and is higher than the combined deaths from malaria, HIV/AIDS and tuberculosis [3]. Depression and a reduced quality of life have also been reported as a common consequence of diabetes. This has been shown to result in compromised ability to self-care, reduced adherence to medical treatment, higher rates of complications and an overall increase in mortality [4].

It is not surprising that there is a substantial economic impact on countries and national health systems with a greater number of people being diagnosed with diabetes and developing complications. Most countries spend between 5% and 20% of their total health expenditure on diabetes [1]. It was estimated that $673 billion USD was spent on treating adults with diabetes in 2015. This was equivalent to 11.6% of total health expenditure worldwide [1].

1.1.2 DIABETES IN AUSTRALIA

Approximately 1 million Australians, or 4.4% of the population, have been diagnosed with diabetes [5]. It is widely acknowledged that the prevalence of diabetes around the world is increasing and this is largely attributed to an aging

population, dietary changes, reduction in physical activity and the concurrent rise in rates of obesity [5]. The projected burden of disease for diabetes in Australia suggests that if there are no changes to the incidence of diabetes by 2025 there could be as many as 3 million Australians living with diabetes [5].

In Australia, diabetes has been ranked in the top 10 leading causes of premature death [5, 6]. In 2005, diabetes and related complications ranked as the eighth most common cause of health-related death in Australia. Over a 10 year period, the ranking has increased to the seventh most common cause of health-related death [6].

Diabetes costs the Australian economy at minimum of $6 billion AUD per year [5]. The average health care costs per person with diabetes greatly increases with the presence of micro-vascular and macro-vascular complications and are also dependent upon the type of diabetes diagnosed. For Australians with complications and type 1 diabetes it is thought to cost $9,645 AUD per person, per year and for type 2 diabetes this value increases to $16,698 AUD [5].

1.1.3 Diabetes-related foot disease

People with diabetes are at a higher risk of developing additional health problems. Foot ulceration is one such complication that people with diabetes commonly develop. The pathophysiology is multifactorial and can be attributed to peripheral sensory where a loss of protective feeling results in injuries to the skin going unnoticed, motor neuropathy where muscles waste and joints stiffen to reduce movement and change normal walking patterns leading to increases in pressure and potential changes to the skin, autonomic neuropathy where skin becomes thinner and more prone to damage, peripheral arterial disease whereby blood vessels narrow or become blocked reducing the amount of oxygen to the skin which may lead to tissue death, and finally foot deformity which results in abnormal pressure loading and increases the risk of tissue damage [7, 8].

The reported frequency of diabetes-related foot ulcers varies, however it is thought that up to 25% of people with diabetes will develop a foot ulcer in their lifetime [9]. It has also been estimated that of the people who develop a foot ulcer, 15% of these will require a lower extremity amputation [1]. Most alarming, is the five year mortality rate of 48% after having had a diabetes-related foot ulcer, which is higher than some cancers, including prostate cancer, breast cancer and Hodgkin's lymphoma [10].

In Australia, diabetes has been acknowledged to be the most common cause of non-traumatic lower limb amputation [5, 11]. Furthermore, acute complications secondary to foot ulceration, including infection, tissue necrosis and failure to achieve healing, have been reported as the leading cause of diabetes-related admissions [12]. For the years 2012-2013 there were 4,402 lower limb amputations provided to patients with a diagnosis of diabetes in Australian hospitals [13]. The estimated acute care cost of a single lower extremity amputation could be as much as $26,700 [12], however this figure does not included costs for rehabilitation, purchase and manufacture of lower limb prosthesis or footwear or time lost from work. Currently, there is no data available in Australia that attribute a cost to people with diabetes and a foot ulcer who do not require admission to hospital or proceed to amputation. However, it has been reported that acute foot complications in people with diabetes could cost as much as $16,700 AUD per year, per person [14].

Given the complications associated with diabetes-related foot ulcers and the time investment required to ensure regular treatment and rapid healing, it is not surprising that lower reduced quality of life is commonly reported in the literature. It has been found that all domains of quality of life can be adversely impacted primary because of a reduction in mobility and the need to modify activities of daily living [15]. Additionally, it is thought that the presence of a foot ulcer imposes restrictions on participation and enjoyment in usual hobbies, which has been shown to correlate with an overall increase in the number of individuals diagnosed with clinical depression [16].

1.1.4 Treatment for diabetes-related foot ulcers and the role of debridement

The primary aim of treatment for diabetes-related foot ulcers is rapid healing in order to reduce the likelihood of associated complications such as soft tissue infection, osteomyelitis and tissue necrosis, all of which can lead to amputation.

Debridement is considered a fundamental component of diabetes-related foot ulcer management [17]. The purpose of debridement is to remove non-viable or foreign material from within, or adjacent to, the ulcer until healthy tissue is exposed [18]. Additionally, by removing this contaminated tissue it reduces pressure on the ulcer base, allows for more thorough assessment of the size and depth of the ulcer, facilitates draining and creates an acute environment all of which facilitate healing [19]. Many different methods of debridement are available to the clinician as identified in a Cochrane review published in 2010 [18, 20]. These methods are described below.

Sharps debridement

A scalpel is used to cut out devitalised tissue from the wound base. Can be performed in an operating theatre (surgical-based sharps debridement) or in a clinical setting (non-surgical sharps debridement) depending on the extent of debridement required [18, 21-23].

Mechanical debridement

Uses wet-to-dry dressings, such as saline soaked gauze, that pull away devitalised tissue from the wound base when changed [18, 21-23].

Autolytic debridement

Achieved through use of wound dressing products that support a moist wound environment, subsequently softening devitalised tissue making it easier to remove from the wound base when the dressing is changed [18, 22].

Biological debridement

Uses sterile larvae or chemical enzymes to breakdown devitalised tissue at the wound base [18, 21-23].

Hydro-debridement

Uses a high pressure water jet at the wound surface to dissect devitalised tissue [23].

Ultrasonic debridement

Uses ultrasound at a low frequency to create micro shock waves to disrupt cells of devitalised tissue during treatment through a liquid medium [23-24].

1.2 THESIS OVERVIEW

This thesis investigates two methods of debridement, non-surgical sharps debridement and low frequency ultrasonic debridement in the management of diabetes-related foot ulcers.

Non-surgical sharps debridement is applied regularly and is recommended as part of standard ulcer care [17]. This technique is regularly used in a clinical setting by podiatrists and vascular surgeons. It involves using a scalpel to remove non-viable tissue from the wound base. Non-surgical sharps debridement is relatively low cost, requires minimal time and equipment and can be performed in a clinic treatment room or hospital ward by skilled a clinician. The time of a single treatment depends on the size of the wound being debrided, however the total session, including time of set up and pack up, full assessment and treatment of the wound, is on average 45 minutes according to anecdotal evidence.

Low frequency ultrasonic debridement is purported to work by delivering a low frequency of ultrasound, or sound waves, through a constant flow of saline causing non-thermal effects at the wound surface; acoustic streaming (a steady mechanical force) and cavitation (formation of gas bubbles in the liquid creating micro-shockwaves). These effects combined are thought to alter cell membrane activity and subsequently have an action of debridement, a bactericidal effect and an ulcer healing stimulator effect. The use of low frequency ultrasonic debridement creates a mist, or aerosolisation of saline. The recommendations around protecting and cleaning the surrounding clinical environment were developed based on laboratory testing [25] and therefore, the effects of its use in the clinical environment are unknown.

This technique is performed in a clinic treatment room as well as in a hospital ward at the bedside by skilled clinicians. The time of a single treatment depends on the size of the wound being debrided, however the total session, including time of set up and pack up, full assessment and treatment of the wound is on average 60 minutes. This technique is more costly than non-surgical sharps debridement with the cost of consumables increasing overall cost to treatment costing $85 AUD. The upfront cost of this unit is $100,000 AUD.

1.3 THESIS AIMS

The thesis is comprised of two studies that aim to:

1. Establish the degree and extent of microbial spread during the use of low frequency ultrasonic debridement (project one)
2. Determine the difference in healing rates of diabetes-related foot ulcers using non-surgical sharps debridement compared to low frequency ultrasonic debridement
3. Determine if there is a difference in pain during and after treatment between non-surgical sharps debridement and low frequency ultrasonic debridement
4. Determine if there is a difference in quality of life measures in individuals receiving treatment with non-surgical sharps debridement versus low frequency ultrasonic debridement

5. Undertake a break even analysis to determine the cost effectiveness of non-surgical sharps debridement and low frequency ultrasonic debridement

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CHAPTER 2 – SYSTEMATIC REVIEW

2.1 PREAMBLE

As outlined in Chapter one, there is limited evidence available around the clinical efficacy, cost effectiveness and environmental impacts of the non-surgical sharps debridement and low frequency ultrasonic debridement, specifically in the management of diabetes-related foot ulcers. A systematic review was conducted to identify the scientific literature that provides an evidence base for use of non-surgical sharps debridement and low frequency ultrasonic debridement.

2.2 PUBLICATION – ARTICLE 1

Michailidis, L., Bergin, S.M., Haines, T.P., Williams, C.M. A Systematic Review to Compare the Effect of Low-frequency Ultrasonic Versus Nonsurgical Sharp Debridement on the Healing Rate of Chronic Diabetes-related Foot Ulcers. *Journal of Ostomy Wound Management, 2018, 64(9): 39-46.*

2.3 DECLARATION FOR THESIS CHAPTER 2

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution
Author	70%

The following co-authors contributed to the work:

Name	Nature of Contribution	Extent of Contribution
Dr. Shan Bergin	Co-author	10%
Prof Terry Haines	Co-author	10%
Dr. Cylie Williams	Co-author	10%

LM, TH, SB & CW conceived and contributed to the study design. LM & SB contributed to the critical review of the literature. LM, CW & TH interpreted the results. LM drafted the manuscript. LM, SB, TH & CW revised the manuscript for important intellectual content. All authors approved the version of the manuscript that has been published.

Declaration by co-authors:

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) There are no other authors of the publication according to these criteria;

(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit

Dr. Shan Bergin	Date: 30/01/2019
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A Systematic Review to Compare the Effect of Low-frequency Ultrasonic Versus Nonsurgical Sharp Debridement on the Healing Rate of Chronic Diabetes-related Foot Ulcers.

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Globally, diabetes is one of the most common noncommunicable diseases. The number of studies describing the epidemiology of diabetes has increased over the last 20 years, and over the past 15 years the global burden estimates of adults living with diabetes has exceeded predictions. In 2000, the International Diabetes Federation[1] estimated 151 million adults were living with diabetes; by 2010, this number was expected to increase to 285 million and estimated to reach 438 million by 2030.[2] The most recent report from the International Diabetes Federation[3] shows the number of adults likely to have diabetes globally in 2015 was 415 million.

According to the Australian Institute of Health and Welfare,[4] people with diabetes may develop complications including peripheral neuropathy, peripheral arterial disease, and foot deformity, which can lead to ulceration, infection, and an increased risk of amputation. One (1) in every 6 people with diabetes in developed countries will have a diabetes-related foot ulcer during their lifetime.[3] According to the International Working Group on the Diabetic Foot,[5] people with diabetes also face a 25 times increased risk of amputation compared to persons without diabetes. Currently, a limb is lost every 20 seconds worldwide as a result of diabetes-related amputation.[3]

Optimal management of these ulcers is vital in preventing lower limb amputation. Treatment routinely involves offloading[6] to redistribute pressure away from the area of ulceration and maintaining a moist wound bed environment[7] to encourage new tissue growth. Additionally, treatment of diabetes-related foot ulcers often involves routine debridement to remove devitalized tissue from the ulcer base. According to guidelines[8] and a systematic review,[9] the process of debridement, regardless of the method applied, is believed to stimulate the inflammatory response and encourage healing. Debridement methods include autolytic debridement using dressings and biological debridement using sterile larvae and chemical enzymes. In addition to these topical agents, mechanical debridement via surgical excision or nonsurgical sharp debridement using either a scalpel or scissors is commonly utilized, according to a Cochrane review[9] and systematic reviews.[10,11]

Contact and/or noncontact, low-frequency ultrasonic debridement (LFUD) offers an alternative to sharp debridement. LFUD generates sound waves ranging from 20 to 40 kHz (undetectable to human hearing), delivered to the ulcer through a liquid medium such as normal saline. According to systematic reviews,[12-14] ultrasound waves have the mechanical effects of cavitation and microstreaming, leading to an increase in cellular activity which, in turn, promotes healing. Specifically, systematic reviews[13,15] of ulcer healing studies also have determined an increase in protein synthesis and an increase in production of growth factors and endothelial cells occurs, all of which stimulate the ulcer toward healing. ***In vitro*** studies[14,16]have found both noncontact and contact LFUD lowers bacterial counts through the mechanical destruction of the bacterial cell wall. An ***in vitro*** study[17] has shown direct-contact LFUD has the added benefit of enhanced fibrinolysis due to an increased intensity of ultrasound; this subsequently leads to ulcer angiogenesis without destroying healthy ulcer tissue.[15]

A Cochrane review[9] on the debridement of diabetes-related foot ulcers included 6 randomized controlled trials; 5 evaluated the effectiveness of hydrogel as a method of debridement against a range of comparators such as combinations of saline dressings and pressure offloading, hydrogel with an additional bacteriostatic action, larval

therapy, and 2 other hydrogel dressings. The sixth trial compared surgical debridement with nonsurgical sharp debridement (NSSD) in addition to relieving the pressure of weight-bearing and providing regular dressing changes. Conclusions from the Cochrane review[9] suggest that although hydrogels increase diabetes-related foot ulcer healing compared with gauze or standard wound care, it is unclear if this effect is directly due to debridement. Additionally, it was noted that randomized controlled trials on debridement for diabetes-related foot ulcers are small in number and of poor methodological quality. The review concluded that while debridement is regarded as an effective intervention to assist healing, more research is needed to evaluate the effects of a wide range of debridement methods and of debridement ***per se***. No subsequent Cochrane review was conducted since its publication, nor a protocol registered for update.

The aim of this systematic review was to compare available evidence on the effectiveness of bedside NSSD via scalpel without using anesthesia versus contact or noncontact LFUD in terms of percentage of ulcers healed for diabetes-related foot ulceration.

Methods

Methodology. The clinical question for this systematic review was generated using the Population Intervention Comparison Outcome[18] (PICO) model for clinical questioning. The question was: In adult patients with chronic diabetes-related foot ulcers, what effect does LFUD have on ulcer healing rates compared to NSSD?

This question was separated into terms to search electronic databases including Ovid, MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health Literature Plus, and the Cochrane Database of Systematic Reviews from the earliest date publications were available in each index until April 2017. Table 1 shows the search terms used. Searches were restricted to human studies and English-language articles.

Table 1: Search strategy built using the PICO question format

PICO Terms	Search Terms	Alternate Terms
Patient	Diabet* foot	Ulcer* Wound* Amp* Chronic
Intervention	"Low frequency ultrasonic debridement"	"Ultrasound assisted wound*" "Ultrasonic therapy" LFUD ultrasono*
Comparison	"Non surgical sharps debridement"	debrid* NSSD
Outcomes	Heal*	Closure

Two (2) authors independently reviewed the title and abstract of all retrieved studies against the eligibility criteria (see Table 2), which specified chronic diabetes-related foot ulcers (>4 weeks' duration) in adults >18 years of age. Publications were excluded if 1) the methods of debridement did not involve comparing LFUD to NSSD, 2) wounds

demonstrated an etiology other than a diabetes-related foot ulceration, or 3) the study involved acute ulcers, ulcers that did not undergo debridement, and diagnostic or dental ultrasound.

Table 2: Inclusion and exclusion criteria for screening titles, abstracts and full texts

Inclusion criteria	Exclusion criteria
Participants: - Adults - 18 years and older - Chronic diabetes-related foot ulcer Intervention: - Low frequency ultrasound debridement contact or noncontact therapy - Non-surgical sharps debridement Outcome measures: - Healing rate	Not a diabetes-related foot ulcer No ulcer / no debridement LFUD/ non-surgical sharps debridement not investigating ulcer healing rates Author opinion Protocols of studies with no outcome data Diagnostic ultrasound Dental ultrasound Acute ulcer or ulcer present less that 30 days Full text articles not published in English

When the 2 authors disagreed regarding study inclusion, a third author helped resolve the issue through discussion. The full text of articles was obtained when the abstract seemed uncertain. Forward and backward searching strategies also utilized the reference lists and Google Scholar citations of articles included within the full text review.

Data extraction. General demographics such as gender, country, age, diabetes type, and method of wound debridement of each participant group were extracted from each included study and tabulated and summarized in Table 3. The primary outcome of interest was healing rates of diabetes-related foot ulcers. The secondary outcome of interest was the percentage of ulcers healed.

Table 3: Summary of included full text studies

First author	Study design	Country	Age combined mean (SD) or range	Sample size	Control treatments	Intervention treatment	Outcome measure	Treatment time frame	Level of evidence
Ennis [24]	Cohort study with historic control	USA	N/A	42	Electrical wound stimulation, therapeutic ultrasound, moist wound dressings, local sharps debridement*	Time according to ulcer size, 3x week, noncontact	% healed, % area reduction, % volume reduction	8 months	4
Ennis [26]	RCT	USA	55(11.6)	133	Local sharps debridement*, moist wound dressings, fixed ankle-foot walker	4 minutes, 3x week, noncontact	% healed	12 weeks	2
Yao [25]	RCT	USA	40-72	12	Local sharps debridement*, offloading, moist wound dressings	5 minutes, 1x week or 3x week, noncontact	% area reduction	5 weeks	2
Amini [27]	RCT	Iran	55.2(9.4)	40	Offloading via total contact cast/felt/boot, antibiotics, surgical sharps debridement	Time according to ulcer size, 1x week, noncontact	Healing rate, % size reduction	6 months	2

* Also known as non-surgical sharps debridement.

All articles included within the review underwent methodological assessment for risk of bias using the quality indicators as outlined by Physiotherapy Evidence Database (PEDro).[19] This scale has 11 indicators to identify any risk of bias. Each indicator was given a score of - if not included, ? if not mentioned, or + if included. According to the PEDro guidelines, criteria 2 to 11 are used for scoring purposes, so a score out of 10 is calculated.

Two (2) authors completed this assessment independently and resolved any disagreements. Articles also were classified into levels of evidence using criteria set out by the Oxford Centre for Evidence-based Medicine.[20] This provides advice on the most appropriate research to guide treatment. Systematic reviews of randomized controlled trials are the highest level of evidence (Level 1), followed by randomized controlled trials (Level 2), nonrandomized controlled cohort/follow-up studies (Level 3), cohort studies and/or case studies (Level 4), and mechanism-based reasoning (Level 5).

Data collection. Primary outcome of percentage of ulcers healed were extracted into an Excel worksheet (Microsoft Excel, version 16.15, Redmond, WA).

Data analysis. Analysis was performed using Stata 13 software (College Station, TX). Random effect meta-analysis was performed where data were available for similar outcomes evaluated in more than 1 study. Authors were contacted to request additional data for studies not reporting sufficient outcome data for inclusion in the meta-analysis; however, no responses were received, thus eliminating 2 of the 4 studies from analysis.

Results

Of the 259 total publications identified using the review search terms after duplicates were removed, 204 titles were determined to be potentially relevant and their abstracts were reviewed. One hundred, ninety-three (193) articles were excluded after reading the abstracts, leaving 11 articles for full text screening. Only 4 articles met the criteria for inclusion in the review. The PRISMA statement lists the reasons for exclusion (see Figure 1).

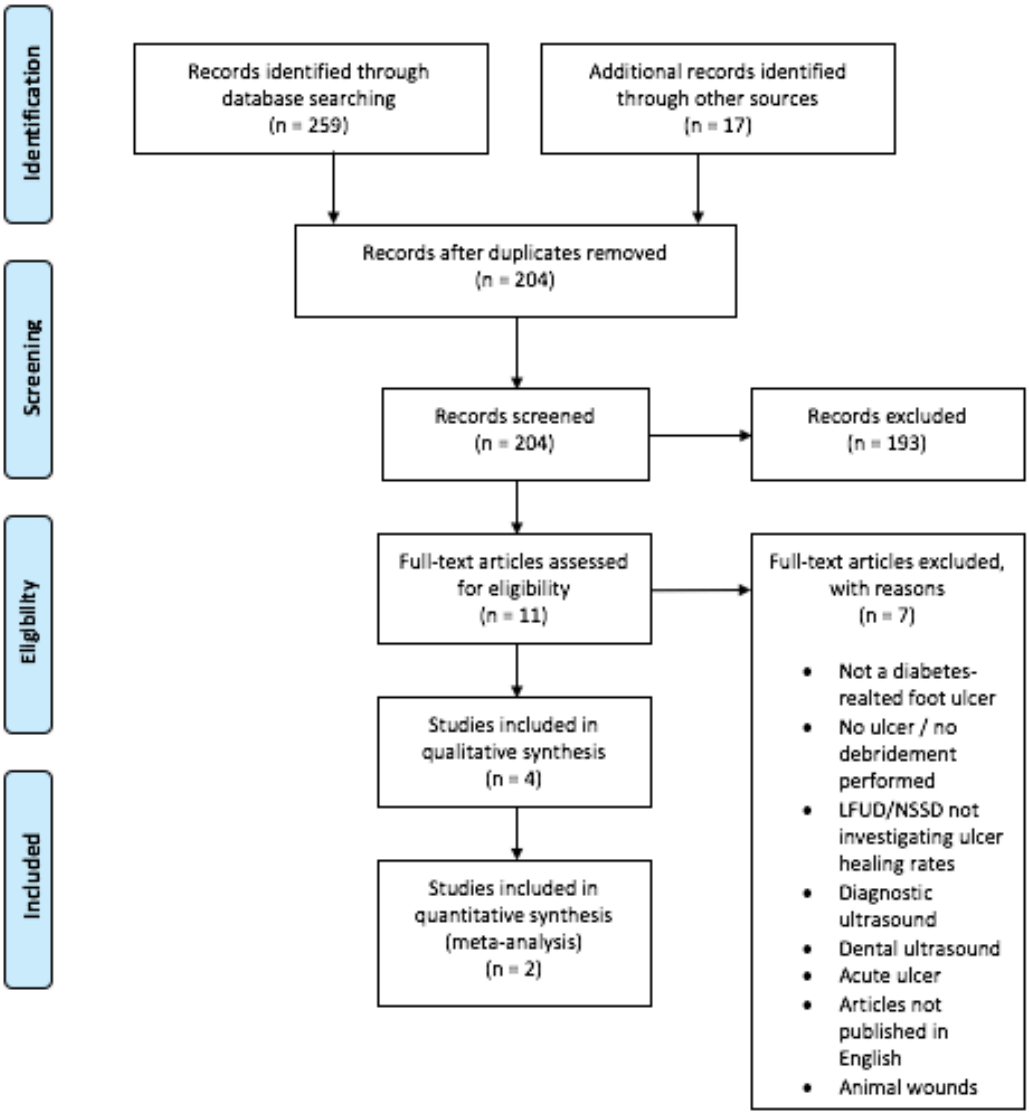

Figure 1: PRISMA diagram showing selection of articles for inclusion in review and pooled analysis

Description of studies. Table 3 provides a summary of the 4 articles included: 3 describe clinical trials involving randomization and 1 used historical data from the same clinic as the control with LFUD as the intervention group. Three (3) of the studies used the MIST® noncontact LFUD (Celularity, Inc, Warren, NJ) with varying debridement times and treatment provided either once or 3 times per week. The fourth study used Sonoca 180® noncontact LFUD (Söring GmbH, Quickborn, Germany) performed once per week with debridement duration calculated based on ulcer total area. The control treatments varied between studies, but all studies included NSSD where required and moist wound dressings. Offloading strategies and other treatment modalities varied between the studies, reflecting the complexity and variability of ulcer management and confounding the validity of pooling these studies. The pooled population included 227 patients ranging in age from 40 to 72 years. The included articles described are for the primary outcome (percentage of ulcers healed).

Meta-analysis/pooling of data. Data extracted included patient demographics, study design and criteria, measurement tool, clinical outcome, and follow-up period. Results from the 2 studies included in the meta-analysis found 30% of the patients in the NSSD groups healed, and 33% in the LFUD groups healed. A meta-analysis was performed on only 2 of the 4 articles; 2 articles had insufficient outcome data, although the current authors attempted to secure the missing data from the original researcher[21,22]in a format that would allow for meta-analysis. Therefore, meta-analysis was performed with 2 articles[23,24] and a total sample size of 173; the analysis did not identify any relationships that suggested a greater effectiveness of either LFUD or NSSD in total healing diabetes-related foot ulcers (RR = 0.92; 95% CI = 0.76-1.11) (see Figure 2).

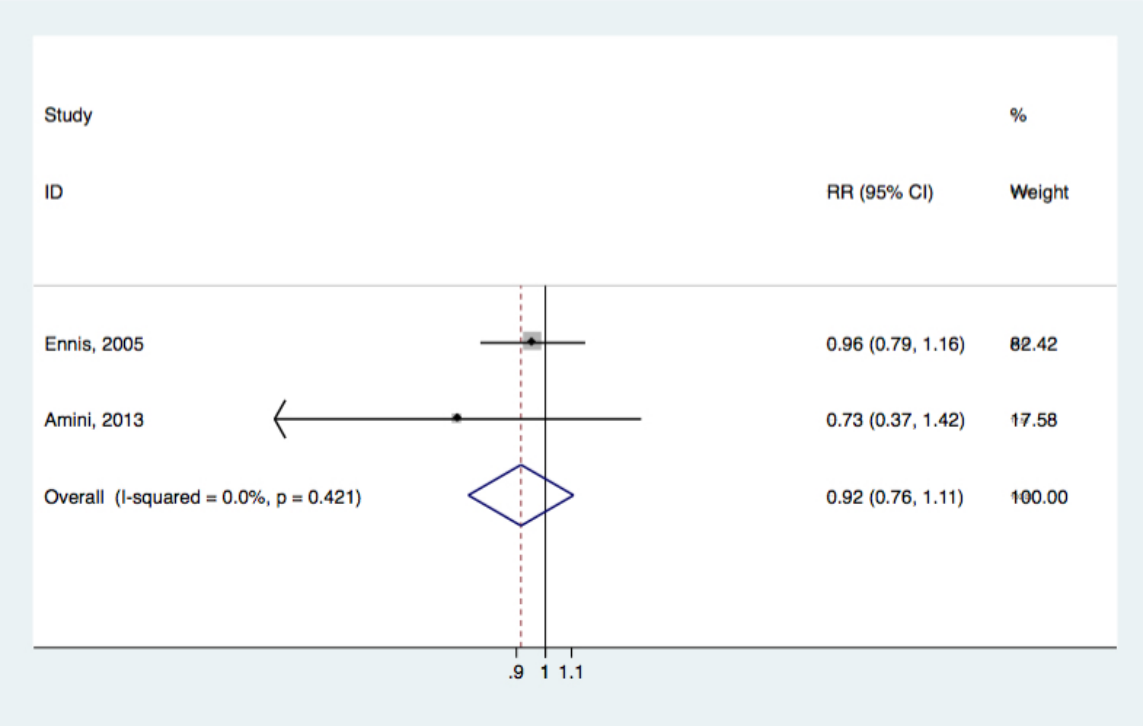

Figure 2: Results from meta-analysis review of two articles

Quality of evidence. Scores of the 4 articles indicated a risk of bias according to the PEDro scale (see Table 4). Three (3) of the studies were randomized controlled trials and the fourth used historical data from the same clinic as the control. Not all criteria on the PEDro scale could be satisfied in these studies (eg, the blinding of participants and clinicians). In 2 of the publications, certain information was not documented and therefore led to a query if the criterion of participant allocation concealment and participants, therapists, and assessors blinding were met. In all 3 randomized controlled trials, participants were randomized to treatment groups and received the allocated treatment or control; these studies also noted between-group statistical comparisons reported for the primary outcome. The 2 studies included in the meta-analysis had a low risk of bias (PEDro score 9/20).

Table 4: Valid measures of methodological quality of clinical trials using PEDro scale

Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Ennis, 2006	+	+	?	-	+	-	+	-	+	+	-
Ennis, 2005	+	-	-	-	-	-	-	+	+	+	-
Yao, 2014	+	+	-	+	-	-	-	+	+	+	-
Amini, 2013	+	+	?	+	?	?	?	+	+	+	+

Column numbers correspond to the following criteria on the PEDro scale:

1 - Eligibility criteria were specified

2 - Subjects were randomly allocated to groups

3 - Allocation was concealed

4 - The groups were similar at baseline regarding the most important prognostic indicators

5 - There was blinding of all subjects

6 - There was blinding of all therapists who administered the therapy

7 - There was blinding of all assessors who measures at least one key outcome

8 - Measure of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups

9 - All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”

10 - The results of between group statistical comparisons are reported for at least one key outcome

11 - The study provides both point measures and measure of variability for at least one key outcome

+ Indicates the criterion was clearly satisfied

- Indicates that it was not

? Indicates that it is not clear if the criterion was clearly satisfied

Discussion

This review identified that available evidence is insufficient to determine whether LFUD or NSSD provides better outcomes in the treatment of diabetes-related foot ulcers. A total of 110 participants that were provided LFUD was compared to 117 participants treated with NSSD within the same studies. Devices that deliver LFUD are available with varying applications (contact vs. noncontact) that influence the ultrasound intensity delivered to the ulcer. Much variation also was evident in the examined studies in the application time for LFUD as well as the frequency of debridement with treatments, ranging from 3 times per week to once per week. Interim therapy also was a confounding factor.

It is important to establish whether LFUD is more effective than NSSD to justify its use in clinical practice. Without high-quality evidence supporting the use of LFUD in the treatment of diabetes-related foot ulcers, clinicians using this technology must rely on expert opinion and guidance from the manufacturer. In the current authors' experience, the different application methods and settings are recommended based on limited research available; clinicians are faced with the potential to be under- or overutilizing this therapy.

This review demonstrated a relative paucity of evidence supporting the use of LFUD as an alternative to NSSD. Use of NSSD for the management of diabetes-related foot ulcers is recommended in several guidelines,[5,8] which is why it was considered in this study an appropriate standard for comparison in this review.

Limitations

It is a limitation of the scope of this review that the effectiveness of NSSD alone was not considered. In addition, the variety of outcome measures among the 4 studies included in this review (percentage of ulcers healed, reduction in ulcer size/volume) made comparisons across the studies difficult. Ideally, a uniform set of outcomes and time points of collection would be reported in the literature to enable pooling across studies. Also, no studies that investigated the use of contact LFUD were found; therefore, the effects of contact versus noncontact LFUD cannot be reported. This was variable outside the study question should other authors wish to undertake further research in this area. Finally, the control groups for all 4 studies were significantly varied. In 3 of the 4 studies, offloading with footwear, orthotics, or padding was not standardized, including the 2 studies in the meta-analysis. Mechanical offloading is known to be vital in managing diabetes-related foot ulcers and plays a large role in healing outcomes,[30]but in this research the variety of offloading approaches was a confounding factor. Finally, other important outcomes such as pain, cost, and provider variables were not considered.

Conclusion

A diabetes-related foot ulcer is a common complication of diabetes that is often a primary cause of hospital admission. LFUD and NSSD are used to manage diabetic foot ulcers, whereby clinicians observe an immediate reduction in nonviable tissue which is believed to facilitate healing. The results of this study showed no difference in healing rates between LFUD and NSSD. More rigorous randomized controlled trials with long follow-up periods and an adequate

sample size are needed to identify whether debridement aids the healing of diabetes-related foot ulcers and if so, which is the optimum method when used as an adjunct with best practice ulcer management.

