Multidimensional aspects of burn wound treatment

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MULTIDIMENSIONAL ASPECTS OF BURN WOUND TREATMENT

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For my parents

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Chapter 1

Introduction and outline of the thesis

INTRODUCTION

Burn injuries in the Netherlands

In the Netherlands, the majority of the patients with burn injuries are treated by general practitioners (about 90,000 patients per year) and at the Emergency Departments of hospitals without burn centres (about 9,000 patients per year). Annually, around 1,000 burn injury patients are admitted and treated in one of the three specialized Dutch burn centres.(1) Patients under 19 years of age account for 43% of the burn centre admissions in the Netherlands. (2) However, new trends have been observed in burn patients because of aging. Patients older than 60 years with burn injury accounted for 48% of the burn injuries that occurred at home. Elderly individuals are more prone to burn injury because of their limited mobility and decreased physical ability to react rapidly. Various attempts are made to optimize burn care in the Netherlands. A clear example is the extensive collaboration between the three Dutch burn centres in the fields of education, research and treatment which is formalized by the Association of Dutch Burn Centres (ADBC). Another example is the Dutch Burns Foundation that also facilitates scientific research and prevention campaigns with financial and logistic support.

Advances in burn care

In the last decades major advances have been made in the field of burn care, including newly developed modalities of wound treatment and improved resuscitation protocols, control of infection, management of inhalation injuries, shock prevention and multidisciplinary approach of burn patients in specialized burn centres.(3-5) These improvements have resulted in a better survival of the burn patients, shifting the focus of burn care from mortality to optimization of burn wound treatment and long-term outcomes including scar formation and quality of life. (6) Alongside the above improvements, there is an increased interest in the development of standardized, reliable and valid tools for diagnostic purposes (e.g. assessment of burn wound depth and burn wound surface area) and for assessment of scar quality (e.g. the Patient and Observer Scar Assessment Scale, POSAS) which are needed for further optimization of burn care.(7, 8) The ongoing advances in burn care also lead to increasing health care costs so that the next challenge is to find an optimal balance between high quality burn care and costs.

Estimation of burn wound size (%TBSA): an unsolved challenge

A correct estimation of the burn size, defined as the percentage of the total body surface area (%TBSA), is an indispensable part of burn wound management. In the acute care setting, %TBSA is used as a criterion for deciding whether a burn patient must be transferred to a specialized burn unit, which initial treatment to start and later on to evaluate the effectiveness of the treatment.(9-11) For clinical purposes, %TBSA determines the need for intravenous fluid resuscitation and is used in the management of nutritional support.(12, 13) Also, a

correct estimation of %TBSA is also needed to support an effective communication between healthcare providers and with patients since today's management of burn care involves a multidisciplinary approach and shared decision-making. For prognostic purposes, %TBSA was found to be a predictor of various scar characteristics including pruritus, quality of life and mortality.(14-17) Finally, in the era of evidence-based medicine a correct estimation of TBSA is essential for a reliable comparison between the results of different studies on burn care.

Estimating %TBSA is challenging in absence of a gold standard. In clinical practice, several methods are used to estimate %TBSA. The rule of nine, which was first devised by Pulaski and Tension in 1947 and first published by *Wallace et al.* in 1951, divides the body surface into anatomic areas that each represent nine percent of the body surface area (BSA).(18) The rule of nine can be applied quickly and easily. However, accuracy of this method is limited, especially in obese patients, because of the varying proportions of major body parts relative to the body surface area (BSA). Also, the rule of nine tends to overestimate %TBSA.(19) Another popular method used in clinical practice is the 'palm method', in which the palm of the burn patient's hand including the fingers is assumed to represent 1% TBSA. Research has shown that the area of the hand palm including the fingers varies between 0.5% to 0.8% of body surface area (BSA) in adults, while in children the hand palm with fingers approximates 1% of the body surface area (BSA).(20-23) Consequently, the burned body area in adults is overestimated when using the palm method. In the mid-1940s, Lund and Browder published another method to estimate %TBSA, which is a chart based on a two-dimensional representation of the body that takes into account the body proportions associated with different ages.(24) The inter-rater reliability of this method is better than that of the rule of nine.(18) However, the Lund & Browder chart does not take into account the three-dimensional aspect of the body, including the breasts in female patients. Nearly seventy years after the introduction of these methods for estimating %TBSA it can be concluded that the reliability of the described methods is highly dependent on the size and irregularity of the wound, the body mass index of the patient, and the experience of the physician.(18, 25, 26)