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CHAPTER 3 – INFECTION CONTROL RISKS ASSOCIATED WITH THE USE OF LOW FREQUENCY ULTRASONIC DEBRIDEMENT

3.1 PREAMBLE

Low frequency ultrasonic debridement uses sound waves conducted through saline to debride non-viable ulcer tissue. During operation the unit produces an airborne mist which theoretically, could carry an increased number of microbes into the surrounding environment thereby posing an infection control risk to the patient, clinician and clinical environment. Low frequency ultrasonic debridement, delivered via Sonoca 185®, can be performed with or without an additional attachment that provides suction to reduce the airborne mist. Research investigating the spread of aerosolised microbes when using low frequency ultrasonic debridement is lacking. The only existing study sought to investigate the level of bacterial air contamination with use of the Versajet™ which provides a type of mechanical debridement. This method of debridement differs from low frequency ultrasound as it uses high velocity water flow delivered via the Venturi effect, which creates a local vacuum. Unlike low frequency ultrasonic debridement, no ultrasound is delivered through the water and there are no effects acoustic streaming or cavitation at the wound surface. Results of the small laboratory-based study with Versajet™ demonstrated a high risk of contamination in the peri-operative environment and up to three metres during and after debridement. Given the vast differences in the delivery of Versajet™ compared to low frequency ultrasonic debridement, findings from this research are unable to be generalised and assist in guiding clinical practice.

The study undertaken as part of this thesis investigates the environmental impacts of using low frequency ultrasonic debridement, delivered via Sonoca 185®, in the clinical setting (inpatient and outpatient) in wounds of differing aetiologies. Treatment was performed with and without the additional suction unit to determine if there is a difference in microbial aerosol spread.

3.2 PUBLICATION – ARTICLE 2

Michailidis, L., Kotsanas, D., Orr, E., Coombes, G., Bergin, S., Haines, T., Williams, C. Does the new technology low-frequency ultrasonic debridement technology pose an infection control risk for clinicians, patients, and the clinic environment? *American Journal of Infection Control, 2016 44(12): 1656-1659.*

3.3 DECLARATION FOR THESIS CHAPTER 3

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution
Author	70%

The following co-authors contributed to the work:

Name	Nature of Contribution	Extent of Contribution
Dr. Despina Kotsanas	Co-author	5%
Ms. Elizabeth Orr	Co-author	5%
Ms. Georgia Coombes	Co-author	5%
Dr. Shan Bergin	Co-author	5%
Prof. Terry Haines	Co-author	5%
Dr. Cylie Wiliams	Co-author	5%

LM, TH, SB, CW, DK & EO conceived and contributed to the study design. LM, GC & DK were responsible for data collection. LM, CW, TH & DK interpreted the results. LM drafted the manuscript. LM, TH, SB, CW, DK, EO & GC revised the manuscript for important intellectual content. All authors approved current version of the manuscript that has been published.

Declaration by co-authors:

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) There are no other authors of the publication according to these criteria;

(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit

Dr. Despina Kotsanas	Date: 30/01/2019
Ms. Elizabeth Orr	Date: 30/01/2019
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Dr. Cylie Williams	Date: 30/01/2019

Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment?

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Background

Treatment of chronic wounds frequently requires a combination of therapies to facilitate healing. Debridement is considered an important part of treatment as it removes devitalised tissue from the wound bed as it can delay healing and harbour infective organisms. There are different methods of wound debridement; sharps debridement that can be performed in theatre or in a clinical setting, mechanical debriding agents, autolytic debriding through dressings, biological debridement through use of sterile larvae and the use of chemical enzymes [1-3]. Low frequency ultrasonic debridement (LFUD) is a newer method of debridement introduced as an alternative method of wound debridement. The size and portability of the LFUD unit make attractive for use within and across different healthcare settings.

The LFUD technique works by delivering sound waves through a constant flow of sterile saline to the wound surface. Ultrasound results when electrical energy is converted to sound waves at a frequency above the range of human hearing (20 kHz). These sound waves are then transmitted to tissue via a liquid medium through the treatment applicator. Non-thermal effects of the ultrasound have been shown to cause two phenomena at the wound surface; acoustic streaming [4-6] (a steady mechanical force) and cavitation [4-6] (formation of gas bubbles causing micro-shockwaves). The combined effects of acoustic streaming and cavitation are thought to alter cell membrane activity and increase the activity of each cell leading to debridement of necrotic and infected tissue, a bactericidal effect and cellular proliferation [5, 7, 8].

Whilst the use of LFUD has been demonstrated to have a positive effect on wound healing rates and outcomes [9-11] there has been little research into the environmental impact on the use of LFUD in the clinical setting. The aim of this study was to establish the degree and extent of microbial spread during the use of LFUD and to determine what infection control risk LFUD poses to the clinical environment, patient and treating clinician.

Methodology

This was a prospective, observational study with repeated measures across each treatment (before, during, after). Quota sampling in a 2 x 2 x 2 factorial design was undertaken so that half of the n=24 treatments were conducted at different sites (Monash Health versus Peninsula Health), in different treatment environments (inpatient versus outpatient) and half were conducted with and without suction. The Human Research Ethics Committees of Monash Health (14077Q) and Peninsula Health (QA/14/PH/4) approved this study.

Patients

Eighteen patients with a foot or leg wound being treated with LFUD were advised that environmental testing was being performed between June 2014 and April 2015. Patient consent was not required for this study as data collection was not related to treatment. Treatments were measured from a convenience sample at two public hospitals, Monash Health (Monash Medical Centre) and Peninsula Health (Frankston Hospital) and performed by two podiatrists according to the pre-determined study protocol. No randomisation of treatment environments or suction use was undertaken. The only inclusion requirement was that a minimum treatment time of ten minutes of LFUD was required. The leading treating clinicians would judge if the clinical appearance and size of the wound were suited to this treatment.

Measurements

Measurement of dependant variables

Colony forming units (CFU) were the main dependent variable used in this study to determine the degree of microbial burden on the clinical environment. To determine baseline airborne microbes pre-treatment, passive air testing using horse blood agar (HBA) plates were used. These plates were placed at 30 centimetres, one metre and two metres, on either side of the wound, on the floor, in both treatment settings. Additional HBA plates were placed at three metres either side of the wound atop a high surface in only the 'outpatient' setting (space available on inpatient wards was insufficient for this test). Active air testing (Merck MAS 100, Germany) was performed with one HBA plate at 1.5 metres from the wound using air sampling.

Post-debridement sampling for both on-ward and outpatient environments included a single swab taken for culture from the LFUD handpiece end plated on HBA. Additional testing was performed in the outpatient environment thirty minutes after treatment to confirm the return of airborne microbes to baseline. Only the Monash Health site had access to the use of the active Merck air sampler while Peninsula Health used an opened HBA passive settle plate. Air sampling was conducted at 1.5m during baseline, debridement and 30 minutes post-treatment time points. Baseline testing of CFUs was undertaken for ten minutes while the clinician set up the room for treatment. Testing during LFUD included both passive and active air sampling in the same set up as the settle plates. Each HBA plate was incubated aerobically at 35°C for 48 hours and microbes counted and reported as CFUs. Microbes were further speciated as per standard laboratory protocols. This testing was undertaken in the Microbiology laboratory at Monash Health.

Measurement of independent variables

The Sonoca 185 (Söring, Germany) LFUD was used for each treatment. The equipment settings for the handpiece (hoof, spatula or double ball), maximum saline flow rate (ml), maximum ultrasound amplitude (%) the treatment time, and the use of suction were variable. Following a thorough wound assessment these settings were determined by the treating clinician based on the clinical appearance of each wound.

Procedure

A total of 24 LFUD treatments on 18 patients were performed as per the study protocol. The settings used for each treatment (handpiece, amplitude and flow rate) were determined by the treating podiatrist based on the clinical presentation of each wound.

Table 1: Participant microbiology results post from settle plates at 2 metre distance during treatment

No Suction		Suction	
Debridement site	**Microbial growth**	**Debridement site**	**Microbial growth**
Foot	SMAL +++ ENT +++	Foot	MSEF +
Heel	SF +	Foot	SF +
Heel	SAUR +	Foot	SAUR +++ SAGA +++
Heel	SAUR +++ SMAL +++ ENT +++ SF+	Leg	SF +
Toe	KLEB +++ SF +++	Foot	SF +
Toe	KLEB +++ SF +++	Foot	SF +
Toe	KEB +++ SF +++	Foot	SF +
Ankle	ECLO ++ CIT ++ ACAL ++ ENT ++	Leg	SAUR +
Ankle	PAER ++ ENT ++	Foot	SF +
Foot	SF ++	Heel	SMAR +
Foot	SF +	Heel	SF +++ ENT +
Heel	SMAR +++ ENT +++ SF +++ KLEB +	Heel	ECOL +

ACAL = *Acinetobacter calcoaceticus*, CIT = *Citrobacter spp*, ECLO = *Enterobacter cloacae*, ECOL = *Escherichia coli*, ENT = *Enterococcus spp.*, KLEB = *Klebsiella spp.*, MSEF = Mixed skin enteric flora, PAER = *Pseudomonas aeruginosa*, SAGA = *Streptococcus agalactiae*, SAUR = *Staphylococcus aureus*, SF = Skin flora, SMAL = *Stenotophomonas maltophili*, SMAR = *Serratia marcescens*

+ = low ≤10 CFU, ++ = Moderate 11-49 CFU, +++ = High 50-499 CFU.

The on-ward treatments were performed with the patient lying on the bed and the privacy curtains or door closed. The layout of the settle plates was designed to minimise interference by the treating podiatrist or other passers-by. The outpatient clinic room treatment was performed with the patient seated on the treatment chair and the door closed. The treatment was performed as per the standard procedure for both sites, as determined by existing clinical practice guidelines within both health organisations.

The treating podiatrist donned personal protective equipment (PPE) during treatment, including plastic disposable long-sleeve gown, surgical mask, face shield with plastic visor and non-sterile gloves. Patients were given the option of

wearing a mask, however no other PPE for patients was offered. Plastic sheeting was placed in the immediate work area to capture aerosolised droplets up to one metre away and was also used to cover exposed shelves. As per standard procedure, gauze was used to shield the end of the handpiece whilst maintaining visibility for the treating podiatrist. After each procedure, a one-metre wipe of the area and instruments was done using the preferred hospital environmental cleaning method, using a low foaming, low alkaline detergent and water and microfiber cloth.

A total of 24 treatments were planned with equal distribution between sites, treatment environments and with or the without suction attachment.

Data analysis

Data was analysed using Stata 13 [12]. Colony forming units were defined as ordinal categorical data with low +<=10 CFUs, moderate ++=11-49 CFUs, high +++=50-499 CFUs, very high ++++=>=500 CFUs. Microbe species type and count (CFUs) was recorded at pre-treatment (baseline) and during treatment testing. A Wilcoxon signed-rank test was used to determine any difference between pre and during LFUD time points. Ordered logistic regression was used to determine the association between independent variables and CFUs. A power analysis of pre versus during treatment testing using the Wilcoxon signed-rank test was computed using G*Power 3.1 and found that a sample size of 24 pairs of measurements within participants provided 80% power to detect a standardised effect size equals 0.54 given a two-tailed alpha of 0.05 [13].

Results

Pre-treatment

Pre-treatment counts for all passive settle plates consisted primarily of low counts of skin and airborne microbes such as coagulase negative staphylococci, Micrococcus *spp* and Corynebacterium *spp.*

LFUD without suction

The same pathogens were detected from patient wound and air samples in 8 of the 12 treatments where the suction attachment was not used during treatment. Heavy growth of bacteria such as *Stenotrophomonas maltophilia, S aureus,* Klebsiella *spp, Pseudomonas aeruginosa and* Enterococcus *spp* were detected as far as two metres away from the wound (Table 1).

LFUD with suction

In five of the twelve patients with suction only one treatment, results showed heavy growth of *S. aureus* and *Streptococcus agalactiae* and two showed light growths of *S. aureus* and *E. coli* at two metres. Four treatments grew low numbers (<10 CFUs) of significant pathogens (*S aureus*, *S marcescens,* Enterococcus *spp* and *E coli*) that would not normally found to be circulating in normal air (Table 1).

Distance

The same microbial isolates that were growing in the patients whose wounds were swabbed immediately after treatment (n=13) were detected on settle plates that had been placed at the furthest distance (two or three metres).

Handpiece

The same microbial isolates detected from patient's wounds were also detected in high numbers (50-499) in eight of the no-suction handpieces, compared to low numbers (<=10) in five handpieces with the suction attachment.

Passive air sampling

There was a significant difference in pre-LFUD and during-LFUD CFU counts for passive air sampling (p = 0.001). High CFU counts during LFUD were also associated with a larger wound area (p=0.002), low LFUD flow (p=0.010), low LFUD amplitude (p=0.028) and the use of no suction attachment (p=>0.001) (Table 2).

Table 2. Variables associated with increased CFU

Variable	Coefficient	95% Confidence Interval	*P* value
Infection	-1.424	[-2.978, 0.128]	0.072
Wound area (cm2)	0.007	[0.002, 0.012]	0.002
Flow (ml)	-0.278	[-0.491, -0.066]	0.010
Amplitude (%)	-0.157	[-0.297, -0.016]	0.028
Suction	-3.636	[1.603, 5.670]	<0.001
Handpiece	-0.383	[-1.937, 1.171]	0.629
Treatment time	-0.121	[-0.933, 0.691]	0.770
Treatment setting	-1.068	[-2.569, 0.432]	0.163

Active air sampling

Air sampling during treatment showed heavy growth in four of the ten episodes. The same pathogens were also detected at thirty minutes post treatment in five instances. Overall, it was found that 30 minutes after LFUD ceased the number of aerosolised microbes had returned again to baseline levels.

Discussion

Findings associated with higher CFUs included a larger total wound area, a lower saline flow rate and lower ultrasound amplitude. While a larger wound area did not mean a longer treatment time, the larger area may have caused the treating podiatrist to use the handpiece in a wider pattern thus potentially increasing the distance of mist dispersion. The LFUD user manual reports that higher ultrasound amplitude results in a finer mist. A finer mist has the potential to increase aerosolisation. It is unknown if there is an interaction between low ultrasound amplitude and low saline flow rate within this research that resulted in high CFUs. This finding has practical implications. Clinicians should, where possible, increase the saline flow rate when increasing the ultrasound amplitude to a level at which a patient is still comfortable, to reduce aerosolisation.

The fact that treatment time and handpiece selection were not associated with higher CFUs is a positive finding and clinicians should continue to make these choices as clinically indicated. The presence of wound infection was approaching statistical significance; therefore clinicians should interpret these results with caution. A larger sample size may influence these results.

The findings from this research provide an outline of the possible infection control risk posed by using LFUD in a clinical environment to guide infection control practices.

This study had a limited sample size, which may have resulted in some independent and dependent variables not being statistically significant even though a relationship may really exist. One was the use of a convenience sample of patients, which meant that patients eligible to receive LFUD based on the clinical presentation of their wound were included, but not randomised to suction or no suction use, nor were the saline flow rate or ultrasound amplitude settings standardised. Patients with wound infection were not excluded from the study and wound size was not standardised.

It was also thought that factors in each treatment room, such as room airflow and ventilation may have influenced microbial dispersion. Additionally, microbial sampling was conducted using HBA incubated under aerobic conditions therefore limiting the growth of anaerobic organisms. Finally, volumetric active air sampling is best to capture an exact amount of air (i.e 1 cubic metre) but was only available at one hospital site for a limited number of treatments.

Conclusions

This is the first study to investigate the environmental impact of LFUD within a clinical setting. The findings that the use of no suction increases the aerosolisation and spread of microorganisms from the wound means that greater consideration needs to be given to using the suction attachment as often as possible. In addition, the flow rate and amplitude settings, whilst determined by the clinical appearance of the wound and amount of patient pain, should also be considered in relation to the risk of environmental contamination. Careful consideration of the location and use of LFUD is necessary prior to treatment to prevent risk of cross-contamination and reduce potential for hospital-acquired infections.

The results from this study should not dissuade clinicians from utilising LFUD as a method of wound debridement but it is vital that this treatment be performed under the correct conditions to mitigate the microorganism aerosolisation associated with its use. This research has assisted in developing guidelines around the minimum requirements for equipment cleaning and the use of personal protective equipment required to protect the staff member and the patient during the use of LFUD, whilst reducing the risk to the clinic environment.

Competing interests

Nil

Funding

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Authors' contributions

LM, CW, TH and SB conceived this study, LM, CW, TH, SB, EO and DK designed the study, LM and GC collected data, all authors contributed to data analysis, interpretation of data and manuscript. All authors have approved the final manuscript.

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3.5 Addendum to Chapter 3

In addition to the published tables, the following images were captured during the research but not used in the publication.

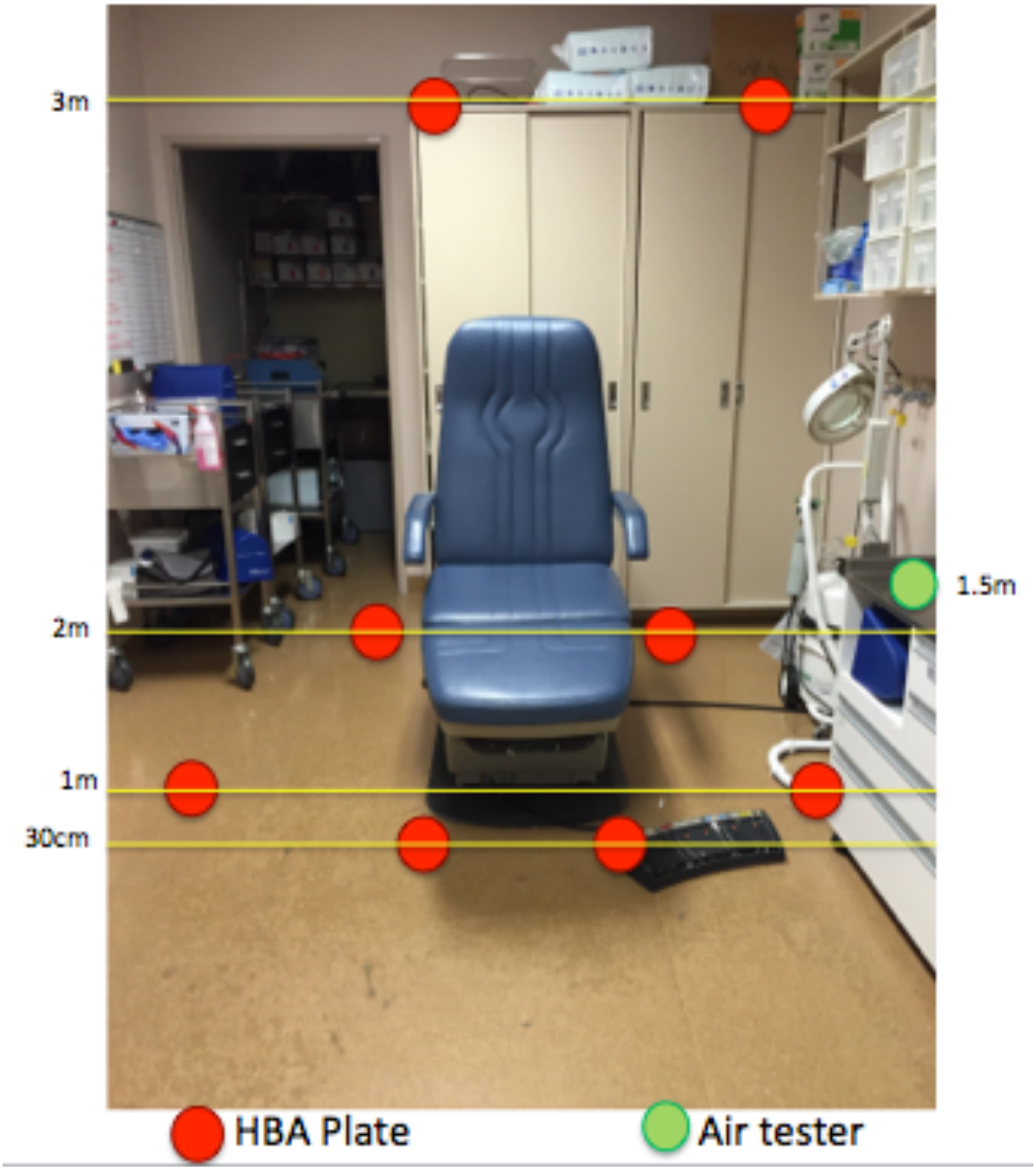

Figure 1: The setup of the test environment in the outpatient setting.

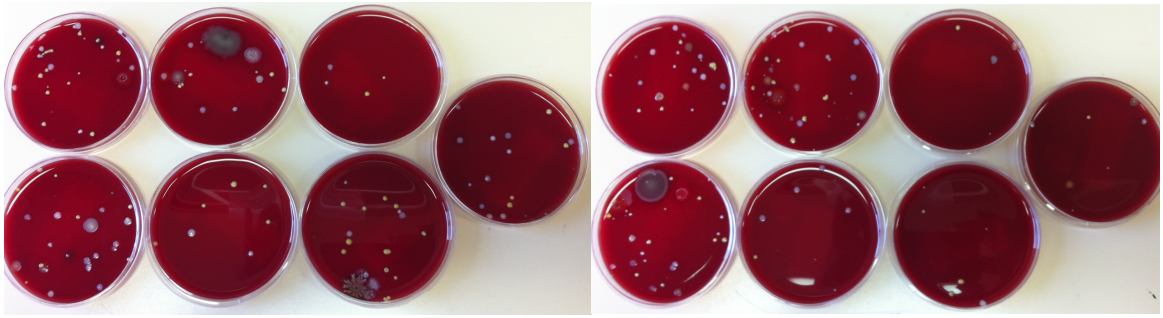

Figure 2: Passive testing when suction was used.

Left image=baseline. Right image=during treatment. Left to right: 30cm, 1m, 2m, 1.5m.

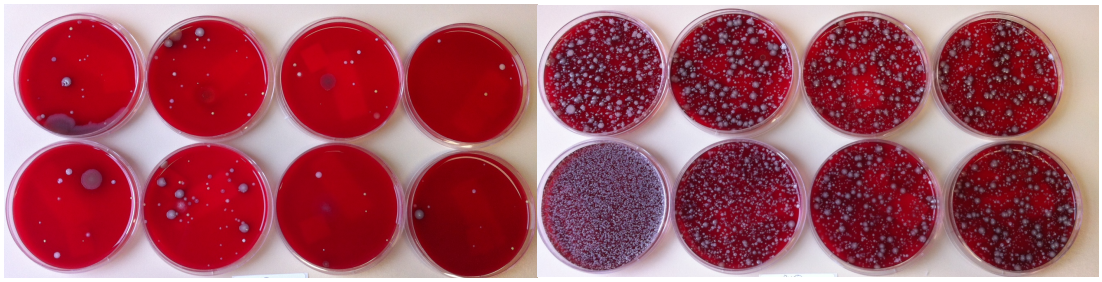

Figure 3: Passive testing when suction was not used.

Left image=baseline. Right=during treatment. Left to right: 30cm, 1m, 2m, 3m.

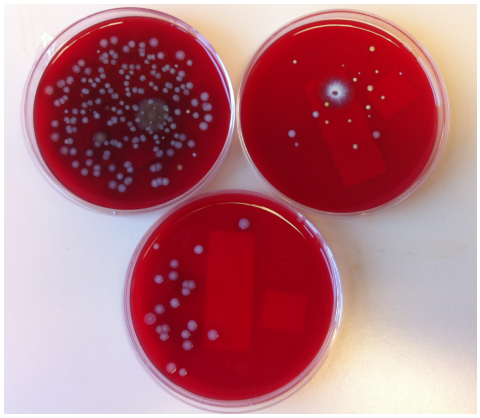

Figure 4: Active air testing at 1.5m.

Left - during treatment. Right – after treatment. Bottom – at baseline.

3.6 TRANSLATION OF FINDINGS

Results from this research immediately changed clinical practice guidelines for use of low frequency ultrasonic debridement at three major health organisations in Australia, including Monash Health (Victoria), Peninsula Health (Victoria) and Central Coast Local Health District (New South Wales). Recommendations enacted:

- Use of the suction attachment unless clinically unable (e.g. sinus or cavity)
- Use of highest flow rate and amplitude percentage as tolerated by the patient
- Use only in outpatient setting with appropriate room protection
- Personal protective equipment to be used for clinician and patient
- Minimum of 30 minutes before using the treatment space after treatment

Additionally, the manufacturer developed a new attachment, Clear Shield that was released in Australia late 2017 following this research. This is a clear silicone dome that attaches to the end of the handpiece and is designed to contain aerosolised liquid during treatment.

The authors are further investigating methods of protecting the treatment space to make this as easy, cheaply and time efficient for clinicians as possible.

CHAPTER 4 – STUDY PROTOCOL

4.1 PREAMBLE

There is limited evidence comparing low frequency ultrasonic debridement and non-surgical sharps debridement for the clinical outcomes for diabetes-related foot ulcers. The systematic review discussed in Chapter two identified a lack of research in this area. Neither low frequency ultrasonic debridement nor non-surgical sharps debridement were included in the contemporary literature reviews. A study protocol was developed to assist in guiding a future randomised controlled trial comparing these two debridement methods in diabetes-related foot ulcers. This chapter details the study protocol.

4.2 PUBLICATION – ARTICLE 3

Michailidis, L., Williams, C.M., Bergin, S.M., Haines, T.P. Comparison of healing rate in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised trial protocol. *Journal of Foot and Ankle Research (2014) 7:1.*

4.3 DECLARATION FOR THESIS CHAPTER 4

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution
Author	70%

The following co-authors contributed to the work:

Name	Nature of Contribution	Extent of Contribution
Dr. Cylie Williams	Co-author	10%
Dr. Shan Bergin	Co-author	10%
Prof. Terry Haines	Co-author	10%

LM, TH, SB & CW conceived and contributed to the study design. LM & CW drafted the manuscript with revision and support from TH & SB. The final manuscript was revised by LM, TH, SB & CW for intellectual content. All authors approved the current version of the manuscript that has been published.

Declaration by co-authors:

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) There are no other authors of the publication according to these criteria;

(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit

Dr. Cylie Williams	Date: 30/01/2019
Dr. Shan Bergin	Date: 30/01/2019
Prof Terry Haines	Date: 30/01/2019

Comparison of healing rate in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised trial protocol.

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Introduction

Background

Diabetes is rapidly increasing in global prevalence, morbidity and mortality. In 2011, 366 million people globally were living with diabetes, a figure that is equivalent to 8.3% of the world's adult population. It was estimated the international community would not reach this figure until 2030 [1].

In Australia the prevalence of type 2 diabetes has increased over the past two decades and continues to rise. Approximately 7% of the Australian population is thought to have type 2 diabetes and it is estimated that 15% of people with diabetes will develop a foot ulcer during their lifetime [2]. The consequences of having diabetes in Australia are significant with over 500,000 hospital admissions and 12,000 deaths attributed to the condition in 2004 alone [1].

The pathophysiology of foot ulceration is complex and usually multi-factorial. Peripheral sensory neuropathy, foot deformity and external trauma, when occurring concurrently, have been identified as being the three most common factors that predispose to diabetes-related foot ulcers (DRFU) [3]. Peripheral arterial disease has also been shown to lead to the development of ischaemic and neuro-ischaemic DRFU [2]. Regardless of the true aetiology, the same complications can arise with all DRFU, including soft tissue infection, osteomyelitis, tissue necrosis and failure of ulcer healing, all of which may require hospital admission and potentially result in amputation [4].

Diabetes has been acknowledged to be the most common cause of non-traumatic lower-limb amputation in Australia [5]. Furthermore, acute complications affecting foot ulceration have been reported as the leading cause of diabetes-related hospital admissions and amputation [4]. For the years 2004 - 2005 the Australian Institute of Health and Welfare reported that DRFU resulted in 9900 acute hospital admissions [4]. In the same period 3400 diabetes-related lower limb amputations were also reported [2].

More recently it has also been suggested that diabetes-related lower limb amputations have increased by 30% between the years 1998 – 2005 [6]. The estimated acute care cost of a single lower extremity amputation in Australia could be as much as $26,700 [4]. This figure does not include costs for rehabilitation, purchase of orthotics/prosthetics or time lost from work. Recent economic evaluations of the cost of a lower limb amputation for a single person found that Australia sits in third place behind France where such a procedure is estimated to cost $46,064 for a single diabetes-related lower extremity amputation and in Germany the same is estimated at a cost of $31, 809 [2]. The cost of amputation secondary to diabetes complications in the United States of America is said to range from $20,000 - $60,000 per patient and similarly does not include the personal, social, or economic aspects of the patient's life [7].

None of the costs noted above consider the direct financial burden on patients with a DRFU. The ongoing costs of ulcer management in the community have not been investigated in the literature to date, however clinicians, patients and their families feel the impact of these costs every day. It has been reported however, that in one study investigated the quality of life of patients with DRFU 50% of patients were no longer in work because of their ulcer. Although

treatment was free the costs associated with travelling to hospital appointments and buying additional footwear [8] placed an additional financial strain on patients.

Given the complications associated with DRFU and the time these ulcers can take to heal it is not surprising that patients report a greatly reduced quality of life [9]. It has been found that all quality of life domains can be adversely impacted primarily because of a reduction in mobility and the consequent need to adapt activities of daily living [8]. Additionally, it is thought that the presence of a foot ulcer imposes restrictions on patient participation and enjoyment of their usual hobbies mainly because of mobility difficulties and the requirements for treatment [9]. This has been shown to have a negative psychological effect with an increase in patients with depression and a lower satisfaction with their personal lives [9]. Reviewing and improving ulcer management interventions that have the potential to result in more effective and faster healing could have the added benefit of improving the quality of life of patients with a DRFU.

Debridement has been identified as a leading treatment for management of DRFU [2]. Debridement has been defined as the removal of devitalised, contaminated or foreign material from within or adjacent to the ulcer until surrounding healthy tissue is exposed [10]. It serves several functions including reduced pressure on the ulcer base, more thorough inspection to determine true ulcer depth and size, facilitation of drainage and creation of an acute ulcer environment [6].

Existing approaches to ulcer debridement can be performed directly by a clinician including theatre-based sharps debridement (TBSD) also known as surgical excision and non-surgical sharps debridement (NSSD) or scalpel debridement in a clinical setting. There are also various topical products that act as debriding agents. These have included wet-dry dressings that act as mechanical debriding agents, dressings that encourage moist wound healing and autolytic debridement, biological debridement through use of sterile larvae and also the use of chemical enzymes [10-13].

Theatre-based sharps debridement has been utilised for removal of deep necrotic tissue, gangrene and deep infection [14] but has not been routinely used as part of standard care. Non-surgical sharps debridement is required more regularly to remove non-viable necrotic tissue from the ulcer surface and is recommended as part of standard ulcer care [13]. The need for and appropriate method of ulcer debridement should be determined based on the clinical presentation [12] and potentially the clinical skillset and equipment available [13].

Sonoca 185^{TM} (SÖering) was introduced in Australia recently as an alternative method for ulcer debridement. The technology works by delivering low frequency ultrasound, or sound waves, through a constant flow of saline. Ultrasound results when electrical energy is converted to sound waves at frequencies above the range of human hearing (20 kHz) with Sonoca 185^{TM} functioning at 25kHz [15]. These sound waves can then be transmitted to tissue, via a liquid medium, through a treatment applicator. It is the non-thermal effects of ultrasound that have been shown to cause two phenomena at the ulcer surface; acoustic streaming [15-17] (a steady mechanical force delivered in a fluid medium i.e. sterile saline) and cavitation [15-17] (formation of gas bubbles in the fluid creating micro-shockwaves).

The combined effects of acoustic streaming and cavitation are thought to alter cell membrane activity and increase the activity of each cell [16]. Subsequently this is thought to have three clinical effects: debridement, a bactericidal effect and an ulcer healing stimulator effect [17-19].

The biological effects indicated through in vitro and animal studies could contribute to ulcer healing [20]. These effects include stimulation of cellular activity and protein synthesis, the activation of inflammatory cells and the production of chemical mediators that activate fibroblasts and may lead to ulcer healing [15, 19, 20]. Additionally, the mechanical forces produced by the ultrasound energy at the cellular and molecular levels may promote ulcer healing by fostering cell division, angiogenesis, the release of growth factors [20] and stimulating collagen synthesis [15, 19]. In vitro data has also found that low frequency ultrasonic debridement (LFUD) is effective in reducing microbe count for methicillin-resistant staphylococcus aureus, vancomycin resistant enterococci, pseudomonas and other commonly occurring bacteria [17, 18].

When comparing LFUD with TBSD significant clinical advantages have been noted in terms of efficacy and safety for debriding ulcers without deep infection or necrosis. Successful TBSD is reliant upon the skill of the surgeon and their ability to distinguish between tissue types. Procedural risks of TBSD have included pain, bleeding [21], damage to underlying structures with a resultant loss of function [13, 22], post-surgical infection and the use and associated risks of general anaesthesia [13].

Comparisons have been made with the use of LFUD and TBSD in DRFU in a randomised controlled trial, which found a mean healing rate that was 2.5 times faster using LFUD compared to TBSD over a two week treatment period. Limitations of this study include the very short follow-up of only two weeks and the small sample size (N=59) [23].

A randomised double-blind controlled trial has compared low-frequency low-intensity ultrasonic debridement to a sham treatment (saline mist without ultrasound) in patients with recalcitrant DRFU. Ennis et al. found that after 12 weeks of treatment 40.7% of patients who underwent LFUD had healed compared to only 14.3% in the sham treatment group. Whilst this is promising data the overall numbers of participants were small (N=55) [24].

A recent meta-analysis investigating the use of non-contact low-frequency high-intensity ultrasonic debridement, reported significant improvement compared to NSSD at three and five months, but no difference at six months. There were only two studies suitable for the meta-analysis, one focused on DRFU (N=40) and the other venous leg ulcers (N=76). Again the overall numbers were small [16].

Another meta-analysis concluded that non-contact LFUD is an efficacious treatment for chronic wounds of varying aetiologies [20]. Despite the quality of the initial evidence being of low quality suggests that LFUD does demonstrate short-term clinical benefits when used as an adjunctive therapy. Recommendations from both meta-analyses were the same; there is no evidence that compares LFUD with standard ulcer management. Additionally, there is a need for further research using larger randomised clinical trials of longer period of time.

Given the evidence available it could be expected that LFUD might be a lower-cost treatment when compared to TBSD in terms of the cost associated with the actual treatment itself and potential savings from healing ulcers faster.

Non-surgical sharps debridement has been considered the leading comparator to TBSD for several reasons; the technique is simple and requires the use of basic instruments by a trained professional; it is time efficient and can be performed in clinic or at the bed-side; does not require the resources of an operating theatre and has a lower overall cost.

Evidence on the most appropriate method, frequency and extent of DRFU debridement is limited and insufficient to draw any conclusions. The National Evidence-Based Guidelines for the Prevention, Identification and Management of Foot Complications in Diabetes recommends that NSSD should be considered first and should occur repeatedly and as often as required to remove all non-viable tissue [2]. This recommendation is based on expert opinion in the absence of evidence pertaining to DRFU debridement.

A recent Cochrane Review [10] on debridement of diabetic foot ulcers notes that while ulcer debridement is recommended as an effective intervention to assist healing, no guidelines identify a specific method of debridement. The methods of debridement reviewed included surgical debridement, topical hydrogels and larval therapy [10]. Neither NSSD nor LFUD were investigated in the Cochrane Review.

The method of choice for ulcer debridement remains inconclusive. Evidence suggests that each ulcer needs to be individually assessed in terms of type, size, position, appearance, patient pain and tolerance, cost effectiveness and available expertise and equipment to determine the most suitable method of debridement [25].

The decision to utilise NSSD as the active control group in this study was based on the expert opinion in clinical guidelines and the low cost and easy accessibility of the treatment for clinicians. The limited data around LFUD leaves a gap in the evidence that warrants further investigation. The limited data available on LFUD with NSSD as standard practice makes this debridement modality a choice comparator.

It is hypothesised that use of LFUD in the treatment of DRFU would improve healing rates when compared with NSSD. There will be four aims within this study. The primary aim is to determine if there is a difference in healing rates for DRFU, using NSSD compared to LFUD. Secondary aims include assessing for differences in pain during and post-treatment, determining if there is a difference between the quality of life of participants who have an ulcer undergoing either method of debridement and if there is a difference in overall costs between NSSD and LFUD.

This clinical trial will provide important information in the field of ulcer management; provide a better understanding of the efficacy of NSSD and the newer technology of LFUD. It will also provide health services with a better understanding of the financial impacts of both treatments. This protocol has been designed and reported to ensure it corresponds to the 33 items of the SPIRIT checklist [26].

Methods

Study design

This is a randomised controlled trial comparing NSSD (active control group) and LFUD (treatment group) in DRFU with a six month follow-up period. A consort flow chart for the design of this study is presented in Figure 1.

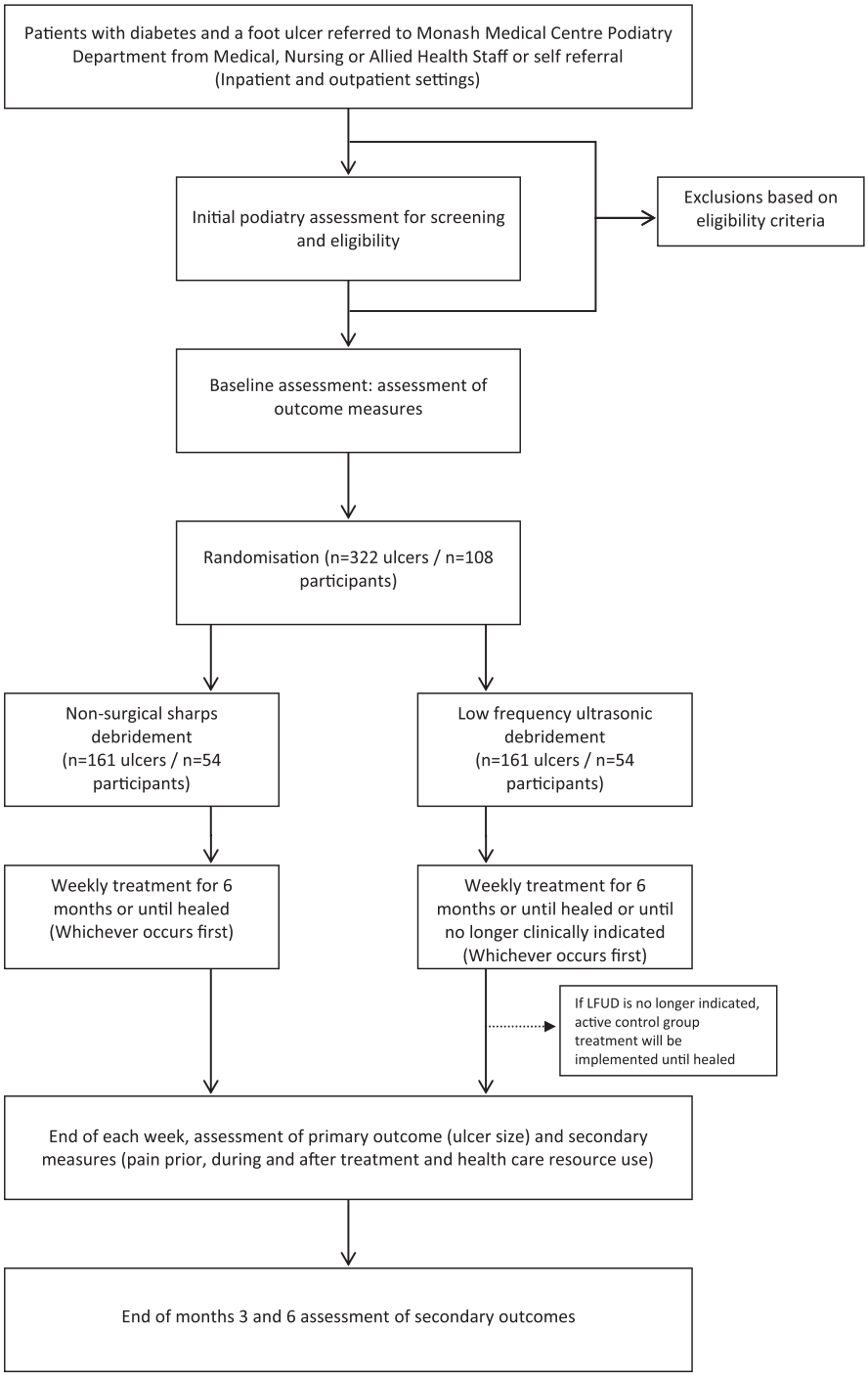

Figure 1: Consort flow chart for the study.

Ethical consideration

Ethical approval for this study has been obtained by the Monash Health Human Research Ethics Committee HREC 12101B. Ethics approval for this study has been obtained by the Monash University Human Research Ethics Committee HREC CF14/2792-2014001557.

Participants and setting

Patients with diabetes and a foot ulcer/s, who are referred to and treated by the Podiatry Department at Monash Health, will be invited to participate in this study. Patients may be inpatients and receiving podiatry care on the ward or outpatients referred by the patient's primary medical care team.

This study is a single centre trial. The average length of stay for an acute hospital admission in Australia is 6 days [27]. Participants may be recruited during their hospital admission but it is anticipated they will receive treatment primarily in the outpatient setting. Inpatients, however, can receive either treatment if they meet inclusion criteria for this study as both study interventions can be undertaken by the bedside as well as in an outpatient clinical setting.

A standard initial podiatric assessment will occur at baseline including a neurovascular assessment, medical and surgical history, medications history, diabetes management and control history including glycated haemoglobin (Hba1c), footwear assessment, ulcer aetiology, ulcer duration and previous management. If the participant meets the inclusion criteria (Table 1) as determined by the treating podiatrist, the patient will be informed about the research project and written consent will be obtained to participate in the study.

Ulcers must be chronic, or greater than 1 month in duration to be included in the study. This is to capture the most accurate data around DRFU, which have been shown in the literature to take longer than 4 weeks to heal [28]. Should a patient have an ulcer infection at the time of recruitment, or develop an infection during the trial they will receive appropriate antibiotic therapy and will be able to continue in the trial. If appropriate infection management is not commenced, irrespective of the reasons, the patient will not be able to continue in the trial.

Table 1: Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
General: ≥ 30 years of age Able to provide informed consent Ulcers present for greater than 1 month Ulcers ≥ 1cm^2	General: Patients taking immunosuppressive medications Known allergy to ulcer dressing products Pre-existing ulcer pain preventing either type of debridement
Vascular: Palpable pedal pulses OR biphasic or triphasic pedal pulses on doppler OR toe pressure ≥ 45mmHg	Vascular: Non-palpable pedal pulses OR monophasic pedal pulses on Doppler OR toe pressure ≤ 45mmHg
Ulcer classification: Infected ulcers being appropriately managed Those meeting The University of Texas Wound classification criteria [38]: *A1, A2, A3 (wounds of varying depth without infection or ischaemia)* *B1, B2, B3 (wounds of varying depth with infection only)*	Wound classification: Dry gangrenous ulcer Fungating ulcers Malignant ulcers Those meeting the University of Texas wound classification criteria [38]: *A0, B0, C0, D0 (pre or post-ulcerative lesion with complete epithelialisation, with or without infection and ischaemia)* *C1, C2, C3 (wounds of varying depth with ischaemia only)* *D1, D2, D3 (wound of varying depth with infection and ischaemia*

Interventions

The two interventions are the two different methods of ulcer debridement, LFUD and NSSD. The techniques for both treatments are as described in Table 2.

Table 2: Standard step-by-step technique for LFUD and NSSD

LFUD	NSSD
1) Constantly move the handpiece to prevent ultrasound burning tissue 2) Start debriding at the distal most aspect of the ulcer 3) Moving the handpiece left to right and from the distal to proximal aspect of the ulcer 4) Once the entire ulcer surface has been debrided re-commence the same technique from the distal most aspect of the ulcer 5) Continue until as much necrotic tissue has be removed as possible 6) Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel. The wound base will not be debrided with the scalpel.	1) Start debriding at the distal most aspect of the ulcer 2) Moving scalpel proximally with each motion 3) Once the distal to proximal ulcer has been debrided then debride from left side to right side 4) Continue until as much necrotic tissue has been removed as possible 5) Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel.

Outcome measures

Primary outcome measure:

The primary outcome measure for this study is the proportion of ulcers healed over the six month follow-up period. An ulcer is defined as healed in the presence of intact skin, i.e. functional epithelial tissue [29], a total surface area of 0cm^2 and restoration of functional and anatomic continuity [30]. Ulcer healing status will be determined by assessing the total ulcer area.

Ulcer surface area will be assessed using photographs taken with a digital camera using a standard technique (Table 3). A one centimetre by one centimetre, transparent grid will be utilised over the printed photograph and the total area calculated. Total surface area measurements will be performed following each weekly treatment. A research assistant blinded to the treatment allocation will collect the data for the primary outcome measure. This is to ensure the treating podiatrist is blinded to the primary outcome during subsequent treatments.

Table 3: Standard step-by-step technique for ulcer measurement

Ulcer measurement	
1)	Ulcers that have tunnels or undermining will be marked on the skin with a black marker.
2)	A white towel will be place under the foot to remove distracting background elements.
3)	A disposable ruler will be labelled with participant number, wound number, participant initials and the date.
4)	Position the disposable ruler alongside the ulcer and secure with paper tape.
5)	Use macro camera setting with flash on, iso set to 200.
6)	Take photograph at a distance of 20cm from the wound
7)	Ulcer measurements will be conducted from print out using the photograph (all photos will be printed as standard A4 size)

The research assistant has been trained by the treating podiatrist and given written instructions on how to use the transparent grid to calculate total ulcer area. To determine reliability fifteen ulcers have been photographed and both the research assistant and treating podiatrist followed the same technique to calculate ulcer area. Inter-rater measurement reliability between the treating podiatrist and research assistant was found to have an ICC of 0.91.

The ulcer depth will be measured by the treating podiatrist following each treatment, as depth cannot be accurately assessed using a photograph. A disposable measurement probe will be used to assess ulcer depth, undermining, sinus or tracking.

A review of available literature around ulcer measurement is scarce and of low evidence. The measurement technique being used in this study, tracing and subsequent counting of centimetre squares, has a high inter-rater and intra-rater reliability when compared to other forms of ulcer measurement [31, 32].

A standard technique will be used for each method of debridement and ulcer measurement ensuring consistency (Tables 2 and 3).

Ulcers being treated in the intervention group will be reviewed after six weeks of treatment. If LFUD is no longer clinically indicated then treatment will be ceased and the ulcers will then receive the control treatment (NSSD). This change is to reflect the pragmatic nature of the treatment and NSSD is considered standard ulcer care. Clinical indications for ceasing LFUD treatment include pain, ulcer size and depth, clinical presentation and no ulcer improvement.

Secondary outcome measures:

Secondary outcome measures will include assessing ulcer pain, quality of life and economic evaluation.

Ulcer pain will be measured weekly using a 100mm Visual Analogue Scale (VAS). Pain will be assessed prior to, during and following each treatment. The far left end of the scale (0mm) will be labelled as no pain and the far right end of the scale (100mm) will be labelled as worst pain imaginable. The VAS has been widely used and has been shown to be a valid and reliable pain assessment tool [33].

A health-related quality of life tool will be used to gain perspective from each participant. This will be undertaken at the initial treatment, at three months and again at six months. If an ulcer heals prior to the end of the six month study period the tool will be applied at that point. The EQ 5D-5L [34] assessment tool analyses five health-related quality of life domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This tool has been widely used and has been validated for use in patient groups with diabetes [35].

All data for the secondary outcome measures will be collected by the treating podiatrist. No blinding will occur for this data.

Each outcome measure and their time points of collection are summarised in Table 4.

Table 4: Outcome measures and timeframes

Data collection	Measurement tool	Data collected method	Timeframe
Measurement of total ulcer area	Centimetres squared; Tracing from photographs and counting squares	Research assistant	Weekly: Post-treatment until healed or at 6 months
Measurement of ulcer depth	Centimetres; Using sterile probe	Treating podiatrist	Weekly: post-treatment until healed or at 6 months
Ulcer pain	Visual analogue pain scale 100mm	Treating podiatrist	Weekly: Pre-treatment, during treatment, post-treatment until healed or 6 months
Quality of life	EQ-5D-5L tool	Participant questionnaire	Initial treatment, at 3 months, at 6 months
Direct health costs			
Consumable costs for treatments	In dollars for each treatment	Treating podiatrist	Weekly, per participant until healed or at 6 months
Medicare Benefit Scheme (MBS)	MBS Care database, in dollars	Extraction from MBS database	End of project for each participant from initial to final treatment
Pharmaceutical Benefit Scheme (PBS)	PBS Care database, in dollars	Extraction from PBS database	End of project for each participant from initial to final treatment
Inpatient data	Monash Health: Admission duration, reason for admission, imaging and interventions, obtained from the patient record and from the Victorian Admitted Episodes Database External organisation: Admission duration, reason for admission, costs of any surgery for diabetes-related foot ulcers will be estimated using WEISS funding	Hospitalisation costs	Monash Health: End of project External organisation: End of project
Hospital based services (outpatient data)	Hours – time spent	Treating podiatrist	Weekly per participant until healed or at 6 months
Medical imaging and pathology for outpatients	Dollars – hospital based costs	Treating podiatrist	Monthly per participant until healed or at 6 months
Community based services	Number and cost of appointments	Participant interview	Monthly until healed or at 6 months
Private health appointments	Number and cost of appointments, eligibility for private health subsidies	Participant interview	Monthly until healed or at 6 months
Royal District Nursing Service for ulcer management	Frequency and cost of service	Participant interview	Monthly until healed or at 6 months
Ongoing ulcer care products	Valued using market prices	Participant interview	Monthly until healed or at 6 months

Parking costs for appointments	Dollars	Participant interview	Monthly until healed or at 6 months
Transportation costs to travel to appointments	Estimated through Australian Tax Office car rate cents per km	Participant interview	Monthly until healed or at 6 months
Productivity costs			
Time taken from work for participant and/or any family member	Salary and hours taken from work	Participant/family interview	Monthly until healed or at 6 months

Sample size

The sample size calculation for this study was based upon the primary outcome comparison between groups of the proportion of ulcers completely healed by the six month follow-up. Previous research indicates that nearly 25% of ulcers treated with NSSD healed within six months [28], while another previous study found that 41% of ulcers treated with LFUD healed within three months [24]. There is no six month data available for the LFUD approach. A sample size of 147 ulcers per group is required to achieve 80% power using a two-tailed alpha of 0.05 to detect an absolute difference in the proportion of ulcers healed of 0.16 (control=0.25, intervention=0.41). To account for the intra-cluster correlation of multiple ulcers being nested within a single participant we adjust this for a design effect (1+(n-1)*ICC) using n=3 ulcers per participant and ICC estimate of 0.05; thus we require 161 ulcers per group. With an average of 3 ulcers per participant we require 54 participants per group.

Randomisation

Randomisation will be undertaken using a permuted-block randomisation approach. Randomisation blocks of two, four or eight participants will be generated and randomly selected and the resultant allocation order will be entered into opaque, sealed envelopes. An investigator not involved in recruitment or assessment (CW) will be responsible for preparing the random allocation sequence and envelopes. The treatment conditions will be provided as per the random allocation sequence following completion of the initial assessment.

Once eligibility has been confirmed, a verbal explanation of the project will be provided and the treating podiatrist will obtain written consent. All participants who consent will have baseline assessments conducted prior to randomisation, as outlined above. All ulcers (where there is more than one per participant) will be numbered and documented according to anatomical location prior to randomisation. Only the treatment condition will be randomised, not each individual ulcer. Where there is more than one ulcer, all will be treated with the same method as per the randomisation process and included in the study. Following randomisation the initial treatment and measurements will commence as outlined in Tables 2 and 3. All participants will receive treatment and have their ulcers photographed and measured on a weekly basis, as is standard podiatry practice at Monash Health. Both groups will receive best practice ulcer management including appropriate ulcer dressings, pressure off-loading and footwear provision as required.

Identifiable outcome data will be stored within the participant's health record. De-identifiable data will be stored within a password-protected Excel spread sheet within a secure hospital data management system as per requirement

of the Human Research Ethics Committee (HREC) for Monash Health. The primary investigator (LM) will be responsible for data entry and a co-investigator (SB) will randomly audit information to monitor data accuracy.
The trial will be managed by the research team and led by the primary investigator (LM). The protocol has undergone external review from the Lions John Cockayne Research Fellowship committee and the research team will give quarterly progress reports. Annual reports will also be required (including adverse events) to the HREC of Monash Health. The research team will meet on a monthly basis to address clinical and data monitoring concerns.

Statistical analysis

The proportion of ulcers that are completely healed by the six month follow-up will be compared between groups using a logistic regression analysis approach with clustering of ulcer within participant. A member of the research team (TH) who will be blinded to the allocation of the participants will assess this.

The rate of change in ulcer size (surface area, using the post-debridement photo) will be compared between groups using a linear mixed model analysis approach where repeated assessments will be nested within ulcer, and ulcers will be nested within participants. The groups will be treated as a fixed factor while assessments, ulcer and participants will be treated as random factors. All analyses will be adjusted for whether the wound was infected at baseline, as infection has been demonstrated to delay healing [36] and HbA1c levels at baseline as poor glycaemic control has been demonstrated to delay healing [37].

A pre-planned interim analysis will be undertaken after 70% of the planned sample size has been recruited. This analysis will use all data available to that point in time and examine the safety and efficacy outcomes from the trial. A data analyst who is blinded to group allocation will be provided with the dataset and mock group codes. The outcome of this analysis will be forwarded to the remaining project investigators who will decide whether there is sufficient evidence to reject the null hypothesis for the primary outcome. The assumptions underlying the sample size calculation (eg. ICC value) will also be examined at this point and revisions to the sample size will be made if indicated.

Economic analysis

Cost effectiveness analysis:

Direct and indirect health care costs will be collected at regular intervals, as explained in Table 3.
The formula for assessing cost effectiveness analysis will be:

$$\frac{\text{Cost}_{LFUD} - \text{Cost}_{NSSD}}{\text{Effect}_{LFUD} - \text{Effect}_{NSSD}} = \text{Incremental cost per additional ulcer healed}$$

Cost utility analysis:

A health related quality of life assessment obtained from the EQ-5D-5L tool will be converted to utility scores as explained in Table 4. The economic evaluation will examine the cost per quality adjusted life year (QALY) gained per patient provided with each intervention. QALY measurements will use the EQ-5D-5L utility-based cost-effectiveness analysis. The formula to calculate QALYs gained from the intervention will be:

$\frac{\text{Cost}_{LFUD} - \text{Cost}_{NSSD}}{\text{QALY}_{LFUD} - \text{QALY}_{NSSD}}$ = Incremental cost per QALY gained

Discussion

Diabetes-related foot ulceration is a significant medical and social problem. Consensus among wound specialists supports the importance of ulcer debridement to encourage ulcer healing. Despite this, there is a paucity of evidence comparing different debridement techniques. Whilst there is evidence available around the efficacy of LFUD it has been limited. Furthermore, there is no randomised controlled trial looking at the healing rates of DRFU that undergo NSSD compared to LFUD.

This clinical trial will provide important information in the field of ulcer management and provide a better understanding of the efficacy of using NSSD treatment. It will also provide health services with a better understanding of the financial impacts of both treatments.

Adverse events will be measured and recorded during the study. The adverse events for both treatment groups may include incidents such as sharps injuries to the participant or treating podiatrist, development of ulcer infection, hospital admission due to ulcer deterioration, excess pain and bleeding from debridement at the ulcer surface.

A limitation of this study is the non-consideration given to nutritional status. Patient nutritional status has potential to impact on ulcer healing, however outside of a controlled inpatient environment it is difficult to enforce a strict food regime. All patients will be encouraged to adhere to a suitable diet, however this will not be controlled as part of this study.

A second limitation is that while a thorough assessment of pain will be undertaken, this measure will only focus on the individual ulcer pain before, during and after debridement with either modality. Where participants have more than one ulcer in close proximity to another ulcer the pain assessment may become difficult to distinguish for each ulcer.

Funding

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Competing interests

The authors declare no competing interests.

Authors' contributions

All the authors contributed to study design and methodology. LM and CW obtained funding for the study. All authors contributed to the study protocol. LM is the chief investigator and drafted the paper. SB, TH, and CW provided editorial assistance. All authors have read and approved of the final paper.

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4.5 Addendum to Chapter 4

Due to events that were not anticipated throughout study period, the protocol was modified from the publication. These issues and how they were addressed to overcome them are summarised below in Table 5. The final method and results of the trial will be discussed further in the upcoming Chapters.

Table 5: Recruitment issues and action plan

Issue	How issue was addressed & outcome
Difficulty recruiting	1. The study inclusion and exclusion criteria were modified to capture more potential participants including: • Renal dialysis removed as an exclusion • Changes to vascular-specific criteria to broaden the inclusion criteria 2. Primary researcher audited all podiatry patients seen across the bed-based service to determine if they were eligible for the study 3. Preliminary discussion with head of Vascular Surgery at Monash Health and invitation made for joining research team to ensure Vascular Outpatient Clinic screened patients 4. Loan LFUD unit secured for 12 months from MediGroup Australia at no cost to be located in Monash Health Community Health or additional outpatients site. This did not increase recruitment due: • Time concerns for training clinicians and recruitment • Site based management in community health services infection control concerns, despite clinical guidelines being in place 5. Preliminary discussion with head of Podiatry at Peninsula Health to make the study multi-site • Unable to proceed due to cost of consumables for six month follow up period • Unsuccessful in funding applications to assist with costs
Did not reach expected sample size	1. No MBS/PBS data extracted or analysed 2. No cost effectiveness analyses undertaken 3. Break even analyses undertaken 4. No statistical analysis undertaken 5. Results presented as observations
Change in research assistant analysing photographs	Interrater reliability was performed

CHAPTER 5 – CLINICAL TRIAL RESULTS

5.1 PREAMBLE

As discussed in Chapter four, there is limited evidence to demonstrate the clinical effectiveness of low frequency ultrasonic debridement in the management of diabetes-related foot ulcers.

This randomised study with a follow-up period of six months investigated the healing rates of diabetes-related foot ulcers using low frequency ultrasonic debridement and non-surgical sharps debridement. Secondary outcomes included cost effectiveness, pain reported before, during and after treatment and quality of life.

The study protocol as outlined in chapter three was followed regarding recruitment, randomisation, treatment and data collection. However, issues with study recruitment meant the intended analysis could not be undertaken. The smaller than anticipated sample size rendered the planned logistic regression analyses insufficiently powered to draw worthwhile conclusions. Graphical survival analysis techniques were used to describe the data. Similarly, quality of life and pain data were not analysed as planned but presented descriptively. No cost-effectiveness analysis was undertaken as part of this study, however, a further study was undertaken to determine cost effectiveness of both debridement modalities and this is outlined in chapter six.

This chapter reports the outcomes of the comparative effectiveness trial. These results provide observations into the clinical efficacy of low frequency ultrasonic debridement in the management diabetes-related foot ulcers compared to non-surgical sharps debridement in diabetes-related foot ulcers. The challenges with recruitment were discussed at length with recommendations for future clinical trials.

5.2 PUBLICATION – ARTICLE 4

Michailidis, L., Bergin, S.M., Haines, T.P., Williams, C.M. Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial. *BMC Research Notes (2018) 11:732*

5.3 DECLARATION FOR THESIS CHAPTER 5

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution
Author	70%

The following co-authors contributed to the work:

Name	Nature of Contribution	Extent of Contribution
Dr. Shan Bergin	Co-author	10%
Prof Terry Haines	Co-author	10%
Dr. Cylie Williams	Co-author	10%

LM, TH, SB & CW conceived and contributed to the study design. LM was responsible for data collection. LM, CW, TH & SB interpreted the results. LM drafted the manuscript. LM, TH, SB & CW revised the manuscript for important intellectual content. All authors approved current version of the manuscript published.

Declaration by co-authors:

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) There are no other authors of the publication according to these criteria;

(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit

Dr. Shan Bergin	Date: 30/01/2019
Prof Terry Haines	Date: 30/01/2019
Dr. Cylie Williams	Date: 30/01/2019

Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: A Randomised Controlled Trial.

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Introduction

Diabetes and its complications are rapidly becoming the world's most significant cause of morbidity and mortality. Globally, the number of adults with diagnosed diabetes is approximately 415 million [1] or one in eleven adults, a worldwide prevalence that was previously predicted to occur in 2030 [2].

Diabetic foot disease is also considered one of the most serious complications of diabetes. The pathophysiology is multifactorial and is predominantly associated with neuropathy, peripheral arterial disease and foot deformity [3-6]. The convergence of one or more of these conditions leads to the development of foot ulceration, which is a significant precursor to lower limb amputation [7]. It is estimated that up to 25% of people with diabetes will develop a foot ulcer in their lifetime, making them 36 times more likely to experience subsequent amputation [7, 8].

The treatment goal for diabetes-related foot ulcers (DRFUs) is to achieve healing as quickly as possible to prevent the onset of serious complications. Treatment commonly includes antibiotic therapy for infection, re-vascularisation in the presence of reduced arterial perfusion, offloading of pressure, appropriate dressings and regular debridement of non-viable tissue [6, 7]. Debridement is fundamental in DRFU management [6] and facilitates healing by ensuring the best possible preparation of the wound bed and margins [9, 10]. Many different methods of debridement exist but there is very little evidence to support a single method or the frequency that it should be performed [6, 10]. Similarly, there are variable costs of debridement methods and there is little economic evaluation of cost versus effectiveness to guide clinicians to make economically feasible treatment choices [11].

The primary outcome of this study is proportion of DRFUs healed using non-surgical sharps debridement (NSSD) versus low frequency ultrasonic debridement (LFUD) over a six-month period. Secondary outcomes include quality of life measure and assessment of pain before, during and after treatment. This study adhered to a previously published protocol [12].

Main text

Participants and setting

From March 2013 to February 2015 all patients with a DRFU receiving treatment by podiatry at Monash Health, Victoria, Australia, were screened against the study inclusion criteria (Table 1).

Table 1: Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
General: ≥ 30 years of age Able to provide informed consent Ulcers present for ≥1 month Ulcers ≥ 1cm^2	General: Patients taking immunosuppressive medications Known allergy to ulcer dressing products Pre-existing ulcer pain preventing either type of debridement
Vascular: Palpable pedal pulses OR toe pressure ≥ 45mmHg OR those meeting Rutherford Classification of peripheral arterial disease stages [13]: 0 (asymptomatic) 1 (mild claudication) 2 (moderation claudication at 200m)	Vascular: Those meeting Rutherford Classification of peripheral arterial disease stages: 3 (severe claudication) 4 (rest pain) 5 (ischaemic ulceration no exceeding ulcer of the digits of the toes) 6 (severe ischaemic ulcers of frank gangrene)
Ulcer classification: Infected ulcers being appropriately managed Those meeting The University of Texas Wound classification criteria [14]: A1, A2, A3 (wounds of varying depth without infection or ischaemia) B1, B2, B3 (wounds of varying depth with infection only)	Wound classification: Dry gangrenous ulcer Fungating ulcers Malignant ulcers Those meeting the University of Texas wound classification criteria: A0, B0, C0, D0 (pre or post-ulcerative lesion with complete epithelialisation, with or without infection and ischaemia) C1, C2, C3 (wounds of varying depth with ischaemia only) D1, D2, D3 (wound of varying depth with infection and ischaemia

Participants identified as meeting the study criteria were informed about the research project by the treating podiatrist. Those agreeable to participating were provided with a patient information and consent form and written consent was obtained. Approval was granted by the Monash Health Human Research Ethics Committee (HREC reference number 12101B).