Implementation of novel methods for assessing %TBSA

An accurate method to estimate %TBSA still remains an unsolved challenge and novel methods are needed to overcome the limitations of the rule of nine, the palm method and Lund & Browder chart to estimate %TBSA. In today's digital era, considerable innovations have been realized that can be used for a better estimation of %TBSA. Various three-dimensional software-based ways of representing the burned patient are available.(27-31) Some of these software applications also enable the combination of two-dimensional digital pictures with a pre-defined three-dimensional model.(27) In short, digital pictures of the burned area can be applied onto a pre-defined digital three-dimensional model. Subsequently, an automated algorithm adapts the digital pictures on the three-dimensional model. The result is a three-

dimensional model that represents the patient with the burned area. Thereafter, the boundaries of the burn wound on the three-dimensional model can be drawn. Finally, the burn surface area and %TBSA can be calculated. Nevertheless, these digital methods for determining %TBSA also have limitations. Adapting a two-dimensional picture on a three-dimensional model and subsequently drawing the burned area introduces a potential source of bias, especially when pictures are taken of anatomically curved areas such as the axilla, breast and head. Moreover, a three-dimensional representation of the patient is not based on the actual patient but rather on a pre-defined three-dimensional model.

The clinimetric properties of such these novel methods must be established before implementation. Clinimetrics is a methodological discipline that focuses on testing the quality of measurement tools in the field of medicine. In clinimetric studies the quality of a measuring tool is expressed in terms of reliability and validity.(32) Reliability refers to the degree of which the measurement is free from measurement error. Validity is used to define the degree of which an instrument truly measures the construct which it is meant to measure.

Burn wound classification

Another cornerstone of the treatment of burn wounds is the assessment of the wound depth, since the classification system of burn wounds is defined by increasing burn depth. Superficial (first degree) burns involve only the epidermis and are limited to erythema caused by inflammation, with a burning feeling that resolves within a few days without scar formation. Partial thickness (second degree) burns are subdivided into superficial and deep partial thickness burns (types 2a and 2b, respectively).(33, 34) Superficial partial thickness burns extend into the superficial (papillary) dermis and heal well with little or no functional or aesthetic problems.(34) Deep partial thickness burns involve the epidermis and the entire dermis, and have a potential to heal spontaneously.(35) If no spontaneous wound healing occurs within two to three weeks, hypertrophic scar formation may occur.(36, 37) Therefore, deep partial thickness burns that are not expected to heal within three weeks, are treated surgically in the three Dutch burn centres. In full-thickness (third degree) burns the epidermis and dermis are entirely destroyed with the involvement of subcutaneous tissue.(33) Full-thickness burns require surgical treatment unless the burn wound is very small. Fourth degree burns extend through the entire skin into underlying fat, muscle and bone. Treatment is always surgical with or without excision and/or amputation.

Partial thickness burn wounds are painful, difficult to manage, and highly susceptible to infection due to wound contamination. Therefore, the ideal treatment of partial thickness burns should focus on promoting rapid wound healing, preventing infection, decreasing pain and suffering, and enabling patients to return to their daily activities as soon as possible.

Lapis infernalis

While there is an extensive range of treatment options available for partial thickness burns in both paediatric and adult patients, there is no consensus about the optimal treatment.(38-40) Silver-containing dressings, in particular silver sulfadiazine (SSD), are widely used treatments since the 1960's.(41-43) The mode of action of the SSD consists of the binding of silver ions to the DNA of bacteria in an aqueous wound environment, which reduces the ability of bacteria to replicate.(44-46) Silver has been used in the treatment of wounds for centuries. There are historical references that suggest that hardened silver nitrate was already used in the Middle Ages for the treatment of wounds.(47) In his book 'The Surgeons' mate', a standard book for ship's surgeons in the 17th century, John Woodall described the importance of "lapis infernalis" (in Dutch: "helse steen") as an indispensable component of each surgeon's box while on sea.(48) Many historians believe that "lapis infernalis", which may be translated as 'infernal stone' (in Dutch: 'helse steen'), referred to the kind of pain that is associated with silver nitrate when applied to the wound.(48, 49)