Interventions

The two interventions included LFUD (intervention) and NSSD (control), which were applied according to a standardised technique. Debridement occurred weekly until healing occurred. The time of each debridement was performed for as long as required to remove as much non-viable tissue as possible from the wound base. Wound dressings, pressure offloading and footwear were applied according to evidence-based practice [6]. This was decided by the treating podiatrist based on clinical need, ulcer appearance and location.

Participant quality of life was assessed at baseline, three months and at six months or once healed using the validated tool EQ-5D-5L [15]. Where multiple ulcers existed at the same time, on a single participant, and resolved at the same time, the data was represented only once. Ulcer pain was measured before, during and after each debridement using a validated 100mm Visual Analogue Scale [16].

Outcomes

The primary outcome measure for this study was the proportion of DRFUs healed over the six-month follow up period. Healing was determined by assessing the total surface area of the ulceration site. Ulcer depth was measured by the treating podiatrist using a disposable probe at the deepest point following each debridement. Where the ulcer depth could not be measured (less than 0.1cm) but the ulcer remained unhealed, a standardised depth of 0.1cm was used. Ulcer undermining was also measured following each debridement using a disposable probe. The extent of undermining was marked on the skin with a black marker.

Photographs were taken using a digital camera following each debridement. A standardised technique was implemented to reduce variation in photographic angles. Calculation of wound surface area was undertaken at the completion of the study by a member of the research team not involved in data collection (CW). A previously established inter-rater measurement reliability of calculating wound surface area between the treating podiatrist and a research team member was 0.99.

Secondary outcome measures included ulcer pain before, during and after each debridement using a validated 100mm Visual Analogue Scale (VAS) [16]. Health related quality of life was assessed using the validated EQ-5D-5L [15]. This tool analyses five health-related quality of life domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants completed this at the initial treatment, three months and again at six months or the final appointment.

Randomisation

After consent had been obtained participants were randomised into either the control group or intervention group. Randomisation was undertaken using a permuted-block approach. Randomisation blocks of two, four or eight participants were generated and randomly selected with the resultant allocation order placed into opaque sealed envelopes by an investigator not involved in recruitment or patient assessment (CW). The treatment for each participant was determined as per the random allocation sequence following completion of initial podiatric assessment. All DRFUs (where a single participant had more than one ulcer) were numbered and documented according to anatomical location prior to randomisation. Only the treatment modality was randomised, therefore, when a single participant had more than one DRFU, all were treated using the same method.

Participants and treating podiatrists were unable to be blinded to treatment as neither method of debridement could be concealed. However, data analysis was undertaken without knowledge of the treatment allocation.

Procedure

The DRFUs being treated in the intervention group were re-assessed after six weeks of treatment. If LFUD was no longer clinically indicated then this method of debridement was ceased and the ulcer was transitioned to the control treatment of NSSD. Clinical indications for ceasing LFUD included pain, small ulcer size or high levels of exudate.

As per the study criteria the ulcers included in this study were greater than four weeks old and therefore had received treatment prior to being enrolled in the study. The treatment prior to enrolment was determined at baseline through patient assessment and included surgical debridement, NSSD, autolytic debridement through dressings, topical negative pressure wound therapy, split skin grafting, offloading via podiatry felt padding, footwear or total contact casting.

Statistical Analysis

All analyses were undertaken using the intention to treat principle. The proportion of DRFUs that were healed by the six month follow up period was compared between the two treatment groups using Kaplan Meier survival analysis approach. Due to the small sample size the planned logistic regression analysis was unable to be completed.

Pain and quality of life scores were not analysed statistically due to insufficient numbers of participants and as a result baseline comparability between the two groups could not be ensured.

Results

A total of 10 participants with 14 ulcers were recruited to this study. Of the 14 ulcers, two ulcers (two different participants) were lost to follow up, one from each group. In one instance this was due to hospital admission to a different health service (intervention) and the other participant changed residential locations (control). Summative data for the primary outcome is presented in Table 2.

Table 2: Outcome data per ulcer

Control group			Intervention group		
Ulcers healed	**Ulcers not healed**	**Lost to follow up**	**Ulcers healed**	**Ulcers not healed**	**Lost to follow up**
5	0	1	5	2	1

A survival analysis estimating time to ulcer healing was undertaken and is presented in Figure 1. Diabetes related foot ulcers treated with NSSD healed in a mean (SD) of 61.6 (24.4) days compared with those treated with LFUD healed in a mean (SD) of 117.6 (40.3) days.

The use of analgesia during treatment was comparable between both groups, with the same three ulcers from each group requiring some form of analgesia for every treatment. It was observed that pain levels increased during treatment but then returned to baseline levels after treatment.

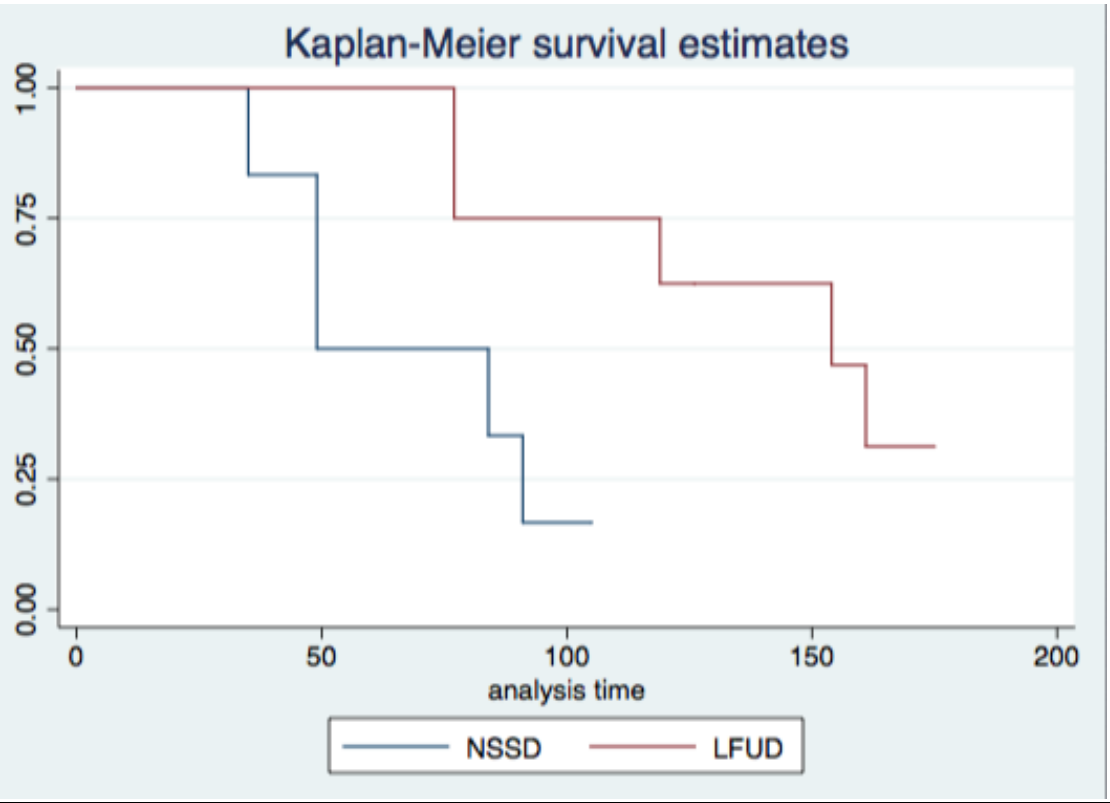

Figure 1: Kaplan-Meier survival estimates

The quality of life reported in both groups demonstrated an improving trend in scores as the ulcers progressed towards healing.

Adverse events

During the follow up period 3 of the 14 ulcers were treated with oral antibiotics for minor soft tissue infections. No ulcer developed ascending cellulitis or osteomyelitis. No participants required surgical intervention, amputation or hospital admission during the follow up period. No other adverse events occurred throughout the study period.

Discussion

Debridement is important to facilitate healing of DRFUs. This research investigated two methods of debridement available to clinicians that has not been widely studied. Whilst it was observed that ulcers treated with NSSD healed at a faster rate than those treated with LFUD, the sample size was too small to determine if this finding is significant. Despite the small sample size, our study findings are consistent with similar studies previously conducted comparing LFUD to NSSD in DRFUs. Four studies have previously been published, with three describing clinical trials involving randomisation and one using historical data as the control [17-20]. Although each of these studies concluded that DRFUs heal faster using NSSD compared to LFUD, between-study comparison was made difficult by heterogenic study design. These included differences between the type of LFUD performed, the frequency of treatments and variation in control treatments including wound dressings and offloading methods.

Limitations

The greatest limitation of this study was the difficulty experienced recruiting participants. This makes it difficult to draw clinically significant conclusions. Furthermore, the planned statistical analyses, including health economics, were not undertaken.

Many attempts were made throughout the study period to address barriers to recruitment and increase participant numbers:

- Medical histories of all patients under podiatry care were reviewed by the primary investigator (LM) on a monthly basis to determine if study criteria were met and the patients could be considered for enrolment
- Study criteria were pragmatically revised multiple times with approval from the relevant human research ethics committee
- Recruitment was extended to include patients with DRFU attending Vascular Outpatient clinics
- A second LFUD unit was secured on loan to allow a second podiatrist to potentially treat patients enrolled in the study at an additional site
- Discussion ensued with the Podiatry Department at a second organisation with a view to implementing a multisite study

Despite numerous attempts to increase recruitment rates the sample size fell short of numbers required to generate broadly applicable findings. These logistic problems were difficult to overcome and highlight the challenges of undertaking clinically unfunded research within populations with complex health needs.

There were a number of limitations that the research also encountered during the design and implications that future researchers should consider when undertaking this type of research with patients who have DRFUs:

- The type of ulcer dressings and pressure offloading used were not standardised
- Inaccuracies in measuring ulcer depth where depth was less than 0.1cm

An important strength of this study design was the use of contact LFUD. Previously, only non-contact LFUD has been investigated in DRFUs [17-20]. Contact LFUD is thought to produce a cavitation effect, resulting in direct and immediate removal of nonviable tissue from the ulcer base. As the name suggests, noncontact LFUD produces the same phenomena but at a lower intensity and does not directly contact the ulcer surface. These slight variances mean that there is no debridement of necrotic tissue when noncontact LFUD is used [21]. This is also the first study to investigate the contact application of LFUD in DRFUs.

This study has revealed some interesting findings, which we believe would benefit from further investigation. Future randomised controlled trials would be of value to evaluate the clinical effectiveness of both debridement methods in the management of DRFUs. This patient population were found more likely to have multiple medical comorbidities that excluded them from ulcer debridement when subsequent patient lists were screened over the two-year study period. This was an unexpected finding as the researchers designed this trial for patients with common traits applicable to DRFUs. Therefore, any future prospective research on this topic would benefit from consideration to a multisite

study to ensure a large enough sample size could be reached. Additionally, the authors recommend including community care podiatry clinics where patients are more likely to be medically stable than those attending outpatient podiatry clinics based in the acute setting. Future research should also further investigate pain and quality of life assessment for patients between groups, as well as, the economic efficiency between both methods of debridement.

Abbreviations

Non-surgical sharps debridement (NSSD), low frequency ultrasonic debridement (LFUD), diabetes-related foot ulcer (DRFU)

Declarations

Ethics, consent and permissions

Monash Health Human Research Ethics Committee (HREC reference number 12101B). Written consent obtained from all participants.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Funding

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Acknowledgements

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Trial registration

Australian New Zealand Clinical Trial Registry: ACTRN12612000490875.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

Author contributions

All the authors (LM, CW, SB, TH) contributed to the study design, methodology and result analysis. LM and CW obtained funding for the study. LM undertook the data collection. LM is the chief investigator and drafted the paper with editorial assistance from CW, SB, TH. All authors (LM, CW, SB, TH) have approved the final manuscript.

Full protocol

The study reported here was part of a doctoral thesis from where the full protocol and further methods can be accessed. (Michailidis, L.; William, CM.; Bergin, SM.; Haines, TP. Comparison of healing rate in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised trial protocol. Journal of Foot and Ankle Research, 7:1, 2014).

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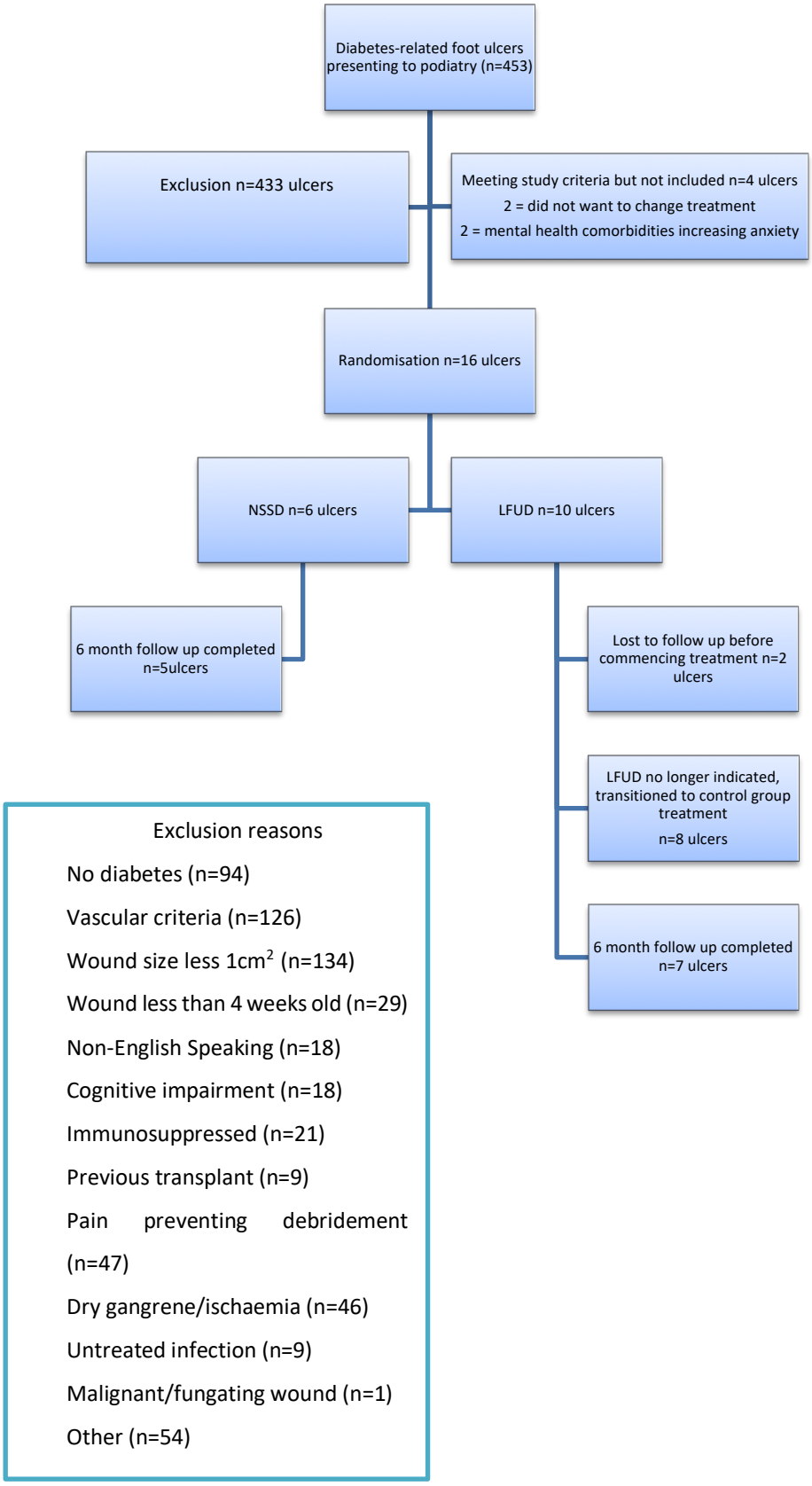
5.5 Addendum to Chapter 5

The following figures and tables were developed during the research but were not submitted for publication.

Figure 2: Consort flowchart



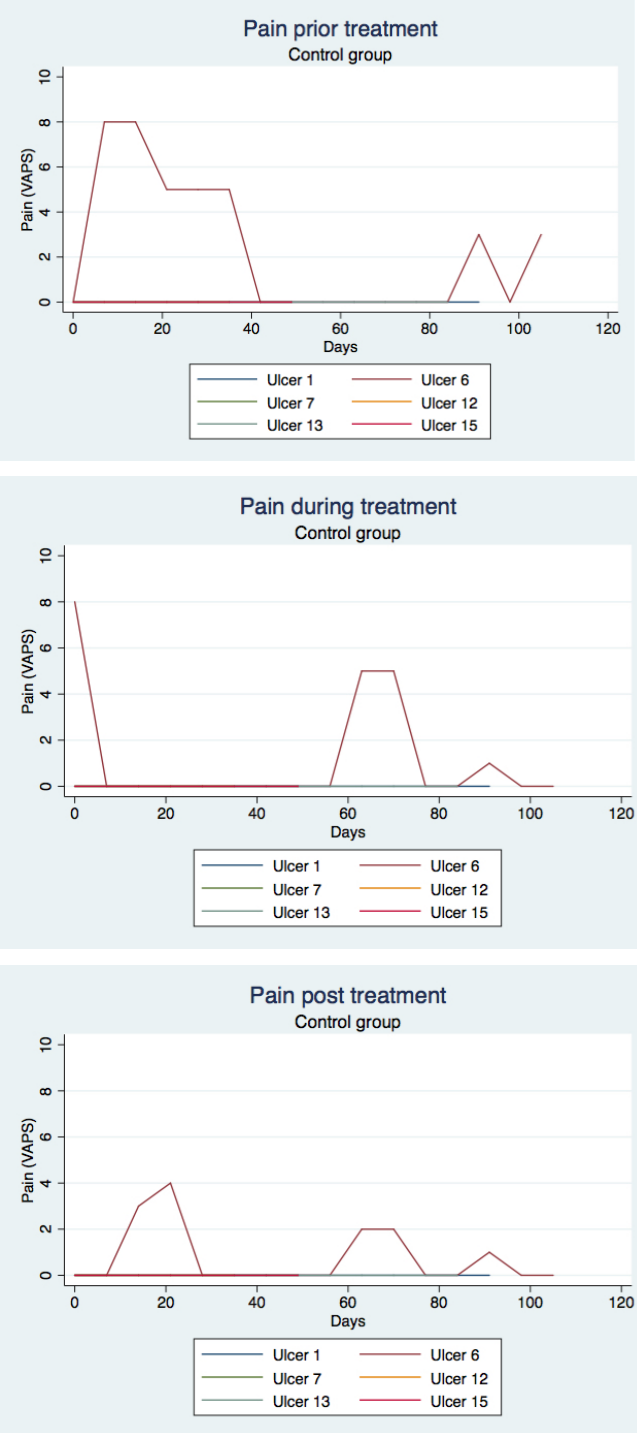
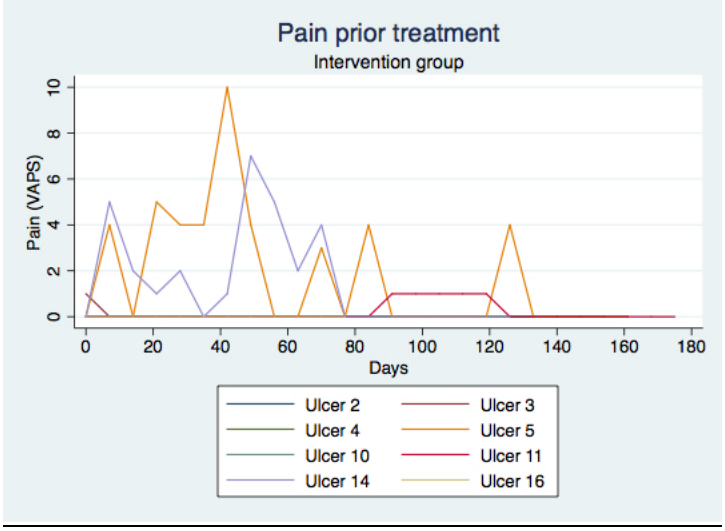
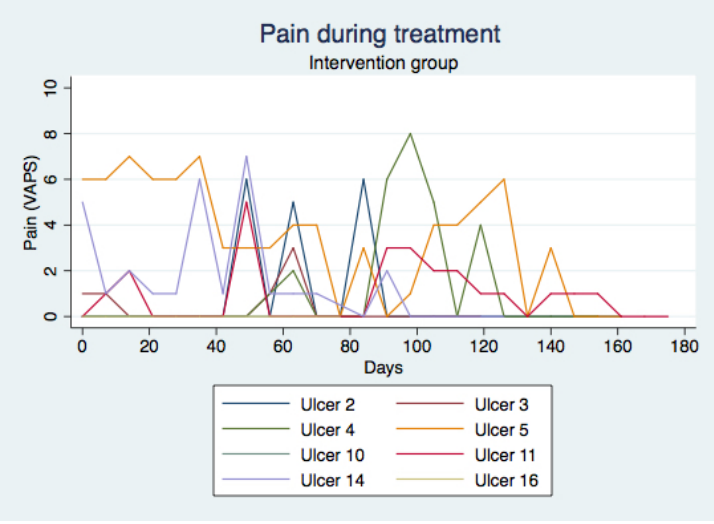


Figure 3 Pain levels before treatment, during treatment, after treatment for control group





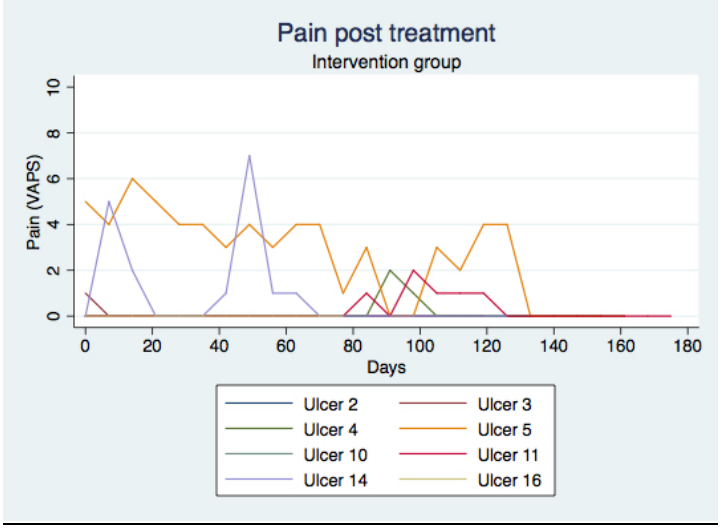


Figure 4 Pain levels before treatment, during treatment, after treatment for intervention group

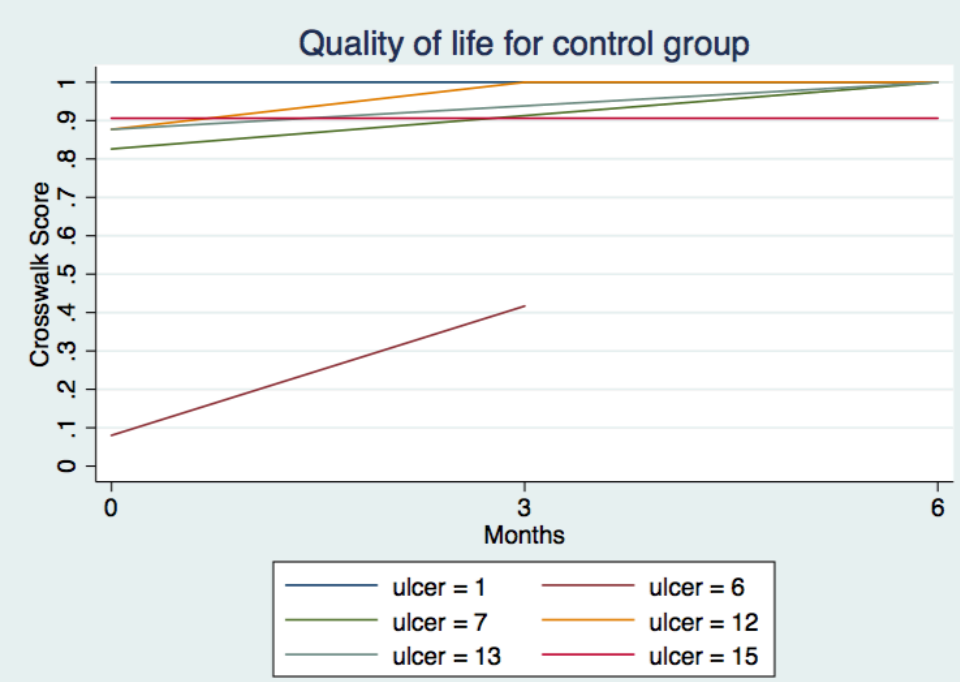


Figure 5 Quality of life data for the control group

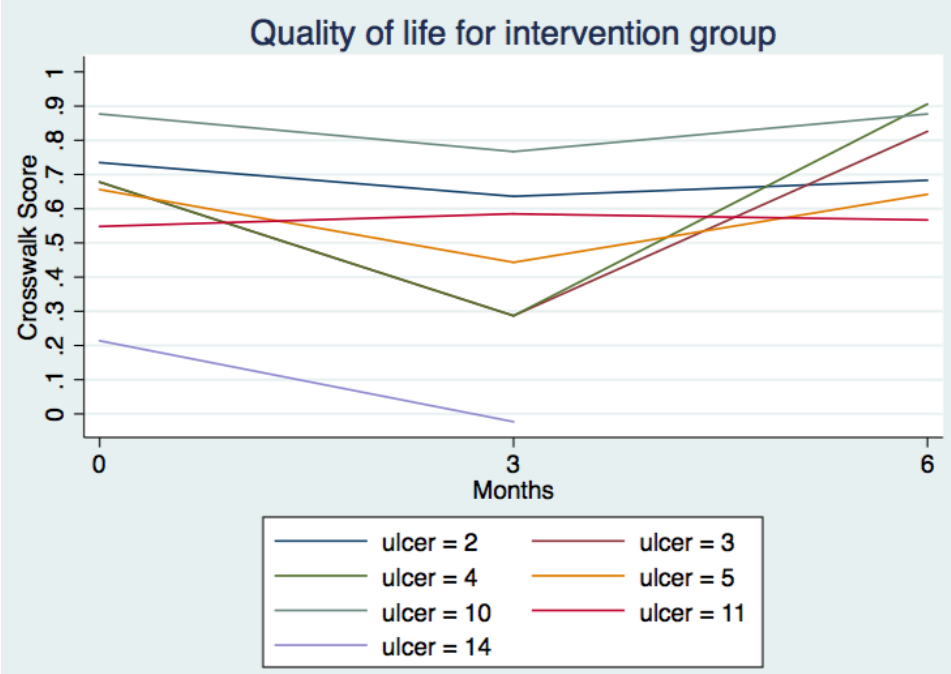


Figure 6 Quality of life data for intervention group

Table 3: Standard step-by-step technique for LFUD and NSSD

LFUD	NSSD
1. Constantly move the handpiece to prevent ultrasound burning tissue 2. Start debriding at the distal most aspect of the ulcer 3. Moving the handpiece left to right and from the distal to proximal aspect of the ulcer 4. Once the entire ulcer surface has been debrided re-commence the same technique from the distal most aspect of the ulcer 5. Continue until as much necrotic tissue has be removed as possible 6. Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel. The wound base will not be debrided with the scalpel.	1. Start debriding at the distal most aspect of the ulcer 2. Moving scalpel proximally with each motion 3. Once the distal to proximal ulcer has been debrided then debride from left side to right side 4. Continue until as much necrotic tissue has been removed as possible 5. Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel.

Table 4: Standard step-by-step technique for ulcer measurement

Ulcer measurement
1. Ulcers that have tunnels or undermining will be marked on the skin with a black marker. 2. A white towel will be place under the foot to remove distracting background elements. 3. A disposable ruler will be labelled with participant number, wound number, participant initials and the date. 4. Position the disposable ruler alongside the ulcer and secure with paper tape. 5. Use macro camera setting with flash on, iso set to 200. 6. Take photograph at a distance of 20cm from the wound 7. Ulcer measurements will be conducted from print out using the photograph (all photos will be printed as standard A4 size)

Table 5 Participant characteristics at baseline

Variable	Total study population Mean (SD) or n (%)	Control group Mean (SD) or n (%)	Intervention group Mean (SD) or n (%)
Age, (years)	65.23 (6.94)	67.8 (3.13)	63 (8.38)
Sex			
Female	2 (20)	1 (25)	1 (17)
Male	8 (80)	3 (75)	5 (83)
Diabetes type			
T1DM	1 (10)	1 (25)	0
T2DM (insulin)	9 (90)	3 (75)	6 (100)
Diabetes duration			
> 10 years	1 (10)	1 (25)	0 (0)
< 10 years	9 (90)	3 (75)	6 (100)
Hba1c (%)			
> 6.5%	1 (10)	0 (0)	1 (17)
6.5 – 7%	0 (0)	0 (0)	0 (0)
< 7%	9 (90)	4 (100)	5 (83)
Neuropathy	9 (90)	4 (100)	5 (83)
Peripheral arterial disease	4 (40)	3 (75)	1 (17)
Ischaemic heart disease	7 (70)	4 (100)	5 (50)
Chronic kidney disease	5 (50)	3 (75)	2 (33)
Dialysis-dependant	2 (20)	1 (25)	1 (17)
Previous amputation	6 (60)	3 (75)	3 (50)

Table 6 Baseline data as categorised per ulcer

Variable	Total study population n (%)	Control group n (%) or mean (SD)	Intervention group n (%) or mean (SD)
Ulcer aetiology			
Post-surgical	6 (43)	3 (50)	3 (38)
Neuropathic	4 (29)	2 (33)	2 (25)
Burn	2 (14)	0 (0)	2 (25)
Trauma	1 (7)	1 (17)	0 (0)
Pressure injury	1 (7)	0 (0)	1 (12)
Ulcer duration (months)			
1-3 months	11 (79)	4 (67)	7 (88)
4-6 months	1 (7)	1 (17)	0 (0)
6-12 months	2 (13)	1 (17)	1 (12)
Ulcer size (cm^3)	-	2.33	2.6

CHAPTER 6 – ECONOMIC EVALUATION

6.1 PREAMBLE

As discussed in Chapters four and five, a number of issues in attempting to conduct the randomised controlled trial that impacted participant recruitment, which altered the intended trajectory of this research. Sample size calculation was based on an estimated minimal important clinical difference of 25% of ulcers treated with non-surgical sharps debridement healing within six months and 41% of ulcers treated with low frequency ultrasonic debridement healing within three months. Using this method, a total of 322 ulcers/108 participants was required. Failure to recruit to the required sample size meant the economic analysis methodology was modified and the minimally important difference was calculated.

Given the difference in cost between provision of non-surgical sharps debridement and low frequency ultrasonic debridement, while at the same time considering the significant costs that arise when diabetes-related foot ulcers fail to heal, we postulate that the minimum sample size for a trial could plausibly have been based on a different effect size. In this study, the estimated cost of both healed and non-healed of diabetes-related foot ulcers treated with non-surgical sharps debridement and treatment with low frequency ultrasonic debridement in conjunction with non-surgical sharps debridement were examined to try to ascertain the minimum effect size necessary to make the use of low frequency ultrasonic debridement in addition to non-surgical sharps debridement economically justifiable. A revision of the planned sample size for the original clinical trial is then undertaken to see how large the trial would have needed to be in order to detect an effect size that could have been considered to be the minimum economically important difference.

6.2 DECLARATION FOR THESIS CHAPTER 6

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of Contribution	Extent of contribution
Author	70%

The following co-authors contributed to the work:

Name	Nature of Contribution	Extent of Contribution
Dr. Cylie Williams	Co-author	10%
Dr. Shan Bergin	Co-author	10%
Prof. Terry Haines	Co-author	10%

LM, TH & CW conceived and contributed to the study design. LM & CW contributed to the data collection. LM, CW & TH interpreted the results. LM drafted the manuscript. LM, TH, SB & CW revised the manuscript for important intellectual content. All authors approved the current version of the manuscript under submission in *Diabetes Care*.

Declaration by co-authors:

The undersigned hereby certify that:

(1) The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) There are no other authors of the publication according to these criteria;

(5) Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit

Dr. Cylie Williams	Date: 30/01/2019
Dr. Shan Bergin	Date: 30/01/2019
Prof Terry Haines	Date: 30/01/2019

Clinical and cost effectiveness of two debridement methods for management of diabetes-related foot ulcers.

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Introduction

Diabetes is one of the most common chronic diseases globally and the associated complications are a recognised cause of early death in most developed and developing countries [1]. Global health care costs for people with diabetes have been found to be two fold higher than for people without diabetes [1]. In 2015, this accounted for 11.6% of total health expenditure globally.

Foot ulceration is one of the many complications that can develop secondary to diabetes. The pathophysiology of diabetes-related foot ulcers is complex and usually multi-factorial. Peripheral sensory neuropathy, foot deformity and external trauma [2], when occurring simultaneously [3], have been identified as being the three most common factors leading to foot ulcer development. Peripheral arterial disease has also been shown to contribute to the development of diabetes-related foot ulcers [4].

Complications affecting diabetes-related foot ulceration (DFU) include infection and tissue necrosis. Such complications have implications for wound healing and can lead to delayed healing, hospital admission and amputation [5]. Management of DFUs is complex and protracted resulting in significant cost to the patient and the health service. In Australia, it was estimated that hospital costs alone for diabetes-related foot ulcers were as much as US$239 million between 2010-2011 [6]. Similarly, in the United States in 2007, it was thought nearly US$352 million was spent on the management of DFUs [7].

Successful resolution of DFUs relies on such fundamental components as moist wound healing, pressure offloading and debridement [4, 8]. The purpose of debridement is to remove non-viable tissue from the wound bed with the aim of reducing the likelihood of infection, to facilitate new tissue growth and allow for visualisation and assessment of the wound base [9, 10]. Different methods of debridement are utilised including: autolytic debridement via moist wound healing, mechanical debridement utilising wet to dry dressings, surgical-based sharps debridement, biological debridement, non-surgical sharps debridement and low frequency ultrasonic debridement [10-13]. There is however, no literature that espouses one method of debridement over another and clinician choice is usually driven by availability of equipment, clinical expertise and the clinical presentation of the ulcer and patient expectations.

In determining the effectiveness of different debridement techniques, it is important to consider the costs associated with each method, alongside their clinical efficacy. In this paper clinical outcomes as well as a break-even economic analysis are reported in order to quantify the minimal economically important difference for two methods of debridement that differ greatly in purchase cost and ongoing consumable cost per session in DFUs. Low frequency ultrasonic debridement, which retails for AUD$100,000 compared to non-surgical sharps debridement which retails for AUD$10. This study also sought to identify how large a randomised trial would need to be to detect a minimal economically important difference.

Method

Design

An economic modelling study was undertaken based upon a retrospective review of health care records. We sought to identify both the cost of service provision and clinical outcomes for patients with a DFU treated with low frequency ultrasonic debridement in conjunction with non-surgical sharps debridement, compared to the use of non-surgical sharps debridement alone. Identifying costs and clinical outcomes, allows for the break-even point and therefore, the minimal economically important difference to be estimated. Study findings provide important information for subsequent clinical trials comparing these treatment approaches and support clinical decision making regarding choice of debridement method.

Participants

Participants were individuals over the age of 18, with a DFU being treated by two tertiary Podiatry Departments in Melbourne Australia, between January and July 2015. Treatment involved use of either non-surgical sharps debridement, or the combination of non-surgical sharps debridement and low frequency ultrasonic debridement. Patients were treated in both the inpatient and outpatient settings. No consent was required as this was a retrospective audit of medical records. Low risk ethics was obtained from both health organisations.

Procedure

Data Collection

All healthcare records relating to podiatry treatment for each DFU were audited from the initial podiatry contact through to discharge from the service or the time of death if that occurred during the treatment period.

Documentation Audit

Two researchers (LM and CW) undertook the documentation audit, one at each health organisation. A data collection sheet was developed to capture the following information:

- Initial and final treatment dates of the ulcer
- Number of debridement sessions using each method (non-surgical sharps debridement or combination debridement)
- Final ulcer outcome (healed, progressed to minor amputation, progressed to major amputation, not healed and receiving ongoing treatment, patients who died prior to ulcer healing)
- Number of podiatry occasions of service within each treatment setting (inpatient acute, inpatient subacute, outpatient, community health)
- Length of hospital stay for any admissions during the treatment period of the ulcer
- Number and type of imaging related to the ulcer (Foot X-Ray, Ankle X-Ray, MRI, Arterial Duplex Ultrasound, Diagnostic Ultrasound, Bone Scan, CT, Angiogram)
- Number and type of pathology taken for the ulcer (wound swab, tissue sample, bone sample)

Cost calculation for inpatient admission

Clinical outcomes for inpatients were categorised using identified Diagnoses Related Group (DRG) codes [14] allocated to the outcomes of amputation for circulatory system – except upper limb and toe, not catastrophic (major amputation – F11B), amputation for circulatory system – upper limb and toe, not catastrophic (minor amputation – F13B) minor amputation, major amputation, skin ulcer in circulatory disorders, not catastrophic (F64B) or rehabilitation, not catastrophic (Z60B). This Australian classification system codes admitted episodes of care in the acute or subacute setting.

Allocated DRG codes were then entered into the National Weighted Activity Unit calculator [15]. This provides a dollar value for a single acute or subacute hospital bed day. The value obtained from the calculator was then multiplied by the total number of ulcers allocated to each DRG for the two treatment groups.

Cost calculation for outpatient/community health appointment

The Finance Department at one of the health organisations was consulted to obtain costs for a single podiatry outpatient appointment. Clinician time and on costs was calculated as AUD$53 per hour. This was based on the Victorian Public Sector award for an experienced podiatrist who had a clinical load with no management requirement.

Service provision

The cost of service provision in hospital and outpatient settings, for both non-surgical sharps debridement and combination debridement, was calculated by adding the market costs of all consumables use and wound pathology and/or medical imaging that resulted for each episode of care. The value of pathology and imaging costs were determined using the Australian Medicare fees as the weight [16] (Table 1).

Table 1: Costs of microbiology and imaging

Item	Cost (AUD)
Wound swab	$40
Foot X-ray	$43.30
Bone scan	$333.55
CT (foot)	$334.65
MRI (foot)	$448
Angiogram (lower limb)	$1800
Duplex arterial ultrasound (lower limb)	$180

Consumable costs associated with both methods have been previously calculated using data collected as part of a randomised controlled trial undertaken in parallel but separate to this audit at Monash Health (Australian New Zealand Clinical Trial Registry: ACTRN 12612000490875). The previously calculated average cost of consumables for one treatment utilising non-surgical sharps debridement is $AUD24 and for low frequency ultrasonic debridement $AUD86.

Overall costing

Two overall costs were calculated for the purpose of the analysis performed. Firstly, the cost of ulcer healing was determined by adding the total inpatient costs, outpatient costs and service provision costs for the total number of

DFUs that healed for both treatment groups. The same was then calculated for ulcers that did not heal (ulcers that resulted in amputation, required ongoing care or mortality before healing) for both treatment groups.

Analysis

A break-even analysis was performed to quantify the minimal economically important difference (i.e. the degree of superiority in clinical outcome) that the combination of low frequency ultrasonic debridement and non-surgical sharps debridement approach would need to have relative to non-surgical sharps debridement alone in order to justify the greater cost of using the combination debridement option.

Non-surgical sharps debridement group costs

First, the cost of providing podiatry treatment was calculated per DFU for non-surgical sharps debridement alone. This was calculated as the total podiatry costs (consumable costs for non-surgical sharps debridement per occasion of service, the total occasions of service across all treatment settings, the total hours of podiatrist time and the cost of podiatrist time per hour) divided by total number of DFUs. For the purpose of the analyses this cost is referred to as "A".

Combination debridement group costs

Second, the cost of providing the podiatry treatment per DFU using combination debridement was calculated. This was calculated as the total podiatry costs (consumable costs for combination debridement per occasions of service, the total occasions of service across all treatment settings, the total hours of podiatrist time and the cost of podiatrist time per hour). For the purpose of the analyses this cost is referred to as "B".

Other health service costs for ulcers that healed

Third, the costs of other health service use were measured (including hospital admission and rehabilitation) for the DFUs that healed. For the purpose of the analyses this cost is referred to as "X".

Other health service costs for ulcers that did not heal

Fourth, the costs of other health service use were measured (including hospital admission, amputation and rehabilitation, for the DFUs that had not healed that were still undergoing treatment at the time of the audit, not healed prior to mortality, minor amputation and major amputation. For the purposes of the analyses this cost is referred to as "Z".

Break even analysis

Using these calculations, the break-even analysis was then undertaken by inputting these into the formula (Z – X) / (B – A).

Power analysis

A power analysis for a trial to detect the minimal economically important difference as identified in the break-even analysis was undertaken using the "sampsi" command for a comparison of proportions in Stata/MP version 14.0 (College Station, Texas). A baseline healing rate was taken from the healing rate observed amongst records included in the retrospective audit from patients exposed to the non-surgical sharps debridement alone management approach. A power of 80% was employed, along with a two-tailed alpha of 0.05.

Results

There were 235 DFUs treated during the audit period (non-surgical sharps debridement = 210 and combination debridement = 25). Of the 210 DFUs treated with non-surgical sharps debridement, 140 (66%) healed and 70 (33%) did not heal. Of the 25 DFUs treated with combination debridement, 11 (44%) healed and 14 (56%) did not heal.

Total health service costs, including podiatrists time, medical imaging, pathology, inpatient and outpatient appointment costs, for both treatment groups are outlined in Table 2.

Table 2: Data collection summary

	Non-surgical sharps debridement				Combination debridement			
	Healed	Not Healed	Amputation	Death	Healed	Not Healed	Amputation	Death
Consumable cost per occasion of service	24	24	48	24	86	86	172	86
Total occasions of service	1708	433	411	83	377	37	293	0
Therapist time hours (OP and CHS)	1366.96	439.38	355	84.19	323.8	37.1	371.31	0
Therapist cost per hour (incl. on costs)	53	53	106	53	53	53	106	53
Number of DFUs	140	29	33	8	11	4	10	0
Total cost - acute hospital	1422530	535519	1264294	113552	504189	135091	1009561	0
Total cost - subacute hospital	588699	10574	71420	84204	21631	0	80293	0
Total cost - imaging	21837	12707.35	27328	15783.1	20936.8	448	27048.5	0
Total cost - microbiology	1960	200	560	120	160	0	320	0

OP = Outpatient; CHS = Community Health Service

Using the formula for break even analysis as described within the methods section, we found that for the more expensive treatment of combination debridement to be cost saving, this treatment approach would only need to heal a minimum of one DFU in every 22 that would not have healed with non-surgical sharps debridement alone. This assumes the one in three diabetes-related foot ulcers do not heal with treated with non-surgical sharps debridement alone.

A power analysis for a trial that compares the effectiveness of the low-frequency ultrasonic debridement combined with non-surgical sharps debridement, to a control approach of non-surgical sharps debridement alone would therefore need to be powered to detect a difference in the proportion of non-healing ulcers of 0.318 (intervention) to 0.333 (control). Assuming that 80% power is required and a two-tailed alpha of 0.05 is employed, such a trial requires n=15,450 in each arm of this trial (n=30,900 in total).

Discussion

The diabetic foot is a significant economic problem. Management of DFUs requires a multifactorial and multidisciplinary approach, which becomes costly given the challenges faced in trying to achieve rapid healing. Such challenges may include infection, hospital admission and theatre-based intervention, all of which significantly prolong time of healing and increase the cost of management. The cost of new methods to manage this problem, such as low-frequency ultrasonic debridement, may be greater than more conventional approaches (such as non-surgical sharps debridement) but this study has demonstrated that relatively more expensive approaches could still be economically efficient even with a very small effect size due to the very high absolute cost of non-healing ulcers.

This finding not only presents a conundrum for trialists and clinicians seeking to compare these approaches, but also interventions in other contexts where the costs associated with the disease of interest are very high. The sample size required for a trail to detect a difference as small as one additional ulcer being healed for every 22 that would otherwise have not been healed (notionally 33% under usual practice conditions) are extremely large (>30,000 participants). Arguably, this quantum of recruitment may be unfeasibly large for a study of this nature, and it may never be conducted. The risk in this situation is that we base our determinations of intervention efficacy on much smaller trials and dismiss those not found to be significantly effective compared to a control in pooled analyses as being ineffective even though the 95% confidence intervals of such a meta-analysis include values greater than what would be considered to be minimal, economically efficient. This would also indicate that use of Cohen's arbitrary, conventional effect sizes to guide sample size determinations in these contexts should also be avoided in preference for knowing what the minimal economically efficient effect size would be.

It was not unexpected that the overall cost of providing the combination of low frequency ultrasonic debridement and non-surgical sharps debridement was higher than non-surgical sharps debridement alone. The former approach uses considerably more consumables in its setup and delivery and has a higher fixed cost associated with purchase of the low frequency ultrasonic debridement machine. It is not clear based on current evidence whether a model of care utilising low frequency ultrasonic debridement in addition to non-surgical sharps debridement is more economically

efficient than non-surgical sharps debridement alone. It is clear that the cost of delivering the former approach is higher, however, a hybrid approach could also be argued for where the combination debridement approach is employed as a secondary approach if non-surgical sharps debridement alone has not led to ulcer size reduction by half within four weeks [17].

Limitations

Several limitations should be acknowledged with this research. First, costs were not allocated to DFUs that required theatre-based interventions (debridement, vascular lower limb angioplasty or bypass procedures) during the management of the ulcer. These procedures would have increased the cost significantly given the additional costs required for surgeons, theatre staff and theatre time. This data was excluded as it was not readily available from the retrospective audit and actual numbers of patients who underwent these procedures could not be confirmed.

The two health organisations that undertook this documentation audit are public health care facilities. Some patients who were included in the study had admissions into private hospitals for the management of their ulcers during the audit period. These records were unavailable for review therefore this data could not be included.

Only fixed and variable costs of health service delivery were included for analysis. Some downstream costs were not obtained and were therefore not included. These costs included patient self-pay items, ulcer dressings and medications. Costs associated with managing diabetes, other health conditions and any complications that developed due to the DFU were not collected.

Conclusion

Treatment with the combination debridement approach of low frequency ultrasonic debridement and non-surgical sharps debridement is more expensive per session than non-surgical sharps debridement alone for management of DFUs. This difference in cost however, is dwarfed where DFUs treated with non-surgical sharps debridement do not heal and go on to require long term management and possibly costly surgical interventions. Consequently, treatment with combination debridement only has to be a little more effective than non-surgical sharps debridement in order for the additional costs to be justified. Clinicians managing chronic DFUs should consider utilising the combination debridement approach where ulcers are not healing as expected.

Ethics

This research was approved by Monash Health (16129Q) and Peninsula Health (QA/16/PH/9) Human Research Committees.

Authors' contributions

All the authors contributed to this manuscript. LM and CW undertook the audit. LM drafted the paper. All authors contributed to data analysis. SB, TH, CW provided editorial assistance. All authors have read and approved the final manuscript.

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CHAPTER 7 – CONCLUSION

7.1 CHAPTER SUMMARY

This thesis has described a series of investigations examining clinical effectiveness, efficiency and infection control risks of using low frequency ultrasonic debridement compared to non-surgical sharps debridement in the management of diabetes-related foot ulcers. This final chapter integrates the findings across the five papers presented in this thesis. It also describes the strengths and limitations of the research, and how best to progress future research in this area.

7.2 SUMMARY OF FINDINGS

The systematic review (Chapter 2) concluded that there was insufficient evidence to support low frequency ultrasonic debridement being more effective approach for healing of diabetes-related foot ulcers when compared to non-surgical sharps debridement.

The potential to spread infectious organisms when using low frequency ultrasonic debridement was investigated and discussed in Chapter 3. This was the first study undertaken in a clinical setting that investigated the extent and number of microbes aerosolised from the use of this treatment modality. The findings from this research indicated that under certain conditions (a lower ultrasound amplitude, lower saline flow rate and no suction) an increased number of microbes become aerosolised during treatment. Greater numbers of circulating microbes pose an increased risk of infection and cross contamination. The results of this study prompted immediate changes in clinical practice at relevant health services in Australia. These clinical practice changes were made in order to reduce these infection control risks and protect the patient, clinician and clinical environment.

A randomised controlled trial protocol (Chapter 4) and results (Chapter 5) was designed to addressed the gaps in the literature found from the systematic review (Chapter 2). The primary aim of the randomised controlled trial was to determine whether low frequency ultrasonic debridement was more effective than non-surgical sharps debridement alone, in terms of the proportion of ulcers healed over a six month follow up period. As discussed within Chapter 5, this randomised controlled trial was ceased early due to the inability to recruit the intended sample size. This resulted in the question of the comparative effectiveness of these two treatment approaches remaining unanswered.

A retrospective health care record audit was subsequently undertaken. The aim of this audit was to compare the clinical outcomes of people with diabetes-related foot ulcers treated being treated using non-surgical sharps debridement, or the combination of non-surgical sharps debridement and low frequency ultrasonic debridement (Chapter 6). This audit facilitated examination of the comparative costs of providing these different treatment approaches, which in turn allowed a break even analysis to be conducted to determine the minimal economically important difference needed to justify the use of the more expensive low frequency ultrasonic debridement method, when used in combination with non-surgical sharps debridement. Results indicated that for the combination of low frequency ultrasonic debridement and non-surgical sharps debridement to be the preferred approach (in terms of economical efficiency), it would only

need to result in the healing of a minimum of one ulcer in every 22 ulcers that would otherwise not have healed when treated with non-surgical sharps debridement alone. This finding was driven by the relatively high cost of treating non-healing diabetes-related foot ulcers with surgical intervention.

When summarising all findings from the different elements of work from this research, low frequency ultrasonic debridement cannot be recommended as the frontline debridement approach in diabetes-related foot ulcers. There remains insufficient evidence of clinical effectiveness and cost efficiency to warrant purchasing this equipment and using it in daily clinical practice. Furthermore, the increased infection control risks associated with the use of this treatment make it more difficult to justify its use as standard practice. Where health services already have this technology, the risk of infection could potentially be mitigated with the appropriate protective personal equipment and treatment area protection, as discussed in Chapter 3. The use of low frequency ultrasonic debridement could however be considered where diabetes-related foot ulcers are not responding to standard practice including non-surgical sharps debridement and evidence based wound care, as a means of potentially avoiding or delaying the need for interventions, such as amputation.

7.3 Clinical implications

Findings from this research have direct clinical implications for all clinicians who treat diabetes-related foot ulcers. The results are also applicable to Australian and international healthcare settings where low frequency ultrasonic debridement equipment is used for wounds of other aetiologies.

This research changed current thinking with regards to infection control risks associated with the use of low frequency ultrasonic debridement in wound management. Previously, the infection control risks and standards for environmental control were based on laboratory studies using a different form of hydrodebridement.

A common complication of diabetes-related foot ulcers is infection, and it is estimated that half of all diabetes-related foot ulcers will become infected and require hospital admission for management, and 20% of these will result in amputation [1]. Wound infection rates, and associated consequences, in this patient population is a recognised problem, so much so, that the International Working Group on the Diabetic Foot have developed a guidance document for clinicians [2]. Given the increased susceptibility to infection of the patient group, clinicians must be cognisant of the risks associated with the use of low frequency ultrasonic debridement resulting in infective microbes becoming airborne and contaminating the clinical environment. It is clearly documented in the literature that environmental contamination contributes to the incidence of hospital acquired infections [3] and The World Health Organisation recommends that any infection control risks associated with new technologies should be investigated prior to their approval for use [4]. The research findings from this thesis prompted immediate change in local clinical practice in relation to the use of low frequency ultrasonic debridement and prompted the implementation of clinical guidelines at the two organisations where this research took place. These guidelines and associated research were presented at both the Wounds Australia, and European Wound Management Association conferences in 2016 and subsequently, several other Australian health services adopted the guidelines, and one health service ceased the use of low frequency

ultrasonic debridement altogether. There is potential that following the publication and presentation of these results, more organisations may have also changed practices around the use of low frequency ultrasonic debridement. Unfortunately, the risk of aerosolised microbes during this treatment is impossible to avoid. It is imperative that organisations who consider purchasing this technology are aware of the infection control implications associated with its use. The company who manufacture this technology has since developed a shield attachment that retro-fits to the low frequency ultrasonic debridement handpiece, to reduce the aerosolisation of microbes. While this new attachment has not been subject to rigorous testing in the clinical environment, this advancement acknowledges the limitations of the equipment and challenges to its use in the health care setting.

The clinical effectiveness of low frequency ultrasonic debridement in diabetes-related foot ulcers remains unclear following completion of this research. The challenges in study recruitment of a homogeneous population to this trial was problematic. The resulting small sample size, and subsequent lack of statistical analysis, means that uncertainty remains for true clinical effectiveness of low frequency ultrasonic debridement on healing rates for diabetes-related foot ulcers. Additionally, justification of the initial upfront expense, ongoing consumable costs, additional staff time required, servicing costs and replacement of faulty equipment may be difficult to justify when the potential clinical benefits are still largely unknown.

In summary, the use of low frequency ultrasonic debridement cannot be recommended as standard practice in the management of diabetes-related foot ulcers, based on the findings from this study. Organisations must give strong consideration to purchasing this technology given the overall expenses, limited clinical effectiveness data available, and significant infection control implications with its use.

7.4 LIMITATIONS OF RESEARCH

The clinical trial investigating clinical effectiveness failed to recruit the required number of participants needed for the desired analysis to be undertaken. A number of avenues were explored to try to increase participant recruitment, as discussed in Chapter 5, however, they were not successful. The results cannot assist in guiding clinical practice without formal analysis. Feasibility data were used to develop the trial but the difficulty in recruitment was not anticipated during data collection. Recently, many challenges in diabetes-related foot ulcer research have been proposed [5]. Some of these challenges include individual or systematic factors. People with diabetes have complex health needs and associated foot ulcers are often caused by multiple factor [6, 7]. Multifactorial treatment is required for diabetes-related foot ulcers [1], which requires many different health professionals involved in a patient's care. People with diabetes-related foot ulcers have also been found to be prone to develop depression [8]. It is possible that their mental health could also influence the decision to be involved in clinical research. These two challenges are just an example of some difficulties that researchers face when attempting to recruit a patient population living with a complex chronic disease.

A possible limitation to the economic evaluation contained within this research was that it was conducted in the Australian healthcare setting and did not consider the costs in other countries. Generalisation of these findings outside

of the Australian healthcare context may not be possible due to differences in the way low frequency ultrasonic debridement is funded. Different international health care models may cost the use of low frequency ultrasonic debridement differently, depending on the setting it is used in (operating theatres or in privately funded clinics), and the clinician who performs the treatment (Allied Health, Nursing, Medical). Similarly, other costs examined as part of this research may vary substantially.

There is need for a large scale clinical trial to determine the effectiveness of low frequency ultrasonic debridement compared to non-surgical sharps debridement, powered to detect even small changes in healing rates and the number of participants who progress to amputation, in order to understand whether low frequency ultrasonic debridement should be used in clinical practice as a front-line treatment.

7.5 FUTURE DIRECTION

There continues to be a lack of research investigating different methods of debridement for diabetes-related foot ulcers. Further studies are required to compare different modalities to help guide clinicians in choosing the most clinically-effective and cost-effective methods.

In order to overcome the issues experienced during the clinical trial described in this thesis, the following recommendations are made:

Undertake a multi-site randomised controlled trial to investigate healing rates of diabetes-related foot ulcers comparing non-surgical sharps debridement and low frequency ultrasonic debridement. Consideration should be made to undertaking this research in a non-acute health care setting such as the community health setting, where patients are likely to have fewer health complications and also more medically stable, in an attempt to recruit a sufficient number of participants. Additionally, engagement with other health professionals who are involved in managing patients with diabetes (e.g. Endocrinologists and Vascular specialists) who could assist in screening and identifying potential participants for inclusion in a larger clinical trial. Finally, seeking funding to assist with consumable costs and research assistance with participant screening and data collection should be considered. This would reduce any potential financial burden on departments with a strict budget, especially to cover the high cost of consumables required for low frequency ultrasonic debridement. The addition of a dedicated research assistant would ensure treating clinicians/clinical investigators could prioritise clinical treatment.

The use of a more accurate wound measurement system, such as a 3D camera, should be considered. The wound measurement technique used in this research relied on the investigators calculating total wound area by counting square centimetres on printed photographs and depth was gained from clinician assessment. Whilst this method has high interrater reliability, it has its limitations. A 3D camera would be able to calculate the three dimensions of length, width and depth in addition to a breakdown of percentage of wound tissue, allowing for a more details and accurate wound assessment.

Undertake cost effectiveness analysis as planned in the original trial protocol. This would include collecting direct and indirect health care costs during a larger randomised controlled trial. The formula for assessing cost effectiveness analysis has already been outlined in Chapter 4.

Undertake cost utility analysis using health-related quality of life data as planned in the original trial protocol. This would include collecting data using a validated tool during a larger randomised controlled trial. The formula for assessing cost utility analysis has already been outlined in Chapter 4.

7.6 Concluding remarks

The rising prevalence of diabetes-related foot ulcers is directly correlated with overall diabetes prevalence. Individuals who present with diabetes-related foot disease are at significant risk of complications such as infection, hospital admission, lower limb amputation and early death. The multifactorial nature of diabetes-related foot ulcers requires a multidisciplinary and multi-therapy approach to address neurological and vascular deficits, manage infection and promote rapid wound healing. Debridement and removal of nonviable tissue is a key component of wound healing. Despite the work undertaken during the conduct of this thesis, the clinical effectiveness of using low frequency ultrasonic debridement in the management of diabetes-related foot ulcers remains unknown. Consideration needs to be given to the treatment environment in which low frequency ultrasonic debridement is performed due to the significant infection control risks associated with its use. Further research, with a larger sample size, is required to examine the clinical outcomes of low frequency ultrasonic debridement and non-surgical sharps debridement in diabetes-related foot ulcers.

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FEATURE

A Systematic Review to Compare the Effect of Low-frequency Ultrasonic Versus Nonsurgical Sharp Debridement on the Healing Rate of Chronic Diabetes-related Foot Ulcers

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Abstract

Management of diabetes-related foot ulcers often involves debridement of devitalized tissue, but evidence regarding the most effective debridement method is limited. **Purpose:** A systematic review was conducted to determine the effectiveness of nonsurgical sharp debridement (NSSD) versus low-frequency ultrasonic debridement (LFUD) for diabetes-related foot ulceration in adults. **Method:** Published studies (earliest date available to April 2017) comparing healing outcomes of LFUD- and NSSD-treated foot ulcers in adults were considered. The quality of publications that met inclusion criteria were assessed using the PEDro scale, and a meta-analysis was undertaken to compare percentage healed and percentage of ulcer size reduction. **Results:** Of the 259 publications identified, 4 met the inclusion criteria but 2 of the 4 did not contain sufficient patient outcomes details for meta-analysis, leaving a sample size of 173 patients. Outcome data for the 2 studies included percentage of ulcers healed between the 2 debridement methods. This difference was not significant (RR = 0.92; 95% CI = 0.76-1.11). The risk of bias for both studies was low. **Conclusion:** No difference in healing outcomes between NSSD and LFUD debridement of diabetic foot ulcers was found. Well-designed, controlled clinical studies are needed to address the current paucity of studies examining the efficacy and comparative effectiveness of debridement methods.

Keywords: review, meta-analysis, foot ulcer, diabetes, debridement

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Globally, diabetes is one of the most common noncommunicable diseases. The number of studies describing the epidemiology of diabetes has increased over the last 20 years, and over the past 15 years the global burden estimates of adults living with diabetes has exceeded predictions. In 2000, the International Diabetes Federation[1] estimated 151 million adults were living with diabetes; by 2010, this number was expected to increase to 285 million and estimated to reach 438 million by 2030.[2] The most recent report from the International Diabetes Federation[3] shows the number of adults likely to have diabetes globally in 2015 was 415 million.

According to the Australian Institute of Health and Welfare,[4] people with diabetes may develop complications including peripheral neuropathy, peripheral arterial disease, and foot deformity, which can lead to ulceration, infection, and an increased risk of amputation. One (1) in every 6 people with diabetes in developed countries will

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Key Points

- A 2010 Cochrane review concluded that although debridement is regarded as an effective intervention to assist foot ulcer healing in persons with diabetes mellitus, more research is needed to evaluate the effects of a wide range of debridement methods and of debridement *per se*.
- The purpose of this systematic literature review and meta-analysis was to examine if healing outcomes differed between wounds debrided using nonsurgical sharp debridement versus low-frequency ultrasonic debridement.
- Only 4 studies were found comparing the 2 methods; of those, 2 included sufficient detail for further analysis.
- No significant healing differences between the 2 methods were found.
- Studies examining wound and patient outcomes of debridement and the efficacy of methods used are needed.

have a diabetes-related foot ulcer during their lifetime.[1] According to the International Working Group on the Diabetic Foot,[1] people with diabetes also face a 25 times increased risk of amputation compared to persons without diabetes. Currently, a limb is lost every 20 seconds worldwide as a result of diabetes-related amputation.[1]

Optimal management of these ulcers is vital in preventing lower limb amputation. Treatment routinely involves offloading[2] to redistribute pressure away from the area of ulceration and maintaining a moist wound bed environment[3] to encourage new tissue growth. Additionally, treatment of diabetes-related foot ulcers often involves routine debridement to remove devitalized tissue from the ulcer base. According to guidelines[4] and a systematic review,[5] the process of debridement, regardless of the method applied, is believed to stimulate the inflammatory response and encourage healing. Debridement methods include autolytic debridement using dressings and biological debridement using sterile larvae and chemical enzymes. In addition to these topical agents, mechanical debridement via surgical excision or nonsurgical sharp debridement using either a scalpel or scissors is commonly utilized, according to a Cochrane review[6] and systematic reviews.[10,11]

Contact and/or noncontact, low-frequency ultrasonic debridement (LFUD) offers an alternative to sharp debridement. LFUD generates sound waves ranging from 20 to 40 kHz (undetectable to human hearing), delivered to the ulcer through a liquid medium such as normal saline. According to systematic reviews,[12-14] ultrasound waves have the mechanical effects of cavitation and microstreaming, leading to an increase in cellular activity which, in turn, promotes healing. Specifically, systematic reviews[10,13] of ulcer healing studies also have determined an increase in protein synthesis and an increase in production of growth factors and endothelial cells occurs, all of which stimulate the ulcer toward healing. *In vitro* studies[14,16] have found both noncontact and contact LFUD lowers bacterial counts through the mechanical destruction of the bacterial cell wall. An *in vitro* study[17] has shown direct-contact LFUD has the added benefit of enhanced fibrinolysis due to an increased intensity of ultrasound; this subsequently leads to ulcer angiogenesis without destroying healthy ulcer tissue.[14]

A Cochrane review[6] on the debridement of diabetes-related foot ulcers included 6 randomized controlled trials; 5 evaluated the effectiveness of hydrogel as a method of debridement against a range of comparators such as combinations of saline dressings and pressure offloading, hydrogel with an additional bacteriostatic action, larval therapy, and 2 other hydrogel dressings. The sixth trial compared surgical debridement with nonsurgical sharp debridement (NSSD) in addition to relieving the pressure of weight-bearing and providing regular dressing changes. Conclusions from the Cochrane review[6] suggest that although hydrogels increase diabetes-related foot ulcer healing compared with gauze or standard wound care, it is unclear if this effect is directly due to debridement. Additionally, it was noted that randomized controlled trials on debridement for diabetes-related foot ulcers are small in number and of poor methodological quality. The review concluded that while debridement is regarded as an effective intervention to assist healing, more research is needed to evaluate the effects of a wide range of debridement methods and of debridement *per se*. No subsequent Cochrane review was conducted since its publication, nor a protocol registered for update.

The aim of this systematic review was to compare available evidence on the effectiveness of bedside NSSD via scalpel without using anesthesia versus contact or noncontact LFUD in terms of percentage of ulcers healed for diabetes-related foot ulceration.

Methods

Methodology. The clinical question for this systematic review was generated using the Population Intervention Comparison Outcome[18] (PICO) model for clinical questioning. The question was: In adult patients with chronic diabetes-related foot ulcers, what effect does LFUD have on ulcer healing rates compared to NSSD?

This question was separated into terms to search electronic databases including Ovid, MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health Literature Plus, and the Cochrane Database of Systematic Reviews from the earliest date publications were available in each index until April 2017. Table 1 shows the search terms

Table 1. Search strategy built using the Population Intervention Comparison Outcome (PICO) question format

PICO terms	Search terms	Alternate terms
Patient	Diabetic* foot	Ulcer* Wound* Amp* Chronic
Intervention	"Low frequency ultrasonic debridement" (LFUD)	"Ultrasound assisted wound*" "Ultrasonic therapy" LFUD ultrasono*
Comparison	"Nonsurgical sharps debridement"	Debrid* Nonsurgical sharp debridement (NSSD)
Outcomes	Heal*	Closure

Table 2. Inclusion and exclusion criteria for screening titles, abstracts, and full texts

Inclusion criteria	Exclusion criteria
Participants:	Not a diabetes-related foot ulcer
Adults	No ulcer/no debridement
18 years and older	LFUD/nonsurgical sharps debridement not investigating ulcer healing rates
Chronic diabetes-related foot ulcer	Author opinion
Intervention:	Protocols of studies with no outcome data
Low-frequency ultrasound debridement (LFUD) contact or noncontact therapy	Diagnostic ultrasound
Nonsurgical sharp debridement	Dental ultrasound
Outcome measures:	Acute ulcer or ulcer present <30 days
Healing rate	Full text articles not published in English

used. Searches were restricted to human studies and English-language articles.

Two (2) authors independently reviewed the title and abstract of all retrieved studies against the eligibility criteria (see Table 2), which specified chronic diabetes-related foot ulcers (>4 weeks' duration) in adults >18 years of age. Publications were excluded if 1) the methods of debridement did not involve comparing LFUD to NSSD, 2) wounds demonstrated an etiology other than a diabetes-related foot ulceration, or 3) the study involved acute ulcers, ulcers that did not undergo debridement, and diagnostic or dental ultrasound.

When the 2 authors disagreed regarding study inclusion, a third author helped resolve the issue through discussion. The full text of articles was obtained when the abstract seemed uncertain. Forward and backward searching strategies also utilized the reference lists and Google Scholar citations of articles included within the full text review.

Data extraction. General demographics such as gender, country, age, diabetes type, and method of wound debridement of each participant group were extracted from each included study and tabulated and summarized in Table 3. The primary outcome of interest was healing rates of diabetes-related foot ulcers. The secondary outcome of interest was the percentage of ulcers healed.

All articles included within the review underwent methodological assessment for risk of bias using the quality indicators as outlined by Physiotherapy Evidence Database (PEDro).[9] This scale has 11 indicators to identify any risk of bias. Each indicator was given a score of - if not included, ? if not mentioned, or + if included. According to the PEDro guidelines, criteria 2 to 11 are used for scoring purposes, so a score out of 10 is calculated.

Two (2) authors completed this assessment independently and resolved any disagreements. Articles also were classified into levels of evidence using criteria set out by the Oxford Centre for Evidence-based Medicine.[10] This provides advice on the most appropriate research to guide treatment. Systematic reviews of randomized controlled trials are the highest level of evidence (Level 1), followed by randomized controlled trials (Level 2), nonrandomized controlled cohort/follow-up studies (Level 3), cohort studies and/or case studies (Level 4), and mechanism-based reasoning (Level 5).

Data collection. Primary outcome of percentage of ulcers healed were extracted into an Excel worksheet (Microsoft Excel, version 16.15, Redmond, WA).

Data analysis. Analysis was performed using Stata 13 software (College Station, TX). Random effect meta-analysis was performed where data were available for similar outcomes evaluated in more than 1 study. Authors were contacted to request additional data for studies not reporting sufficient outcome data for inclusion in the meta-analysis; however, no responses were received, thus eliminating 2 of the 4 studies from analysis.

Results

Of the 259 total publications identified using the review search terms after duplicates were removed, 204 titles were determined to be potentially relevant and their abstracts were reviewed. One hundred, ninety-three (193) articles were excluded after reading the abstracts, leaving 11 articles for full text screening. Only 4 articles met the criteria for inclusion in the review. The PRISMA statement lists the reasons for exclusion (see Figure 1).

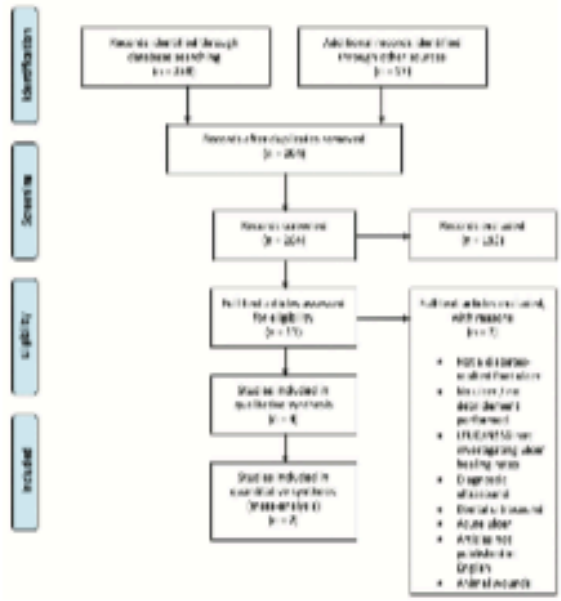

Figure 1. PRISMA diagram showing selection of articles for inclusion in review and pooled analysis.
LFUD=low-frequency ultrasound debridement
NSSD=nonsurgical sharp debridement

Description of studies. Table 3 provides a summary of the 4 articles included: 3 describe clinical trials involving randomization and 1 used historical data from the same clinic as the control with LFUD as the intervention group. Three (3) of the studies used the MIST® noncontact LFUD (Celularity, Inc, Warren, NJ) with varying debridement times and treatment provided either once or 3 times per week. The fourth study used Sonoca 180® noncontact LFUD (Söring GmbH, Quickborn, Germany) performed once per week with debridement duration calculated based on ulcer total area. The control treatments varied between studies, but all studies included NSSD where required and moist wound dressings. Offloading strategies and other treatment modalities varied between the studies, reflecting the complexity and variability of ulcer management and confounding the validity of pooling these studies. The pooled population included 227 patients ranging in age from 40 to 72 years. The included articles described are for the primary outcome (percentage of ulcers healed).

Meta-analysis/pooling of data. Data extracted included patient demographics, study design and criteria, measurement tool, clinical outcome, and follow-up period. Results from the 2 studies included in the meta-analysis found 30% of the patients in the NSSD groups healed, and 33% in the LFUD groups healed. A meta-analysis was performed on only 2 of the 4 artides; 2 articles had

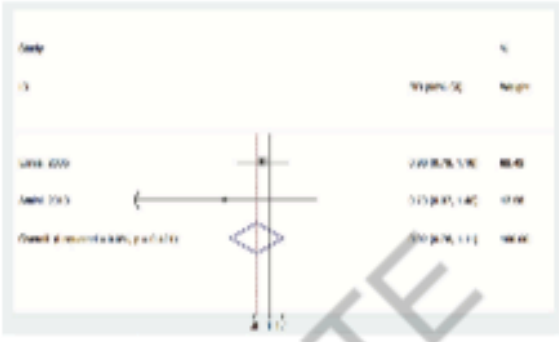

Figure 2. Results from meta-analysis review of 2 articles.[23,24]

insufficient outcome data, although the current authors attempted to secure the missing data from the original researcher[21,22] in a format that would allow for meta-analysis. Therefore, meta-analysis was performed with 2 articles[23,24] and a total sample size of 173; the analysis did not identify any relationships that suggested a greater effectiveness of either LFUD or NSSD in total healing diabetes-related foot ulcers (RR = 0.92; 95% CI = 0.76-1.11) (see Figure 2).

Quality of evidence. Scores of the 4 articles indicated a risk of bias according to the PEDro scale (see Table 4). Three (3) of the studies were randomized controlled trials and the fourth used historical data from the same clinic as the control. Not all criteria on the PEDro scale could be satisfied in these studies (eg, the blinding of participants and clinicians). In 2 of the publications, certain information was not documented and therefore led to a query if the criterion of participant allocation concealment and participants, therapists, and assessors blinding were met. In all 3 randomized controlled trials, participants were randomized to treatment groups and received the allocated treatment or control; these studies also noted between-group statistical comparisons reported for the primary outcome. The 2 studies included in the meta-analysis had a low risk of bias (PEDro score 9/20).

Discussion

This review identified that available evidence is insufficient to determine whether LFUD or NSSD provides better outcomes in the treatment of diabetes-related foot ulcers. A total of 110 participants that were provided LFUD was compared to 117 participants treated with NSSD within the same studies. Devices that deliver LFUD are available with varying applications (contact vs. noncontact) that influence the ultrasound intensity delivered to the ulcer. Much variation also was evident in the examined studies in the application time for LFUD as well as the frequency of debridement with treatments, ranging from 3 times per week to once per week. Interim therapy also was a confounding factor.

Table 3. Summary of included full-text studies

First author	Study design	Country	Age combined (mean [SD] or range)	Sample size	Control treatments	Intervention (LFUD treatment)	Outcome measure	Treatment timeframe	Level of evidence
Ennis[21]	Cohort study with historic control	USA	N/A	42	Electrical wound stimulation, therapeutic ultrasound, moist wound dressings, local sharp debridement[a]	Duration according to ulcer size, 3x/week., noncontact	% healed, % area eduction, % volume reduction	8 months	4
Ennis[23]	RCT	USA	55 (11.6)	193	Local sharp debridement,[a] moist wound dressings, fixed ankle-foot walker	4 minutes, 3x/week., noncontact	% healed	12 weeks	2
Yao[20]	RCT	USA	40-72	12	Local sharp debridement,[a] offloading, moist wound dressings	5 minutes, 1x/week or 3x week, noncontact	% area reduction	5 weeks	2
Amini[24]	RCT	Iran	55.2 (9.4)	40	Offloading via total contact cast/felt/boot, antibiotics, surgical sharp debridement	Time according to ulcer size, 1x/week., noncontact	Healing rate, % size reduction	6 months	2

[a]Also known as nonsurgical sharps debridement.
LFUD=low-frequency ultrasound debridement; *RCT*=randomized controlled trial; *SD*=standard deviation

It is important to establish whether LFUD is more effective than NSSD to justify its use in clinical practice. Without high-quality evidence supporting the use of LFUD in the treatment of diabetes-related foot ulcers, clinicians using this technology must rely on expert opinion and guidance from the manufacturer. In the current authors' experience, the different application methods and settings are recommended based on limited research available, clinicians are faced with the potential to be under- or overutilizing this therapy.

This review demonstrated a relative paucity of evidence supporting the use of LFUD as an alternative to NSSD. Use of NSSD for the management of diabetes-related foot ulcers is recommended in several guidelines,[1,4] which is why it was considered in this study an appropriate standard for comparison in this review.

Limitations

It is a limitation of the scope of this review that the effectiveness of NSSD alone was not considered. In addition, the variety of outcome measures among the 4 studies included in this review (percentage of ulcers healed, reduction in ulcer size/volume) made comparisons across the studies difficult. Ideally, a uniform set of outcomes and time points of collection would be reported in the literature to enable pooling across studies. Also, no studies that investigated the use of contact LFUD were found; therefore, the effects of contact versus noncontact LFUD cannot be reported. This was variable outside the study question should other authors wish to undertake further research in this area. Finally, the control groups for all 4 studies were significantly varied. In 3 of the 4 studies, offloading with footwear, orthotics, or padding was not standardized, including the 2 studies in the meta-analysis. Mechanical offloading is known to be vital in managing diabetes-related foot ulcers and plays a large role in healing outcomes,[10] but in this research the variety of offloading approaches was a confounding factor. Finally, other important outcomes such as pain, cost, and provider variables were not considered.

Conclusion

A diabetes-related foot ulcer is a common complication of diabetes that is often a primary cause of hospital admission. LFUD and NSSD are used to manage diabetic foot ulcers, whereby clinicians observe an immediate reduction in nonviable tissue which is believed to facilitate healing. The results of this study showed no difference in healing rates between LFUD and NSSD. More rigorous randomized

Table 4. Valid measures of methodological quality of clinical trials using PEDro scale

Study	1	2	3	4	5	6	7	8	9	10	11
Ennis[21]	+	+	?	-	+	-	+	-	+	+	-
Ennis[23]	+	-	-	-	-	-	-	+	+	+	-
Yao[30]	+	+	-	+	-	-	-	+	+	+	-
Amini[24]	+	+	?	+	?	?	?	+	+	+	+

Column numbers correspond to the following criteria on the PEDro scale:

1 - Eligibility criteria were specified

2 - Subjects were randomly allocated to groups

3 - Allocation was concealed

4 - The groups were similar at baseline regarding the most important prognostic indicators

5 - There was blinding of all subjects

6 - There was blinding of all therapists who administered the therapy

7 - There was blinding of all assessors who measures at least one key outcome

8 - Measures of at least 1 key outcome were obtained from more than 85% of the subjects initially allocated to groups

9 - All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"

10 - The results of between group statistical comparisons are reported for at least one key outcome

11 - The study provides both point measures and measure of variability for at least one key outcome

+ indicates the criterion was clearly satisfied
- indicates that it was not
? indicates that it is not clear if the criterion was clearly satisfied

controlled trials with long follow-up periods and an adequate sample size are needed to identify whether debridement aids the healing of diabetes-related foot ulcers and if so, which is the optimum method when used as an adjunct with best practice ulcer management. ■

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APPENDIX 2 – PUBLICATION ARTICLE 2

ARTICLE IN PRESS

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Major Article

Does the new low-frequency ultrasonic debridement technology pose an infection control risk for clinicians, patients, and the clinic environment?

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Key Words:
Infection control
Bacterial
Spread
Ulcer
Wound
Aerosol

Background: Low-frequency ultrasonic debridement (LFUD) is a technology that uses sound waves conducted through saline mist to debride wound tissue. Whilst this technology purportedly reduces wound-healing times, the airborne mist generated is potentially problematic. Theoretically, the saline mist could carry an increased number of microbes into the surrounding environment, posing an infection control risk to the patient, clinician, and clinical environment. This research aimed to establish the degree and extent to which there is microbial spread during the use of, and following the use of, LFUD. The total number of colony forming units was identified for use of LFUD without the suction attachment (control) and with the suction attachment (intervention).

Methods: This was a prospective, observational study with repeated measures across each treatment (before, during, and after). Quota sampling in a 2 × 2 × 2 factorial design was undertaken so that half of the 24 treatments were conducted at each health service (Monash Health vs Peninsula Health), in different treatment environments (inpatient vs outpatient), and half were conducted with and without suction. The use of suction was not randomized but was determined at the treating clinician's discretion. Patients treated in the inpatient environment lay on their beds, whereas patients in the outpatient environment sat in a treatment chair.

Results: There was higher microbial count during treatment ($P < .001$) with a higher microbial count associated with lower ultrasound amplitude ($P = .028$), lower saline flow rate ($P = .030$), no suction attachment ($P = > .001$), and a larger wound area ($P = .002$). All were independently associated with greater microorganism aerosolization. There was no correlation between the type of handpiece selected, the presence of wound infection, and the treatment time or treatment environment.

Conclusions: This research has assisted in developing guidelines for cleaning of equipment and environments following treatment, as well as around the use of personal protective equipment required to protect the staff member and the patient during the use of LFUD. Additionally, recommendations have been made regarding the specific LFUD settings to reduce the risk of cross-infection to the clinic environment. These include selecting a higher ultrasound amplitude and saline flow rate as well as the use of suction where clinically possible.

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Conflicts of interest: None to report.

LM, CW, TH, and SB conceived this study: LM, CW, TH, SB, EO, and DK designed the study: LM and GC collected data: and all authors contributed to data analysis, interpretation of data, and the manuscript. All authors approved the final manuscript.

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Treatment of chronic wounds frequently requires a combination of therapies to facilitate healing. Debridement is considered an important part of treatment because it removes devitalized tissue from the wound bed that can delay healing and harbor infective organisms. There are different methods of wound debridement, including sharps debridement that can be performed in an operating room or in a clinical setting, mechanical debriding agents, autolytic debriding through dressings, biological debridement through use of sterile larvae, and the use of chemical enzymes.[1-3] Low-frequency ultrasonic debridement (LFUD) is a newer method of debridement introduced as an alternative method of wound debridement. The size and portability of the LFUD unit make it attractive for use within and across different health care settings.

The LFUD technique works by delivering sound waves through a constant flow of sterile saline to the wound surface. Ultrasound results when electric energy is converted to sound waves at a frequency above the range of human hearing (20 kHz). These sound waves are then transmitted to tissue via a liquid medium through the treatment applicator. Nonthermal effects of the ultrasound waves have been shown to cause 2 phenomena at the wound surface: acoustic streaming[4-6] (a steady mechanical force) and cavitation[4-6] (the formation of gas bubbles causing microshockwaves). The combined effects of acoustic streaming and cavitation are thought to alter cell membrane activity and increase the activity of each cell, leading to debridement of necrotic and infected tissue, a bactericidal effect, and cellular proliferation.[5,7,8]

Whilst the use of LFUD has been demonstrated to have a positive effect on wound healing rates and outcomes,[9-11] there has been little research into the effects on the environment related to the use of LFUD in clinical settings. The aim of this study was to establish the degree and extent of microbial spread during the use of LFUD and to determine what infection control risk LFUD poses to clinical environments, to patients, and to clinicians administering the treatment.

METHODOLOGY

This was a prospective, observational study with repeated measures across each treatment (before, during, and after). Quota sampling in a $2 \times 2 \times 2$ factorial design was undertaken so that half of the 24 treatments were conducted at different sites (Monash Health vs Peninsula Health), in different treatment environments (inpatient vs outpatient), and half were conducted with and without suction. The Human Research Ethics Committees of Monash Health (14077Q) and Peninsula Health (QA/14/PH/4) approved this study.

Patients

Eighteen patients with a foot or leg wound being treated with LFUD were advised that environmental testing was being performed between June 2014 and April 2015. Patient consent was not required for this study because data collection was not related to treatment. Treatments were measured from a convenience sample at 2 public hospitals—Monash Health (Monash Medical Centre) and Peninsula Health (Frankston Hospital)—and performed by 2 podiatrists according to the predetermined study protocol. No randomization of treatment environments or suction use was undertaken. The only inclusion requirement was that a minimum treatment time of 10 minutes of LFUD was required. The leading treating clinicians judged whether the appearance and size of the wound were suited to this treatment.

Measurements

Measurement of dependent variables

Colony forming units were the main dependent variable used in this study to determine the degree of microbial burden on the environment. To determine baseline airborne microbes before treatment, passive air testing using horse blood agar (HBA) plates were used. These plates were placed at 30 cm, 1 m, and 2 m on either side of the wound, on the floor, in both treatment settings. Additional HBA plates were placed 3 m from either side of the wound atop a high surface in only the outpatient setting (space available on inpatient wards was insufficient for this test). Active air testing (Merck MAS 100; Merck, Darmstadt, Germany) was performed with a single HBA plate at 1.5 m from the wound using air sampling.

Postdebridement sampling for both on-ward and outpatient environments included a single swab taken for culture from the LFUD handpiece end plated on HBA. Additional testing was performed in the outpatient environment 30 minutes after treatment to confirm the return of airborne microbes to baseline. Only the Monash Health site had access to the use of the active Merck air sampler. Peninsula Health used an opened HBA passive settle plate. Air sampling was conducted at 1.5 m at the baseline, debridement, and 30-minutes posttreatment time points. Baseline testing of colony forming units was undertaken for 10 minutes while the clinician set up the room for treatment. Testing during LFUD included both passive and active air sampling in the same setup as the settle plates. Each HBA plate was incubated aerobically at 35 °C for 48 hours and microbes were counted and reported as colony forming units. Microbes were further speciated per standard laboratory protocols. This testing was undertaken in the Microbiology Laboratory at Monash Health.

Measurement of independent variables

The Sonoca 185 (Söring, Germany) LFUD was used for each treatment. The equipment settings for the handpiece (hoof, spatula, or double ball), maximum saline flow rate (milliliters), maximum ultrasound amplitude (%), the treatment time, and the use of suction were variable. Following a thorough wound assessment these settings were determined by the treating clinician based on the clinical appearance of each wound.

Procedure

A total of 24 LFUD treatments on 18 patients were performed per the study protocol. The settings used for each treatment (handpiece, amplitude, and flow rate) were determined by the treating podiatrist based on the clinical presentation of each wound.

The on-ward treatments were performed with the patient lying on his or her bed and the privacy curtains or door closed. The layout of the settle plates was designed to minimize interference by the treating podiatrist or other passers-by. The outpatient clinic room treatment was performed with the patient seated on the treatment chair and the door closed. The treatment was performed per standard procedure for both sites, as determined by existing clinical practice guidelines within both health organizations.

The treating podiatrist donned personal protective equipment during treatment, including a plastic disposable long-sleeve gown, surgical mask, face shield with plastic visor, and nonsterile gloves. Patients were given the option of wearing a mask; however, no other personal protective equipment for patients was offered. Plastic sheeting was placed in the immediate work area to capture aerosolized droplets up to 1 m away and was also used to cover exposed shelves. Per standard procedure, gauze was used to shield the end of the handpiece whilst maintaining visibility for the treating podiatrist. After each procedure, a 1-m wipe of the area and instruments was

done using the preferred hospital environmental cleaning method; that is, a low-foaming, low-alkaline detergent, water, and a microfiber cloth. A total of 24 treatments were planned with equal distribution between sites, treatment environments, and with or without the suction attachment.

Data analysis

Data were analyzed using Stata version 13 (StataCorp, College Station, TX). Colony forming units were defined as ordinal categorical data with low (≤ 10 CFUs), moderate (11–49 CFUs), high (50–499 CFUs), or very high (≥ 500 CFUs) categories. Microbe species type and count (in colony forming units) were recorded at pretreatment (baseline) and during treatment testing. A Wilcoxon signed-rank test was used to determine any difference between before and during LFUD time points. Ordered logistic regression was used to determine the association between independent variables and colony forming units. A power analysis of before versus during treatment testing using the Wilcoxon signed-rank test was computed using G*Power 3.1 (Heinrich-Heine University, Dusseldorf, Germany) and it was determined that a sample size of 24 pairs of measurements within participants provided 80% power to detect a standardized effect size equal to 0.54 given a 2-tailed alpha of 0.05.[12]

RESULTS

Pretreatment

Pretreatment counts for all passive settle plates consisted primarily of low counts of skin and airborne microbes such as coagulase negative staphylococci, *Micrococcus* spp, and *Corynebacterium* spp.

LFUD without suction

The same pathogens were detected from patient wound and air samples in 8 of the 12 treatments where the suction attachment was not used during treatment. Heavy growth of bacteria such as *Stenotrophamonas maltophilia*, *Staphylococcus aureus*, *Klebsiella* spp, *Pseudomonas aeruginosa*, and *Enterococcus* spp were detected as far as 2 m away from the wound (Table 1).

LFUD with suction

In 5 of 12 patients with suction only, 1 treatment showed heavy growth of *Staphylococcus aureus* and *Streptococcus agalactiae* and 2 showed light growths of *Staphylococcus aureus* and *Escherichia coli* at 2 m. Four treatments grew low numbers (< 10 CFU) of significant pathogens (*Staphylococcus aureus*, *Sarratia marcescens*, *Enterococcus* spp, and *Escherichia coli*) that would not normally found to be circulating in air (Table 1).

Distance

The same microbial isolates that were growing in the patients whose wounds were swabbed immediately after treatment (n = 13) were detected on settle plates that had been placed at the farthest distance (2 or 3 m).

Handpiece

The same microbial isolates detected from patient's wounds were also detected in high numbers (50–499) in 8 of the no-suction handpieces, compared with low numbers (≤ 10) in 5 handpieces with the suction attachment.

Table 1
Participant microbiology results from settle plates at 2 m distance during treatment

No suction		Suction	
Debridement site	Microbial growth	Debridement site	Microbial growth
Foot	SMAL[†]	Foot	MSEF[*]
	ENT[‡]		
Heel	SF[*]	Foot	SF[*]
Heel	SAUR[*]	Foot	SAUR[‡]
			SAGA[‡]
Heel	SAUR[‡]	Leg	SF[*]
	SMAL[‡]		
	ENT[‡]		
	SF[*]		
Toe	KLEB[‡]	Foot	SF[*]
	SF[‡]		
Toe	KLEB[‡]	Foot	SF[*]
	SF[‡]		
Toe	KLEB[‡]	Foot	SF[*]
	SF[‡]		
Ankle	ECLO[†]	Leg	SAUR[*]
	CIT[†]		
	ACAL[†]		
	ENT[‡]		
Ankle	PAER[‡]	Foot	SF[*]
	ENT[‡]		
Foot	SF[‡]	Heel	SMAR[*]
Foot	SF[*]	Heel	SF[‡]
			ENT[*]
Heel	SMAR[‡]	Heel	ECOL[*]
	ENT[‡]		
	SF[‡]		
	KLEB[*]		

ACAL, *Acinetobacter calcoaceticus*; *CIT*, *Citrobacter* spp; *ECLO*, *Enterobacter cloacae*; *ECOL*, *Escherichia coli*; *ENT*, *Enterococcus* spp; *KLEB*, *Klebsiella* spp; *MSEF*, mixed skin enteric flora; *PAER*, *Pseudomonas aeruginosa*; *SAGA*, *Streptococcus agalactiae*; *SAUR*, *Staphylococcus aureus*; *SF*, skin flora; *SMAL*, *Stenotrophomonas maltophili*; *SMAR*, *Serratia marcescens*.
[*]Low: ≤ 10 CFU.
[†]Moderate: 11–49 CFU.
[‡]High: 50–499 CFU.

Table 2
Variable associated with increased colony forming units

Variable	Coefficient	95% Confidence interval	*P* value
Infection	−1.424	−2.978 to 0.128	.072
Wound area (cm²)	.007	0.002 to 0.012	.002
Flow (mL)	−0.278	−0.491 to −0.066	.010
Amplitude (%)	−0.157	−0.297 to −0.016	.028
Suction	−3.036	1.603 to 5.670	<.001
Handpiece	−0.383	−1.937 to 1.171	.629
Treatment time	−0.121	−0.933 to 0.691	.770
Treatment setting	−1.068	−2.569 to 0.432	.163

Passive air sampling

There was a significant difference in pre-LFUD and during-LFUD colony forming units counts for passive air sampling ($P = .001$). High colony forming units counts during LFUD were also associated with a larger wound area ($P = .002$), low LFUD flow ($P = .010$), low LFUD amplitude ($P = .028$), and the use of no suction attachment ($P \geq .001$) (Table 2).

Active air sampling

Air sampling during treatment showed heavy growth in 4 of the 10 episodes. The same pathogens were also detected at 30 minutes posttreatment in 5 instances. Overall, it was found that 30 minutes after LFUD ceased the number of aerosolized microbes had returned to baseline levels.

DISCUSSION

Findings associated with higher CFUs included a larger total wound area, a lower saline flow rate, and lower ultrasound amplitude. Although a larger wound area did not mean a longer treatment time, the larger area may have caused the treating podiatrist to use the handpiece in a wider pattern, potentially increasing the distance of mist dispersion. The LFUD users' manual states that higher ultrasound amplitude results in a finer mist. A finer mist has the potential to increase aerosolization. It is unknown whether there was an interaction between low ultrasound amplitude and low saline flow rate within this research that resulted in high colony forming units. This finding has practical implications. Clinicians should, where possible, increase the saline flow rate when increasing the ultrasound amplitude to a level at which a patient is still comfortable, to reduce aerosolization.

The fact that treatment time and handpiece selection were not associated with higher colony forming units is a positive finding and clinicians should continue to make these choices as clinically indicated. The presence of wound infection approached statistical significance; therefore, clinicians should interpret these results with caution. A larger sample size may influence these results.

To guide infection control practices, the findings from this research provide an outline of the possible infection control risk posed by using an LFUD device in a clinical environment.

This study had a limited sample size, which may have resulted in some independent and dependent variables not being statistically significant, although a relationship may really exist. One was the use of a convenience sample of patients, which meant that patients eligible to receive LFUD based on the clinical presentation of their wound were included, but patients were not randomized to suction or no suction use, nor were the saline flow rate or ultrasound amplitude settings standardized. Patients with wound infection were not excluded from the study and wound size was not standardized. It is also possible that factors in each treatment room, such as room airflow and ventilation, may have influenced microbial dispersion. Additionally, microbial sampling was conducted using HBA incubated under aerobic conditions, limiting the growth of anaerobic organisms. Finally, volumetric active air sampling is best to capture an exact amount of air (ie, 1 m^3) but was only available at a single hospital site for a limited number of treatments.

CONCLUSIONS

This is the first study to investigate the environmental influence of LFUD within a clinic setting. The findings that the use of no suction increases the aerosolization and spread of microorganisms from the wound means that greater consideration needs to be given to using the suction attachment as often as possible. In addition, the flow rate and amplitude settings, whilst determined by the clinical appearance of the wound and amount of patient pain, should also be considered in relation to the risk of environmental contamination. Careful consideration of the location and use of LFUD is necessary before treatment to prevent risk of cross-contamination and reduce potential for hospital-acquired infections.

The results from this study should not dissuade clinicians from utilizing LFUD as a method of wound debridement, but it is vital that this treatment be performed under the correct conditions to mitigate the microorganism aerosolization associated with its use. This research has assisted in developing guidelines around the minimum requirements for equipment cleaning and the use of personal protective equipment required to protect the staff member and the patient during the administration of LFUD, whilst reducing the risk to the clinic environment.

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APPENDIX 3 – PUBLICATION ARTICLE 3

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STUDY PROTOCOL Open Access

Comparison of healing rate in diabetes-related foot ulcers with low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised trial protocol

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Abstract

Background: Foot ulceration has been reported as the leading cause of hospital admission and amputation in individuals with diabetes. Diabetes-related foot ulcers require multidisciplinary management and best practice care, including debridement, offloading, dressings, management of infection, modified footwear and management of extrinsic factors.
Ulcer debridement is a commonly applied management approach involving removal of non-viable tissue from the ulcer bed. Different methods of debridement have been reported in the literature including autolytic debridement via moist wound healing, mechanical debridement utilising wet to dry dressings, theatre based sharps debridement, biological debridement, non-surgical sharps debridement and newer technology such as low frequency ultrasonic debridement.

Methods: People with diabetes and a foot ulcer, referred to and treated by the Podiatry Department at Monash Health and who meet the inclusion criteria will be invited to participate in this randomised controlled trial. Participants will be randomly and equally allocated to either the non-surgical sharps debridement (control) or low frequency ultrasonic debridement (intervention) group (n = 322 ulcers/n = 108 participants).
Where participants have more than one ulcer, only the participant will be randomised, not the ulcer. An investigator not involved in participant recruitment or assessment will be responsible for preparing the random allocation sequence and envelopes.
Each participant will receive weekly treatment for six months including best practice podiatric management. Each ulcer will be measured on a weekly basis by calculating total area in centimetres squared. Measurement will be undertaken by a trained research assistant to ensure outcomes are blinded from the treating podiatrist. Another member of the research team will assess the final primary outcome.

Discussion: The primary aim of this study is to compare healing rates for diabetes-related foot ulcers using non-surgical sharps debridement versus low frequency ultrasonic debridement over a six month period. The primary outcome measure for this study is the proportion of ulcers healed by the six month follow-up period.
Secondary outcomes will include a quality of life measure, assessment of pain and health care resource use between the two treatment modalities.

Trial registration: Australian New Zealand Clinical Trial Registry: ACTRN12612000490875.

Keywords: Debridement, Diabetes complications, Wound healing, Ultrasonics

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Introduction

Background

Diabetes is rapidly increasing in global prevalence, morbidity and mortality. In 2011, 366 million people globally were living with diabetes, a figure that is equivalent to 8.3% of the world's adult population. It was estimated the international community would not reach this figure until 2030 [1].

In Australia the prevalence of type 2 diabetes has increased over the past two decades and continues to rise. Approximately 7% of the Australian population is thought to have type 2 diabetes and it is estimated that 15% of people with diabetes will develop a foot ulcer during their lifetime [2]. The consequences of having diabetes in Australia are significant with over 500,000 hospital admissions and 12,000 deaths attributed to the condition in 2004 alone [1].

The pathophysiology of foot ulceration is complex and usually multi-factorial. Peripheral sensory neuropathy, foot deformity and external trauma, when occurring concurrently, have been identified as being the three most common factors that predispose to diabetes-related foot ulcers (DRFU) [3]. Peripheral arterial disease has also been shown to lead to the development of ischaemic and neuro-ischaemic DRFU [2]. Regardless of the true aetiology, the same complications can arise with all DRFU, including soft tissue infection, osteomyelitis, tissue necrosis and failure of ulcer healing, all of which may require hospital admission and potentially result in amputation [4].

Diabetes has been acknowledged to be the most common cause of non-traumatic lower-limb amputation in Australia [5]. Furthermore, acute complications affecting foot ulceration have been reported as the leading cause of diabetes-related hospital admissions and amputation [4]. For the years 2004–2005 the Australian Institute of Health and Welfare reported that DRFU resulted in 9900 acute hospital admissions [4]. In the same period 3400 diabetes-related lower limb amputations were also reported [2].

More recently it has also been suggested that diabetes-related lower limb amputations have increased by 30% between the years 1998 – 2005 [6]. The estimated acute care cost of a single lower extremity amputation in Australia could be as much as $26,700 [4]. This figure does not include costs for rehabilitation, purchase of orthotics/prosthetics or time lost from work. Recent economic evaluations of the cost of a lower limb amputation for a single person found that Australia sits in third place behind France where such a procedure is estimated to cost $46,064 for a single diabetes-related lower extremity amputation and in Germany the same is estimated at a cost of $31,809 [2]. The cost of amputation secondary to diabetes complications in the United States of America is said to range from $20,000 - $60,000 per patient and similarly does not include the personal, social, or economic aspects of the patient's life [7].

None of the costs noted above consider the direct financial burden on patients with a DRFU. The ongoing costs of ulcer management in the community have not been investigated in the literature to date, however clinicians, patients and their families feel the impact of these costs every day. It has been reported however, that in one study investigated the quality of life of patients with DRFU 50% of patients were no longer in work because of their ulcer. Although treatment was free the costs associated with travelling to hospital appointments and buying additional footwear [8] placed an additional financial strain on patients.

Given the complications associated with DRFU and the time these ulcers can take to heal it is not surprising that patients report a greatly reduced quality of life [9]. It has been found that all quality of life domains can be adversely impacted primarily because of a reduction in mobility and the consequent need to adapt activities of daily living [8]. Additionally it is thought that the presence of a foot ulcer imposes restrictions on patient participation and enjoyment of their usual hobbies mainly because of mobility difficulties and the requirements for treatment [9]. This has been shown to have a negative psychological effect with an increase in patients with depression and a lower satisfaction with their personal lives [9]. Reviewing and improving ulcer management interventions that have the potential to result in more effective and faster healing could have the added benefit of improving the quality of life of patients with a DRFU.

Debridement has been identified as a leading treatment for management of DRFU [2]. Debridement has been defined as the removal of devitalised, contaminated or foreign material from within or adjacent to the ulcer until surrounding healthy tissue is exposed [10]. It serves several functions including reduced pressure on the ulcer base, more thorough inspection to determine true ulcer depth and size, facilitation of drainage and creation of an acute ulcer environment [6].

Existing approaches to ulcer debridement can be performed directly by a clinician including theatre-based sharps debridement (TBSD) also known as surgical excision and non-surgical sharps debridement (NSSD) or scalpel debridement in a clinical setting. There are also various topical products that act as debriding agents. These have included wet-dry dressings that act as mechanical debriding agents, dressings that encourage moist wound healing and autolytic debridement, biological debridement through use of sterile larvae and also the use of chemical enzymes [10-13].

Theatre-based sharps debridement has been utilised for removal of deep necrotic tissue, gangrene and deep infection [14] but has not been routinely used as part of

standard care. Non-surgical sharps debridement is required more regularly to remove non-viable necrotic tissue from the ulcer surface and is recommended as part of standard ulcer care [13]. The need for and appropriate method of ulcer debridement should be determined based on the clinical presentation [12] and potentially the clinical skillset and equipment available [13].

Sonoca 185® (SÖering) was introduced in Australia recently as an alternative method for ulcer debridement. The technology works by delivering low frequency ultrasound, or sound waves, through a constant flow of saline. Ultrasound results when electrical energy is converted to sound waves at frequencies above the range of human hearing (20 kHz) with Sonoca 185® functioning at 25 kHz [15]. These sound waves can then be transmitted to tissue, via a liquid medium, through a treatment applicator. It is the non-thermal effects of ultrasound that have been shown to cause two phenomena at the ulcer surface; acoustic streaming [15-17] (a steady mechanical force delivered in a fluid medium i.e. sterile saline) and cavitation [15-17] (formation of gas bubbles in the fluid creating micro-shockwaves). The combined effects of acoustic streaming and cavitation are thought to alter cell membrane activity and increase the activity of each cell [16]. Subsequently this is thought to have three clinical effects: debridement, a bactericidal effect and an ulcer healing stimulator effect [17-19].

The biological effects indicated through in vitro and animal studies could contribute to ulcer healing [20]. These effects include stimulation of cellular activity and protein synthesis, the activation of inflammatory cells and the production of chemical mediators that activate fibroblasts and may lead to ulcer healing [15,19,20]. Additionally the mechanical forces produced by the ultrasound energy at the cellular and molecular levels may promote ulcer healing by fostering cell division, angiogenesis, the release of growth factors [20] and stimulating collagen synthesis [15,19]. In vitro data has also found that low frequency ultrasonic debridement (LFUD) is effective in reducing microbe count for methicillin-resistant staphylococcus aureus, vancomycin resistant enterococci, pseudomonas and other commonly occurring bacteria [17,18].

When comparing LFUD with TBSD significant clinical advantages have been noted in terms of efficacy and safety for debriding ulcers without deep infection or necrosis. Successful TBSD is reliant upon the skill of the surgeon and their ability to distinguish between tissue types. Procedural risks of TBSD have included pain, bleeding [21], damage to underlying structures with a resultant loss of function [13,22], post-surgical infection and the use and associated risks of general anaesthesia [13].

Comparisons have been made with the use of LFUD and TBSD in DRFU in a randomised controlled trial, which found a mean healing rate that was 2.5 times faster using LFUD compared to TBSD over a two week treatment period. Limitations of this study include the very short follow-up of only two weeks and the small sample size (N = 59) [23].

A randomised double-blind controlled trial has compared low-frequency low-intensity ultrasonic debridement to a sham treatment (saline mist without ultrasound) in patients with recalcitrant DRFU. Ennis et al. found that after 12 weeks of treatment 40.7% of patients who underwent LFUD had healed compared to only 14.3% in the sham treatment group. Whilst this is promising data the overall numbers of participants were small (N = 55) [24].

A recent meta-analysis investigating the use of non-contact low-frequency high-intensity ultrasonic debridement, reported significant improvement compared to NSSD at three and five months, but no difference at six months. There were only two studies suitable for the meta-analysis, one focused on DRFU (N = 40) and the other venous leg ulcers (N = 76). Again the overall numbers were small [16].

Another meta-analysis concluded that non-contact LFUD is an efficacious treatment for chronic wounds of varying aetiologies [20]. Despite the quality of the initial evidence being of low quality suggests that LFUD does demonstrate short-term clinical benefits when used as an adjunctive therapy. Recommendations from both meta-analyses were the same; there is no evidence that compares LFUD with standard ulcer management. Additionally, there is a need for further research using larger randomised clinical trials of longer period of time.

Given the evidence available it could be expected that LFUD might be a lower-cost treatment when compared to TBSD in terms of the cost associated with the actual treatment itself and potential savings from healing ulcers faster.

Non-surgical sharps debridement has been considered the leading comparator to TBSD for several reasons; the technique is simple and requires the use of basic instruments by a trained professional; it is time efficient and can be performed in clinic or at the bed-side; does not require the resources of an operating theatre and has a lower overall cost.

Evidence on the most appropriate method, frequency and extent of DRFU debridement is limited and insufficient to draw any conclusions. The National Evidence-Based Guidelines for the Prevention, Identification and Management of Foot Complications in Diabetes recommends that NSSD should be considered first and should occur repeatedly and as often as required to remove all non-viable tissue [2]. This recommendation is based on expert opinion in the absence of evidence pertaining to DRFU debridement.

A recent Cochrane Review [10] on debridement of diabetic foot ulcers notes that while ulcer debridement is recommended as an effective intervention to assist healing, no guidelines identify a specific method of debridement. The methods of debridement reviewed included surgical debridement, topical hydrogels and larval therapy [10]. Neither NSSD nor LFUD were investigated in the Cochrane Review.

The method of choice for ulcer debridement remains inconclusive. Evidence suggests that each ulcer needs to be individually assessed in terms of type, size, position, appearance, patient pain and tolerance, cost effectiveness and available expertise and equipment to determine the most suitable method of debridement [25].

The decision to utilise NSSD as the active control group in this study was based on the expert opinion in clinical guidelines and the low cost and easy accessibility of the treatment for clinicians. The limited data around LFUD leaves a gap in the evidence that warrants further investigation. The limited data available on LFUD with NSSD as standard practice makes this debridement modality a choice comparator.

It is hypothesised that use of LFUD in the treatment of DRFU would improve healing rates when compared with NSSD. There will be four aims within this study. The primary aim is to determine if there is a difference in healing rates for DRFU, using NSSD compared to LFUD. Secondary aims include assessing for differences in pain during and post-treatment, determining if there is a difference between the quality of life of participants who have an ulcer undergoing either method of debridement and if there is a difference in overall costs between NSSD and LFUD.

This clinical trial will provide important information in the field of ulcer management; provide a better understanding of the efficacy of NSSD and the newer technology of LFUD. It will also provide health services with a better understanding of the financial impacts of both treatments. This protocol has been designed and reported to ensure it corresponds to the 33 items of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [26].

Methods

Study design

This is a randomised controlled trial comparing NSSD (active control group) and LFUD (treatment group) in DRFU with a six month follow-up period. A consort flow chart for the design of this study is presented in Figure 1.

Ethical consideration

Ethical approval for this study has been obtained by the Monash Health Human Research Ethics Committee HREC 12101B.

Participants and setting

Patients with diabetes and a foot ulcer/s, who are referred to and treated by the Podiatry Department at Monash Health, will be invited to participate in this study. Patients may be inpatients and receiving podiatry care on the ward or outpatients referred by the patient's primary medical care team.

This study is a single centre trial. The average length of stay for an acute hospital admission in Australia is 6 days [27]. Participants may be recruited during their hospital admission but it is anticipated they will receive treatment primarily in the outpatient setting. Inpatients, however, can receive either treatment if they meet inclusion criteria for this study as both study interventions can be undertaken by the bedside as well as in an outpatient clinical setting.

A standard initial podiatric assessment will occur at baseline including a neurovascular assessment, medical and surgical history, medications history, diabetes management and control history including glycated haemoglobin (Hba1c), footwear assessment, ulcer aetiology, ulcer duration and previous management. If the participant meets the inclusion criteria (Table 1) as determined by the treating podiatrist, the patient will be informed about the research project and written consent will be obtained to participate in the study.

Ulcers must be chronic, or greater than 1 month in duration to be included in the study. This is to capture the most accurate data around DRFU, which have been shown in the literature to take longer than 4 weeks to heal [29]. Should a patient have an ulcer infection at the time of recruitment, or develop an infection during the trial they will receive appropriate antibiotic therapy and will be able to continue in the trial. If appropriate infection management is not commenced, irrespective of the reasons, the patient will not be able to continue in the trial.

Interventions

The two interventions are the two different methods of ulcer debridement, LFUD and NSSD. The techniques for both treatments are as described in Table 2.

Outcome measures

Primary outcome measure

The primary outcome measure for this study is the proportion of ulcers healed over the six month follow-up period. An ulcer is defined as healed in the presence of intact skin, i.e. functional epithelial tissue [30], a total surface area of 0 cm^2 and restoration of functional and anatomic continuity [31]. Ulcer healing status will be determined by assessing the total ulcer area.

Ulcer surface area will be assessed using photographs taken with a digital camera using a standard technique

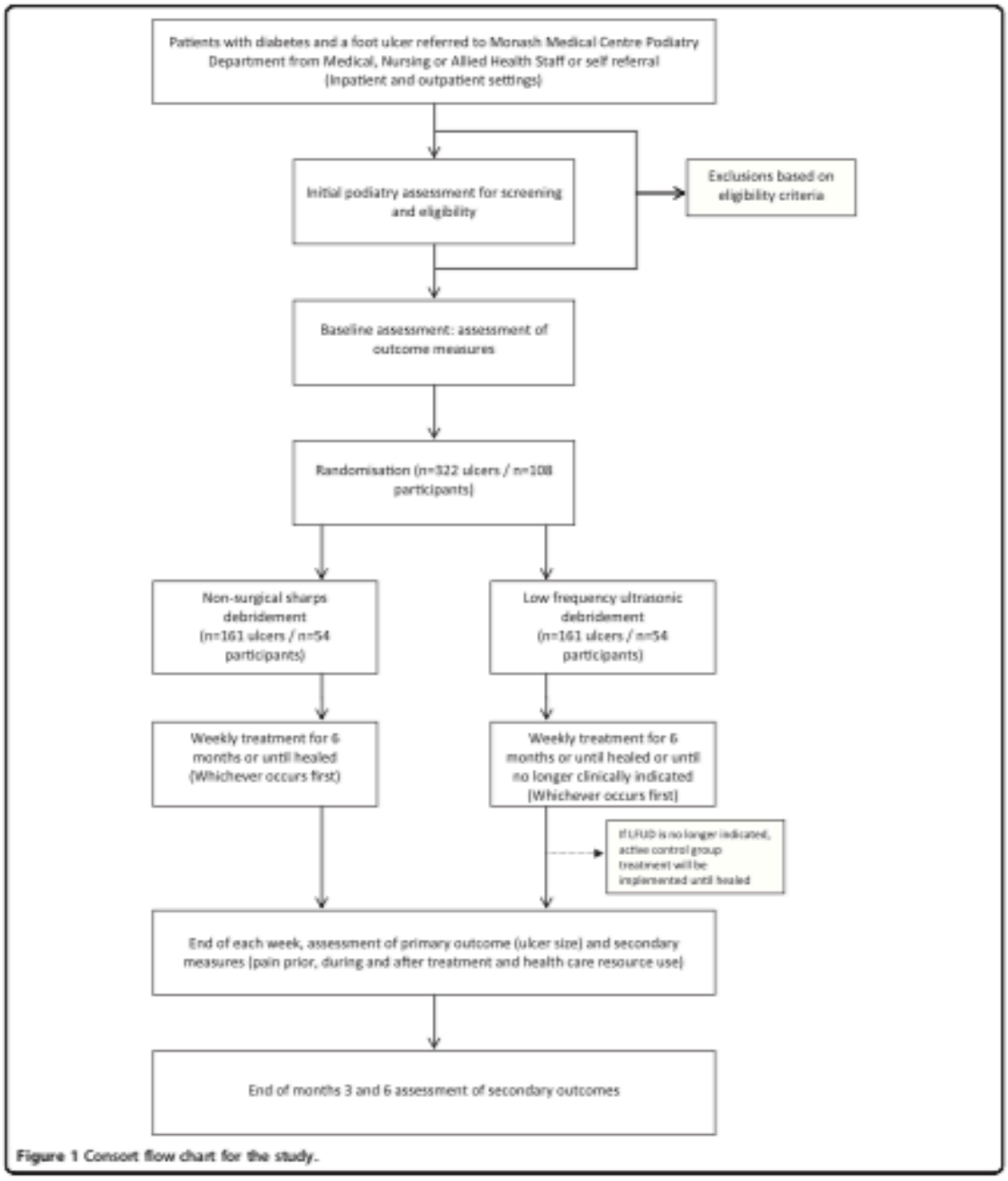

Figure 1 Consort flow chart for the study.

(Table 3). A one centimetre by one centimetre, transparent grid will be utilised over the printed photograph and the total area calculated. Total surface area measurements will be performed following each weekly treatment. A research assistant blinded to the treatment allocation will collect the data for the primary outcome measure. This is to ensure the treating podiatrist is blinded to the primary outcome during subsequent treatments.

The research assistant has been trained by the treating podiatrist and given written instructions on how to use

Table 1 Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
General:	***General:***
≥ 30 years of age	Patients taking immunosuppressive medications
Able to provide informed consent	Known allergy to ulcer dressing products
Ulcers present for greater than 1 month	Pre-existing ulcer pain preventing either type of debridement
Ulcers ≥ 1 cm^2	
Vascular:	***Vascular:***
Palpable pedal pulses OR biphasic or triphasic pedal pulses on doppler OR toe pressure ≥ 45 mmHg	Non-palpable pedal pulses OR monophasic pedal pulses on Doppler OR toe pressure ≤ 45 mmHg
Ulcer classification:	***Ulcer Classification:***
Infected ulcers being appropriately managed	Dry gangrenous ulcer
Those meeting The University of Texas Wound classification criteria (28):	Fungating ulcers
A1, A2, A3 (wounds of varying depth without infection or ischaemia)	Malignant ulcers
B1, B2, B3 (wounds of varying depth with infection only)	***Those meeting the University of Texas wound classification criteria (28):***
	A0, B0, C0, D0 (pre or post-ulcerative lesion with complete epithelialisation, with or without infection and ischaemia)
	C1, C2, C3 (wounds of varying depth with ischaemia only)
	D1, D2, D3 (wound of varying depth with infection and ischaemia)

the transparent grid to calculate total ulcer area. To determine reliability fifteen ulcers have been photographed and both the research assistant and treating podiatrist followed the same technique to calculate ulcer area. Inter-rater measurement reliability between the treating podiatrist and research assistant was found to have an ICC of 0.91.

The ulcer depth will be measured by the treating podiatrist following each treatment, as depth cannot be accurately assessed using a photograph. A disposable measurement probe will be used to assess ulcer depth, undermining, sinus or tracking.

A review of available literature around ulcer measurement is scarce and of low evidence. The measurement technique being used in this study, tracing and subsequent counting of centimetre squares, has a high inter-rater and intra-rater reliability when compared to other forms of ulcer measurement [32,33].

A standard technique will be used for each method of debridement and ulcer measurement ensuring consistency (Tables 2 and 3).

Ulcers being treated in the intervention group will be reviewed after six weeks of treatment. If LFUD is no longer clinically indicated then treatment will be ceased and the ulcers will then receive the control treatment (NSSD). This change is to reflect the pragmatic nature of the treatment and NSSD is considered standard ulcer care. Clinical indications for ceasing LFUD treatment include pain, ulcer size and depth, clinical presentation and no ulcer improvement.

Secondary outcome measures

Secondary outcome measures will include assessing ulcer pain, quality of life and economic evaluation.

Ulcer pain will be measured weekly using a 100 mm Visual Analogue Scale (VAS). Pain will be assessed prior

Table 2 Standard step-by-step technique for LFUD and NSSD

LFUD	NSSD
1) Constantly move the handpiece to prevent ultrasound burning tissue	1) Start debriding at the distal most aspect of the ulcer
2) Start debriding at the distal most aspect of the ulcer	2) Moving scalpel proximally with each motion
3) Moving the handpiece left to right and from the distal to proximal aspect of the ulcer	3) Once the distal to proximal ulcer has been debrided then debride from left side to right side
4) Once the entire ulcer surface has been debrided re-commence the same technique from the distal most aspect of the ulcer	4) Continue until as much necrotic tissue has been removed as possible
5) Continue until as much necrotic tissue has be removed as possible	5) Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel.
6) Any peri-wound tissue that requires removal (i.e. callus, maceration) will occur using a scalpel. The wound base will not be debrided with the scalpel.	

Table 3 Standard step-by-step technique for ulcer measurement

Ulcer measurement
1) Ulcers that have tunnels or undermining will be marked on the skin with a black marker
2) A white towel will be place under the foot to remove distracting background elements
3) A disposable ruler will be labelled with participant number, wound number, participant initials and the date
4) Position the disposable ruler alongside the ulcer and secure with paper tape
5) Use macro camera setting with flash on, iso set to 200
6) Take photograph at a distance of 20 cm from the wound
7) Ulcer measurements will be conducted from print out using the photograph (all photos will be printed as standard A4 size)

to, during and following each treatment. The far left end of the scale (0 mm) will be labelled as no pain and the far right end of the scale (100 mm) will be labelled as worst pain imaginable. The VAS has been widely used and has been shown to be a valid and reliable pain assessment tool [34].

A health-related quality of life tool will be used to gain perspective from each participant. This will be undertaken at the initial treatment, at three months and again at six months. If an ulcer heals prior to the end of the six month study period the tool will be applied at that point. The Eq 5D-5 L [35] assessment tool analyses five health-related quality of life domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This tool has been widely used and has been validated for use in patient groups with diabetes [36].

All data for the secondary outcome measures will be collected by the treating podiatrist. No blinding will occur for this data.

Each outcome measure and their time points of collection are summarised in Table 4.

Sample size

The sample size calculation for this study was based upon the primary outcome comparison between groups of the proportion of ulcers completely healed by the six month follow-up. Previous research indicates that nearly 25% of ulcers treated with NSSD healed within six months [29], while another previous study found that 41% of ulcers treated with LFUD healed within three months [24]. There is no six month data available for the LFUD approach. A sample size of 147 ulcers per group is required to achieve 80% power using a two-tailed alpha of 0.05 to detect an absolute difference in the proportion of ulcers healed of 0.16 (control = 0.25, intervention = 0.41). To account for the intra-cluster correlation of multiple ulcers being nested within a single participant we adjust this for a design effect $(1+(n-1)*ICC)$ using n = 3 ulcers per participant and ICC estimate of 0.05; thus we require 161 ulcers per group. With an average of 3 ulcers per participant we require 54 participants per group.

Randomisation

Randomisation will be undertaken using a permuted-block randomisation approach. Randomisation blocks of two, four or eight participants will be generated and randomly selected and the resultant allocation order will be entered into opaque, sealed envelopes. An investigator not involved in recruitment or assessment (CW) will be responsible for preparing the random allocation sequence and envelopes. The treatment conditions will be provided as per the random allocation sequence following completion of the initial assessment.

Once eligibility has been confirmed, a verbal explanation of the project will be provided and the treating podiatrist will obtain written consent. All participants who consent will have baseline assessments conducted prior to randomisation, as outlined above. All ulcers (where there is more than one per participant) will be numbered and documented according to anatomical location prior to randomisation. Only the treatment condition will be randomised, not each individual ulcer. Where there is more than one ulcer, all will be treated with the same method as per the randomisation process and included in the study. Following randomisation the initial treatment and measurements will commence as outlined in Tables 2 and 3. All participants will receive treatment and have their ulcers photographed and measured on a weekly basis, as is standard podiatry practice at Monash Health. Both groups will receive best practice ulcer management including appropriate ulcer dressings, pressure off-loading and footwear provision as required.

Identifiable outcome data will be stored within the participant's health record. De-identifiable data will be stored within a password-protected Excel spread sheet within a secure hospital data management system as per requirement of the Human Research Ethics Committee (HREC) for Monash Health. The primary investigator (LM) will be responsible for data entry and a co-investigator (SB) will randomly audit information to monitor data accuracy.

The trial will be managed by the research team and led by the primary investigator (LM). The protocol has undergone external review from the Lions John Cockayne Research Fellowship committee and the research team will give quarterly progress reports. Annual reports will also be required (including adverse events) to the HREC of Monash Health. The research team will meet on a monthly basis to address clinical and data monitoring concerns.

Table 4 Outcome measures and timeframes

Data collection	Measurement tool	Data collected method	Timeframe
Measurement of total ulcer area	Centimetres squared; Tracing from photographs and counting squares	Research assistant	Weekly: Post-treatment until healed or at 6 months
Measurement of ulcer depth	Centimetres; Using sterile probe	Treating podiatrist	Weekly: post-treatment until healed or at 6 months
Ulcer pain	Visual analogue pain scale 100 mm	Treating podiatrist	Weekly: Pre-treatment, during treatment, post-treatment until healed or 6 months
Quality of life	EQ-5D-5 L tool	Participant questionnaire	Initial treatment, at 3 months, at 6 months
Direct health costs			
Consumable costs for treatments	In dollars for each treatment	Treating podiatrist	Weekly, per participant until healed or at 6 months
Medicare Benefit Scheme (MBS)	MBS Care database, in dollars	Extraction from MBS database	End of project for each participant from initial to final treatment
Pharmaceutical Benefit Scheme (PBS)	PBS Care database, in dollars	Extraction from PBS database	End of project for each participant from initial to final treatment
Inpatient data	Monash Health: Admission duration, reason for admission, imaging and interventions, obtained from the patient record and from the Victorian Admitted Episodes Database External organisation: Admission duration, reason for admission, costs of any surgery for diabetes-related foot ulcers will be estimated using WEISS funding	Hospitalisation costs	Monash Health: End of project External organisation: End of project
Hospital based services (outpatient data)	Hours – time spent	Treating podiatrist	Weekly per participant until healed or at 6 months
Medical imaging and pathology for outpatients	Dollars – hospital based costs	Treating podiatrist	Monthly per participant until healed or at 6 months
Community based services	Number and cost of appointments	Participant interview	Monthly until healed or at 6 months
Private health appointments	Number and cost of appointments, eligibility for private health subsidies	Participant interview	Monthly until healed or at 6 months
Royal District Nursing Service for ulcer management	Frequency and cost of service	Participant interview	Monthly until healed or at 6 months
Ongoing ulcer care products	Valued using market prices	Participant interview	Monthly until healed or at 6 months
Parking costs for appointments	Dollars	Participant interview	Monthly until healed or at 6 months
Transportation costs to travel to appointments	Estimated through Australian Tax Office car rate cents per km	Participant interview	Monthly until healed or at 6 months
Productivity costs			
Time taken from work for participant and/or any family member	Salary and hours taken from work	Participant/family interview	Monthly until healed or at 6 months

Statistical analysis

The proportion of ulcers that are completely healed by the six month follow-up will be compared between groups using a logistic regression analysis approach with clustering of ulcer within participant. A member of the research team (TH) who will be blinded to the allocation of the participants will assess this.

The rate of change in ulcer size (surface area, using the post-debridement photo) will be compared between groups using a linear mixed model analysis approach where repeated assessments will be nested within ulcer, and ulcers will be nested within participants. The groups will be treated as a fixed factor while assessments, ulcer and participants will be treated as random factors. All

analyses will be adjusted for whether the wound was infected at baseline, as infection has been demonstrated to delay healing [37] and HbA1c levels at baseline as poor glycaemic control has been demonstrated to delay healing [38].

A pre-planned interim analysis will be undertaken after 70% of the planned sample size has been recruited. This analysis will use all data available to that point in time and examine the safety and efficacy outcomes from the trial. A data analyst who is blinded to group allocation will be provided with the dataset and mock group codes. The outcome of this analysis will be forwarded to the remaining project investigators who will decide whether there is sufficient evidence to reject the null hypothesis for the primary outcome. The assumptions underlying the sample size calculation (e.g. ICC value) will also be examined at this point and revisions to the sample size will be made if indicated.

Economic analysis

Cost effectiveness analysis

Direct and indirect health care costs will be collected at regular intervals, as explained in Table 3.

The formula for assessing cost effectiveness analysis will be:

$$\frac{\text{Cost}_{\text{LFUD}} - \text{Cost}_{\text{NSSD}}}{\text{Effect}_{\text{LFUD}} - \text{Effect}_{\text{NS\&D}}} = \text{Incremental cost per additional ulcer healed}$$

Cost utility analysis

A health related quality of life assessment obtained from the EQ-5D-5 L tool will be converted to utility scores as explained in Table 4. The economic evaluation will examine the cost per quality adjusted life year (QALY) gained per patient provided with each intervention. QALY measurements will use the EQ-5D-5 L utility-based cost-effectiveness analysis. The formula to calculate QALYs gained from the intervention will be:

$$\frac{\text{Cost}_{\text{LFUD}} - \text{Cost}_{\text{NSSD}}}{\text{QALY}_{\text{LFUD}} - \text{QALY}_{\text{NSSD}}} = \text{Incremental cost per QALY gained}$$

Discussion

Diabetes-related foot ulceration is a significant medical and social problem. Consensus among wound specialists supports the importance of ulcer debridement to encourage ulcer healing. Despite this, there is a paucity of evidence comparing different debridement techniques. Whilst there is evidence available around the efficacy of LFUD it has been limited. Furthermore, there is no randomised controlled trial looking at the healing rates of DRFU that undergo NSSD compared to LFUD.

This clinical trial will provide important information in the field of ulcer management and provide a better understanding of the efficacy of using NSSD treatment. It will also provide health services with a better understanding of the financial impacts of both treatments.

Adverse events will be measured and recorded during the study. The adverse events for both treatment groups may include incidents such as sharps injuries to the participant or treating podiatrist, development of ulcer infection, hospital admission due to ulcer deterioration, excess pain and bleeding from debridement at the ulcer surface.

A limitation of this study is the non-consideration given to nutritional status. Patient nutritional status has potential to impact on ulcer healing, however outside of a controlled inpatient environment it is difficult to enforce a strict food regime. All patients will be encouraged to adhere to a suitable diet, however this will not be controlled as part of this study.

A second limitation is that while a thorough assessment of pain will be undertaken, this measure will only focus on the individual ulcer pain before, during and after debridement with either modality. Where participants have more than one ulcer in close proximity to another ulcer the pain assessment may become difficult to distinguish for each ulcer.

Abbreviations

NSSD: Non-surgical sharps debridement; LFUD: Low frequency ultrasonic debridement; TBSD: Theatre-based sharps debridement; DRFU: Diabetes-related foot ulceration.

Competing interests

The authors declare no competing interests.

Authors' contributions

All the authors contributed to study design and methodology. LM and CW obtained funding for the study. All authors contributed to the study protocol. LM is the chief investigator and drafted the paper. SB, TH, and CW provided editorial assistance. All authors have read and approved of the final paper.

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APPENDIX 4 – PUBLICATION ARTICLE 4

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BMC Research Notes

RESEARCH NOTE Open Access

Healing rates in diabetes-related foot ulcers using low frequency ultrasonic debridement versus non-surgical sharps debridement: a randomised controlled trial

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Abstract

Objective: Current clinical practice varies around debridement techniques used to promote healing of diabetes-related foot ulcers. This randomised controlled study will compare healing rates for diabetes-related foot ulcers treated with low frequency ultrasonic debridement versus non-surgical sharps debridement. Individuals with diabetes-related foot ulcers being managed by podiatry at a metropolitan hospital were screened against study criteria. Eligible participants were randomly allocated to either the non-surgical sharps debridement group or the low frequency ultrasonic debridement group and received weekly treatment for 6 months. Participants also completed a quality of life measure and visual analogue pain scale.

Results: This trial was ended early due to recruitment issues. Ten participants with 14 ulcers participated. Results were analysed using a survival analysis approach. Ulcers treated with non-surgical sharps debridement healed more quickly (61.6 days ± 24.4) compared with low frequency ultrasonic debridement (117.6 days ± 40.3). In both groups, quality of life was observed to improve as ulcers healed and pain levels reduced as ulcers improved. Observations from this study found faster healing using non-surgical sharps debridement. However, these results are unable to be generalised due to the small sample size. Further research is recommended.

Trial registration Australian New Zealand Clinical Trial Registry: ACTRN12612000490875

Keywords: Debridement, Diabetes complications, Wound healing, Ultrasonics

Introduction

Diabetes and its complications are rapidly becoming the world's most significant cause of morbidity and mortality. Globally, the number of adults with diagnosed diabetes is approximately 415 million [1] or one in eleven adults, a workwide prevalence that was previously predicted to occur in 2030 [2].

Diabetic foot disease is also considered one of the most serious complications of diabetes. The pathophysiology is multifactorial and is predominantly associated with neuropathy, peripheral arterial disease and foot deformity [3–6]. The convergence of one or more of these conditions leads to the development of foot ulceration, which is a significant precursor to lower limb amputation [7]. It is estimated that up to 25% of people with diabetes will develop a foot ulcer in their lifetime, making them 36 times more likely to experience subsequent amputation [7, 8].

The treatment goal for diabetes-related foot ulcers (DRFUs) is to achieve healing as quickly as possible to prevent the onset of serious complications. Treatment commonly includes antibiotic therapy for infection, revascularisation in the presence of reduced arterial perfusion, offloading of pressure, appropriate dressings and regular debridement of non-viable tissue [6, 7]. Debridement is fundamental in DRFU management [6] and

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facilitates healing by ensuring the best possible preparation of the wound bed and margins [9, 10]. Many different methods of debridement exist but there is very little evidence to support a single method or the frequency that it should be performed [6, 10]. Similarly, there are variable costs of debridement methods and there is little economic evaluation of cost versus effectiveness to guide clinicians to make economically feasible treatment choices [11].

The primary outcome of this study is proportion of DRFUs healed using non-surgical sharps debridement (NSSD) versus low frequency ultrasonic debridement (LFUD) over a 6-month period. Secondary outcomes include quality of life measure and assessment of pain before, during and after treatment. This study adhered to a previously published protocol [12].

Main text

Participants and setting

From March 2013 to February 2015 all patients with a DRFU receiving treatment by podiatry at Monash Health, Victoria, Australia, were screened against the study inclusion criteria (Table 1).

Participants identified as meeting the study criteria were informed about the research project by the treating podiatrist. Those agreeable to participating were provided with a patient information and consent form and written consent was obtained. Approval was granted by the Monash Health Human Research Ethics Committee (HREC Reference Number 12101B).

Interventions

The two interventions included LFUD (intervention) and NSSD (control), which were applied according to a standardised technique. Debridement occurred weekly until healing occurred. The time of each debridement was performed for as long as required to remove as much non-viable tissue as possible from the wound base. Wound dressings, pressure offloading and footwear were applied according to evidence-based practice [6]. This was decided by the treating podiatrist based on clinical need, ulcer appearance and location.

Participant quality of life was assessed at baseline, 3 months and at 6 months or once healed using the validated tool EQ-5D-5L [15]. Where multiple ulcers existed at the same time, on a single participant, and resolved at the same time, the data was represented only once. Ulcer pain was measured before, during and after each debridement using a validated 100 mm Visual Analogue Scale [16].

Outcomes

The primary outcome measure for this study was the proportion of DRFUs healed over the 6-month follow up period. Healing was determined by assessing the total surface area of the ulceration site. Ulcer depth was measured by the treating podiatrist using a disposable probe at the deepest point following each debridement. Where the ulcer depth could not be measured (less than 0.1 cm) but the ulcer remained unhealed, a standardised depth of 0.1 cm was used. Ulcer undermining was also measured following each debridement using a disposable probe. The extent of undermining was marked on the skin with a black marker.

Table 1 Participant inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
General: ≥ 30 years of age Able to provide informed consent Ulcers present for ≥ 1 month Ulcers ≥ 1 cm^2	General: Patients taking immunosuppressive medications Known allergy to ulcer dressing products Pre-existing ulcer pain preventing either type of debridement
Vascular: Palpable pedal pulses OR toe pressure ≥ 45 mmHg OR those meeting Rutherford Classification of peripheral arterial disease stages [13]: 0 (Asymptomatic) 1 (Mild claudication) 2 (Moderation claudication at 200 m)	Vascular: Those meeting Rutherford Classification of peripheral arterial disease stages: 3 (Severe claudication) 4 (Rest pain) 5 (Ischaemic ulceration no exceeding ulcer of the digits of the toes) 6 (Severe ischaemic ulcers of frank gangrene)
Ulcer classification: Infected ulcers being appropriately managed Those meeting The University of Texas Wound classification criteria [14]: A1, A2, A3 (wounds of varying depth without infection or ischaemia) B1, B2, B3 (wounds of varying depth with infection only)	Wound classification: Dry gangrenous ulcer Fungating ulcers Malignant ulcers Those meeting the University of Texas wound classification criteria: A0, B0, C0, D0 (pre or post-ulcerative lesion with complete epithelialisation, with or without infection and ischaemia) C1, C2, C3 (wounds of varying depth with ischaemia only) D1, D2, D3 (wound of varying depth with infection and ischaemia

Photographs were taken using a digital camera following each debridement. A standardised technique was implemented to reduce variation in photographic angles. Calculation of wound surface area was undertaken at the completion of the study by a member of the research team not involved in data collection (CW). A previously established inter-rater measurement reliability of calculating wound surface area between the treating podiatrist and a research team member was 0.99.

Secondary outcome measures included ulcer pain before, during and after each debridement using a validated 100 mm Visual Analogue Scale (VAS) [16]. Health related quality of life was assessed using the validated EQ-5D-5L [15]. This tool analyses five health-related quality of life domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants completed this at the initial treatment, 3 months and again at 6 months or the final appointment.

Randomisation

After consent had been obtained participants were randomised into either the control group or intervention group. Randomisation was undertaken using a permuted-block approach. Randomisation blocks of two, four or eight participants were generated and randomly selected with the resultant allocation order placed into opaque sealed envelopes by an investigator not involved in recruitment or patient assessment (CW). The treatment for each participant was determined as per the random allocation sequence following completion of initial podiatric assessment.

All DRFUs (where a single participant had more than one ulcer) were numbered and documented according to anatomical location prior to randomisation. Only the treatment modality was randomised, therefore, when a single participant had more than one DRFU, all were treated using the same method.

Participants and treating podiatrists were unable to be blinded to treatment as neither method of debridement could be concealed. However, data analysis was undertaken without knowledge of the treatment allocation.

Procedure

The DRFUs being treated in the intervention group were re-assessed after 6 weeks of treatment. If LFUD was no longer clinically indicated then this method of debridement was ceased and the ulcer was transitioned to the control treatment of NSSD. Clinical indications for ceasing LFUD included pain, small ulcer size or high levels of exudate.

As per the study criteria the ulcers included in this study were greater than 4 weeks old and therefore had received treatment prior to being enrolled in the study. The treatment prior to enrolment was determined at baseline through patient assessment and included surgical debridement, NSSD, autolytic debridement through dressings, topical negative pressure wound therapy, split skin grafting, offloading via podiatry felt padding, footwear or total contact casting.

Statistical analysis

All analyses were undertaken using the intention to treat principle. The proportion of DRFUs that were healed by the 6 month follow up period was compared between the two treatment groups using Kaplan–Meier survival analysis approach. Due to the small sample size the planned logistic regression analysis was unable to be completed.

Pain and quality of life scores were not analysed statistically due to insufficient numbers of participants and as a result baseline comparability between the two groups could not be ensured.

Results

A total of 10 participants with 14 ulcers were recruited to this study. Of the 14 ulcers, two ulcers (two different participants) were lost to follow up, one from each group. In one instance this was due to hospital admission to a different health service (intervention) and the other participant changed residential locations (control). Summative data for the primary outcome is presented in Table 2.

A survival analysis estimating time to ulcer healing was undertaken and is presented in Fig. 1. Diabetes related foot ulcers treated with NSSD healed in a mean (SD) of 61.6 (24.4) days compared with those treated with LFUD healed in a mean (SD) of 117.6 (40.3) days.

The use of analgesia during treatment was comparable between both groups, with the same three ulcers from each group requiring some form of analgesia for every treatment. It was observed that pain levels increased during treatment but then returned to baseline levels after treatment.

The quality of life reported in both groups demonstrated an improving trend in scores as the ulcers progressed towards healing.

Table 2 Outcome data per ulcer

Control group			Intervention group		
Ulcers healed	Ulcers not healed	Lost to follow up	Ulcers healed	Ulcers not healed	Lost to follow up
5	0	1	5	2	1

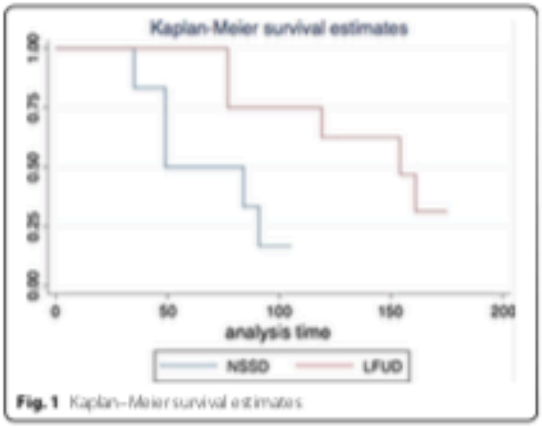

Fig. 1 Kaplan–Meier survival estimates

Adverse events

During the follow up period 3 of the 14 ulcers were treated with oral antibiotics for minor soft tissue infections. No ulcer developed ascending cellulitis or osteomyelitis. No participants required surgical intervention, amputation or hospital admission during the follow up period. No other adverse events occurred throughout the study period.

Discussion

Debridement is important to facilitate healing of DRFUs. This research investigated two methods of debridement available to clinicians that has not been widely studied. Whilst it was observed that ulcers treated with NSSD healed at a faster rate than those treated with LFUD, the sample size was too small to determine if this finding is significant. Despite the small sample size, our study findings are consistent with similar studies previously conducted comparing LFUD to NSSD in DRFUs. Four studies have previously been published, with three describing clinical trials involving randomisation and one using historical data as the control [17–20]. Although each of these studies concluded that DRFUs heal faster using NSSD compared to LFUD, between-study comparison was made difficult by heterogenic study design. These included differences between the type of LFUD performed, the frequency of treatments and variation in control treatments including wound dressings and offloading methods.

Limitations

The greatest limitation of this study was the difficulty experienced recruiting participants. This makes it difficult to draw clinically significant conclusions. Furthermore, the planned statistical analyses, including health economics, were not undertaken.

Many attempts were made throughout the study period to address barriers to recruitment and increase participant numbers:

- Medical histories of all patients under podiatry care were reviewed by the primary investigator (LM) on a monthly basis to determine if study criteria were met and the patients could be considered for enrolment.
- Study criteria were pragmatically revised multiple times with approval from the relevant human research ethics committee.
- Recruitment was extended to include patients with DRFU attending Vascular Outpatient clinics.
- A second LFUD unit was secured on loan to allow a second podiatrist to potentially treat patients enrolled in the study at an additional site.
- Discussion ensued with the Podiatry Department at a second organisation with a view to implementing a multisite study.

Despite numerous attempts to increase recruitment rates the sample size fell short of numbers required to generate broadly applicable findings. These logistic problems were difficult to overcome and highlight the challenges of undertaking clinically unfunded research within populations with complex health needs.

There were a number of limitations that the research also encountered during the design and implications that future researchers should consider when undertaking this type of research with patients who have DRFUs:

- The type of ulcer dressings and pressure offloading used were not standardised.
- Inaccuracies in measuring ulcer depth where depth was less than 0.1 cm.

An important strength of this study design was the use of contact LFUD. Previously, only non-contact LFUD has been investigated in DRFUs [17–20]. Contact LFUD is thought to produce a cavitation effect, resulting in direct and immediate removal of nonviable tissue from the ulcer base. As the name suggests, noncontact LFUD produces the same phenomena but at a lower intensity and does not directly contact the ulcer surface. These slight variances mean that there is no debridement of necrotic tissue when noncontact LFUD is used [21]. This is also the first study to investigate the contact application of LFUD in DRFUs.

This study has revealed some interesting findings, which we believe would benefit from further

investigation. Future randomised controlled trials would be of value to evaluate the clinical effectiveness of both debridement methods in the management of DRFUs. This patient population were found more likely to have multiple medical comorbidities that excluded them from ulcer debridement when subsequent patient lists were screened over the 2-year study period. This was an unexpected finding as the researchers designed this trial for patients with common traits applicable to DRFUs. Therefore, any future prospective research on this topic would benefit from consideration to a multisite study to ensure a large enough sample size could be reached. Additionally, the authors recommend including community care podiatry clinics where patients are more likely to be medically stable than those attending outpatient podiatry clinics based in the acute setting. Future research should also further investigate pain and quality of life assessment for patients between groups, as well as, the economic efficiency between both methods of debridement.

Abbreviations
NSSD: non-surgical sharps debridement; LFUD: low frequency ultrasonic debridement; DRFU: diabetes-related foot ulcer.

Authors' contributions
All the authors (LM, CW, SB, TH) contributed to the study design, methodology and result analysis. LM and CW obtained funding for the study. LM undertook the data collection. LM is the chief investigator and drafted the paper with editorial assistance from CW, SB, TH. All authors read and approved the final manuscript.

Author details
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Acknowledgements
The authors thank the podiatrists at Monash Medical Centre for their assistance in data collection during 2013–2015.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Monash Health Human Research Ethics Committee (HREC Reference Number 121018). Written consent obtained from all participants.

Full protocol
The study reported here was part of a doctoral thesis from where the full protocol and further methods can be accessed [12].

Funding
This study was funded in part by a grant from the Lions John Cockayne Memorial Fellowship Trust for consumables at the Monash Health site. Support in kind is also provided by the Monash Health Podiatry Department and Allied Health Clinical Research Unit. CW is supported by a National Health and Medical Research Council Early Career Health Professional Fellowship.

Publisher's Note

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APPENDIX 5 – ETHICS APPROVAL 1

Southern Health/Monash Health approval for randomised clinical trial.

Southern Health

248 Clayton Road
Clayton, Victoria 3168
Australia

Postal address:
Locked Bag 29
Clayton South, Victoria 3169
Australia

tel 03 9594 6666
fax 03 9594 6727

3 August 2012

Ms Lucia Michailidis
Podiatry
The Kingston Centre
Warrigal Road
Cheltenham Vic 3192

Dear Ms Michailidis

Study title: Improved Healing Rates in Diabetes Related Foot Ulcers with Low Frequency Ultrasonic Debridement (LFUD) Versus Non-surgical Sharps Debridement - A Randomised Control Trial

Southern Health HREC Ref: 12101B

The Southern Health HREC B reviewed the above application at the meeting held on 19 April 2012 In addition; the HREC is satisfied that the responses to our correspondence of 30 April 2012 have been sufficiently addressed.

The HREC approved the above application on the basis of the information provided in the application form, protocol and supporting documentation.

This reviewing HREC is accredited by the Consultative Council for Human Research Ethics under the single ethical review system.

Approval

The HREC and Site Specific Authorisation approval is from 3 August 2012.

Approval is given in accordance with the research conforming to the *National Health and Medical Research Council Act 1992* and the *National Statement on Ethical Conduct in Human Research (2007)*. The HREC has ethically approved this research according to the Memorandum of Understanding between the Consultative Council and the participating organisations conducting the research.

Approval is given for this research project to be conducted at the following sites and campuses:

- Southern Health, Monash Medical Centre, Clayton Campus

You must comply with the following conditions:

The Chief Principal Investigator is required to notify the Administrative Officer, Research Directorate, Southern Health of:

1. Any change in protocol and the reason for that change together with an indication of ethical implications (if any)
2. Serious or unexpected adverse effects of project on subjects and steps taken to deal with them
3. Any unforeseen events that might affect continued ethical acceptability of the project
4. Any expiry of the insurance coverage provided in respect of sponsored trials

5. Discontinuation of the project before the expected date of completion, giving reasons
6. Any change in personnel involved in the research project including any study member resigning from Southern Health &/or the study team.

At the conclusion of the project or every twelve months if the project continues, the Principal Investigator is required to complete and forward an annual report to the Committee.

Annual report forms will be forwarded to the researcher.

Approved documents

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Participant Information and Consent Form	3	19 June 2012

If you should have any queries about your project please contact Deborah Dell or Julie Gephart by email deborah.dell@southernhealth.org.au /julie.gephart@southernhealth.org.au

The HREC wishes you and your colleagues every success in your research.

Yours sincerely

[redacted]

Dr James Doery
Medical Administrator

APPENDIX 6 – ETHICS APPROVAL 2

Southern Health/Monash Health approval for infection control study.

MonashHealth

Research Directorate
Monash Health
Monash Medical Centre
246 Clayton Road
Clayton Victoria 3168
Australia

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Clayton South Vic 3169
Australia

Tel (03) 9594 4611
Fax (03) 9594 6306

18 March 2014

Ms Lucia Michailidis
Podiatry
Monash Medical Centre
246 Clayton Road
Clayton Vic 3168

Dear Researcher,

Research Project Application No. 14077Q: Does the New Technology of Low Frequency Ultrasound Debridement Pose an Infection Control Risk for Clinicians, Patients and the Clinic Environment?

Thank you for your email dated 17 March 2014. It is our understanding that this project is a quality assurance exercise involving collection, use and disclosure of data in a de-identified format to be conducted at Monash Health. Such data is to be accessed by a Monash Health employee only. As such, we advise that it does not raise any ethical concerns and does not fall within the category of a 'research' project within the *National Statement on Ethical Conduct In Human Research* (NHMRC, 2007). This project does not require submission to the Monash Health Human Research Ethics Committee. In addition, this quality assurance activity can be described as an activity to monitor, improve and evaluate the quality of health services provided by Monash Health.

For our record-keeping purposes, we will deem this activity will be in progress for 12 months from this date, unless we hear from you to the contrary. It will then be classified as completed.

Please note this letter only pertains to the QA activity being conducted at Monash Health. If it is intended the QA activity will be conducted at another institution appropriate review and authorisation will be required prior to commencement at another institution.

Should you have any queries please contact me on 03 9594 4090.

Yours sincerely

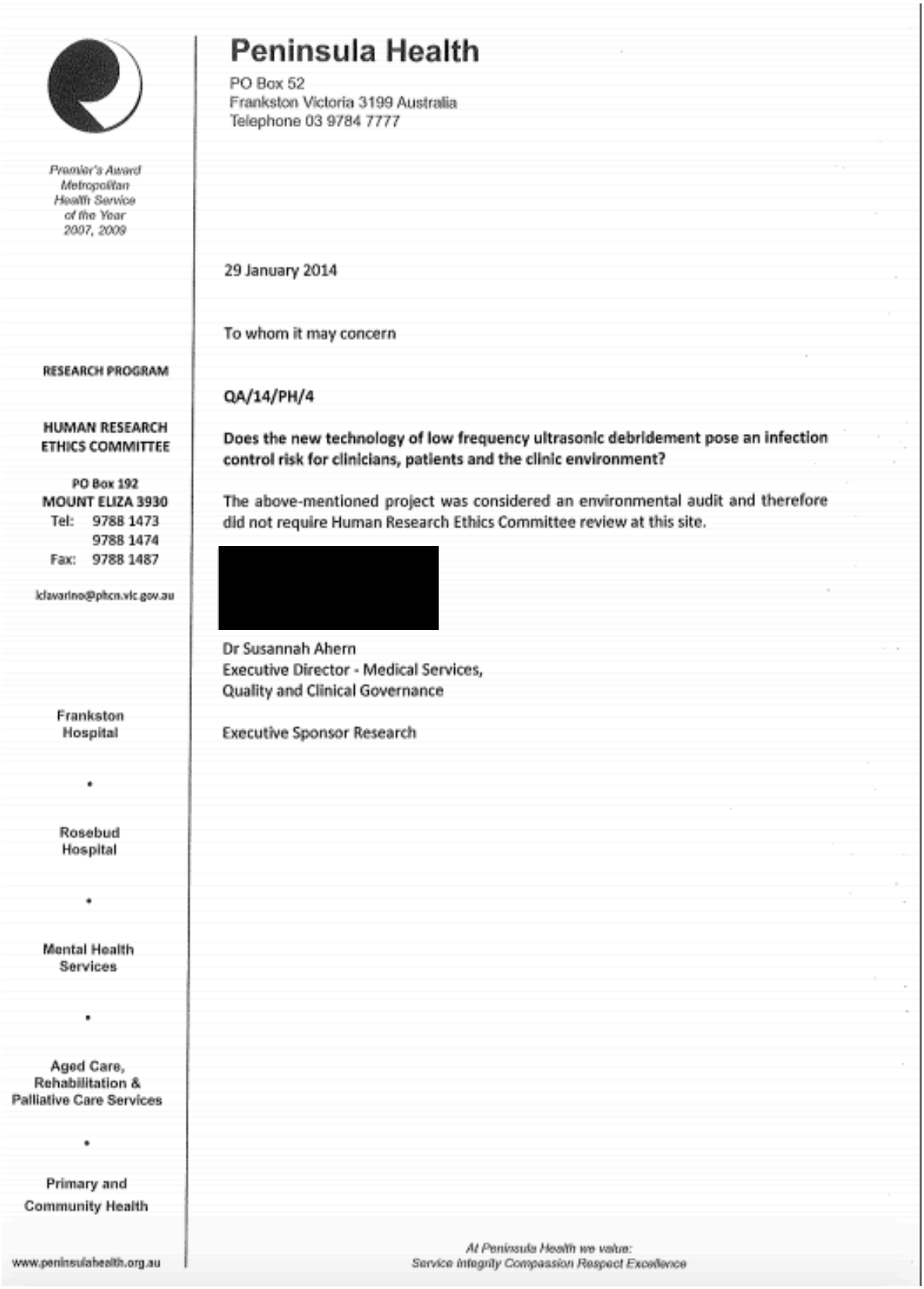
[redacted]

MICHAEL KIOS
Research Governance Officer
Research Directorate

Cc: Ms Bev Desilva Quality Unit

APPENDIX 7 – ETHICS APPROVAL 3

Peninsula Health approval for infection control study.



Peninsula Health

PO Box 52
Frankston Victoria 3199 Australia
Telephone 03 9784 7777

Premier's Award Metropolitan Health Service of the Year 2007, 2009

29 January 2014

To whom it may concern

RESEARCH PROGRAM

HUMAN RESEARCH ETHICS COMMITTEE

PO Box 192
MOUNT ELIZA 3930
Tel: 9788 1473
9788 1474
Fax: 9788 1487

kclavarino@phcn.vic.gov.au

QA/14/PH/4

Does the new technology of low frequency ultrasonic debridement pose an infection control risk for clinicians, patients and the clinic environment?

The above-mentioned project was considered an environmental audit and therefore did not require Human Research Ethics Committee review at this site.

[redacted]

Dr Susannah Ahern
Executive Director - Medical Services,
Quality and Clinical Governance

Executive Sponsor Research

Frankston Hospital

•

Rosebud Hospital

•

Mental Health Services

•

Aged Care, Rehabilitation & Palliative Care Services

•

Primary and Community Health

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Service Integrity Compassion Respect Excellence

APPENDIX 8 – ETHICS APPROVAL 4

Southern Health/Monash Health approval for economic analysis study.

MonashHealth

Research Support Services
Monash Health
Monash Medical Centre
246 Clayton Road
Clayton Victoria 3168
Australia

Level 2 I Block
Australia

Tel (03) 9594 4611
Fax (03) 9594 6306

11 March 2016

Ms Lucia Michailidis
Podiatry
Monash Medical Centre
246 Clayton Road
Clayton Vic 3168

Dear Researcher,

Research Project Application No. 16129Q: Understanding the diabetic foot wound occasions of service and separations within a podiatry service

Thank you for your email dated 08 March 2016. It is our understanding that this project is a quality & service improvement exercise involving collection, use and disclosure of data in a de-identified format to be conducted at Monash Health. Such data is to be accessed by a Monash Health employee only. As such, we advise that it does not raise any ethical concerns and does not fall within the category of a 'research' project within the *National Statement on Ethical Conduct In Human Research* (NHMRC, 2007). This project does not require submission to the Monash Health Human Research Ethics Committee. In addition, this Quality & Service Improvement activity can be described as an activity to monitor, improve and evaluate the quality of health services provided by Monash Health.

For our record-keeping purposes, we will deem this activity will be in progress for 12 months from this date, unless we hear from you to the contrary. It will then be classified as completed.

Please note this letter only pertains to the Quality & Service Improvement activity being conducted at Monash Health. If it is intended the Quality & Service Improvement activity will be conducted at another institution appropriate review and authorisation will be required prior to commencement at another institution.

Should you have any queries please contact me on 03 9594 4090.

Yours sincerely

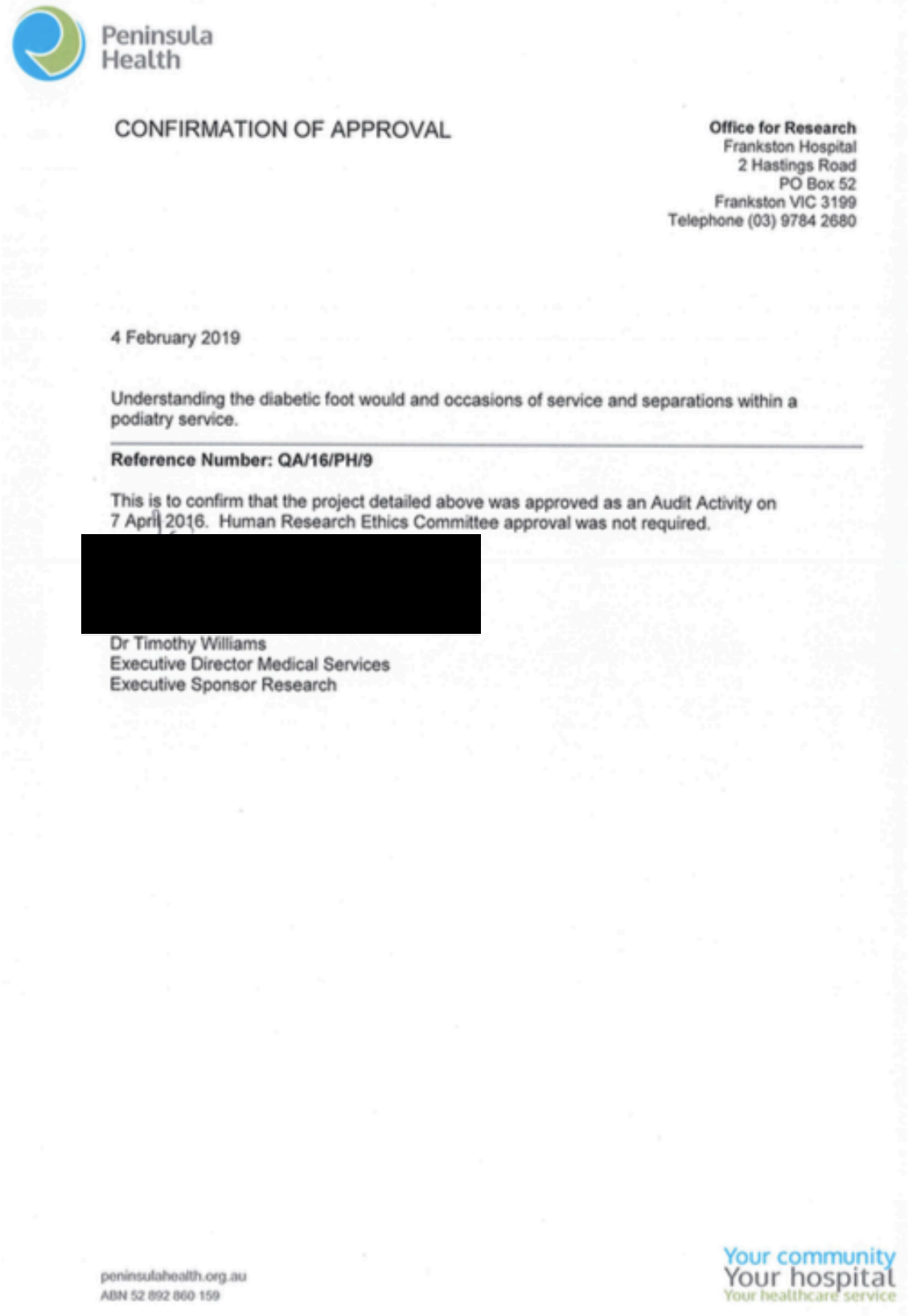
[redacted]

JULIE GEPHART
HREC Coordinator
Research Support Services

Cc: Ms Bev Desilva Quality Unit
Mr Ross Major, Medical Records

APPENDIX 9 – ETHICS APPROVAL 5

Peninsula Health approval for economic analysis study.



Peninsula Health

CONFIRMATION OF APPROVAL

Office for Research
Frankston Hospital
2 Hastings Road
PO Box 52
Frankston VIC 3199
Telephone (03) 9784 2680

4 February 2019

Understanding the diabetic foot would and occasions of service and separations within a podiatry service.

Reference Number: QA/16/PH/9

This is to confirm that the project detailed above was approved as an Audit Activity on 7 April 2016. Human Research Ethics Committee approval was not required.

[redacted]

Dr Timothy Williams
Executive Director Medical Services
Executive Sponsor Research