There are several explanations for the popularity of SSD over the past decades. First, in vitro studies have shown that SSD has an antimicrobial effect against a wide range of gram-positive and gram-negative microorganisms.(50-52) Reviews on this subject however found insufficient evidence to establish that silver-containing dressings or topical agents prevent wound infection.(41) Second, SSD is easy to apply on burn wounds. Finally, studies have shown that silver containing dressings are less costly compared with other forms of burn wound management.(53-55)

There are also some disadvantages of SSD in the treatment of partial thickness burns. SSD forms a pseudoeschar that can promote bacterial proliferation if not removed or debrided frequently. Frequent removal and debridement of pseudo eschar are also necessary for the optimal assessment of the wound state and to facilitate reepithelialisation. However, frequent dressing changes may also impair the reepithelialisation process and delay wound healing.(56) The pseudoeschar does not dislodge spontaneously and the removal is painful. Furthermore, SSD is often used with non-adhering dressings and absorbing gauzes that require daily dressing changes that are often painful (procedural pain) and can induce significant anxiety and distress in burn patients.(57) In addition, several studies have shown that silver is highly toxic to both keratinocytes and fibroblasts in in-vitro models.(58, 59) In line with these findings, recent publications even suggest that SSD itself may delay the wound healing and may have a toxic effect on skin cells.(60) Finally, prolonged use of SSD could lead to wound maceration which will increase the risk of infection and prolong wound healing.

Burn treatment in paediatric patients

Children and adolescents younger than nineteen years old account for 43% of all the admissions at the Dutch burn centres.(2) The relative risk for young children (0 - 4 years) with burn injury to be admitted at one of the three specialized burn centres is five times

higher compared with older children (517 years) and adults.(10) The most common causes of burn wounds in young children are hot fluids and steam. Most of these young children have TBSA < 10% at admission.(2) Severe burns (TBSA > 20%) are less frequently compared with adult patients (3.3% versus 11.9%).(2) The overall mortality in paediatric patients (< 0.7%) is low compared to that in adults (2.9% – 18.8% depending on the age group) and has decreased over time.(2, 10, 61)

Treatment options in paediatric burn patients include topical antiseptics such as SSD, which requires frequent dressing changes. To address this problem, membranous dressings are on the rise, which are designed to limit the number of dressing changes, prevent wound colonisation and promote the wound healing process. Membranous dressings are divided in several groups. Silver containing dressings, which continuously release silver into the wound, are widely used despite the lack of evidence for their effectiveness in preventing wound infection and promoting wound healing in burns.(38, 39, 43) Biological dressings like amnion membrane are widely available in low and middle income countries while allograft skin is available in the developed countries, e.g. in the Netherlands due to access to a well-organized skin bank. Semi-synthetic dressings like Biobrane® for example, are frequently studied in paediatric burn patients. Nevertheless, the clinical experience with these dressings is limited because of cultural or religious objections against its animal derived porcine dermal collagen that is harvested from pigs.(62) Biosynthetic dressings are relatively new in the treatment of partial thickness burn wounds. Biosynthetic dressings such as Suprathel® are non-animal derived materials that also serve as temporary dressings to function as the epidermis and dermis.(63) When indicated, surgical interventions (excision, grafting, and/or keratinocytes) are also part of the treatment of paediatric burns. Debriding enzymes seem promising in reducing the need for surgical intervention in partial thickness burns.(64) Regardless of such advances in treatment, SSD still is the standard treatment for paediatric partial thickness burns in many clinics.(43) Despite the extensive amount of other treatment options, treatment of partial thickness burns in paediatric patients remains an unsolved challenge and there is no consensus on this subject.(38-41, 65)

Burn treatment in adult patients

A Cochrane review published in 2013 on the treatment of superficial and deep partial thickness burns could not establish which wound dressing is the optimal treatment for partial thickness burns in adult patients.(39) Although SSD was consistently associated with poorer wound healing when compared with biosynthetic, silicon-coated and silver containing dressings, the conclusion of this Cochrane review was that there was a paucity of high-quality evidence because of the high risk of bias of the 30 included clinical trials. Four other systematic reviews on this topic found insufficient evidence whether silver-containing dressings or topical agents promote wound healing or prevent wound infection.(38, 40, 41, 66)

In the three Dutch burn centres, various treatment strategies are currently available for treating partial thickness wounds in adults, although there is no consensus about which of these treatments is the gold standard. Presently, SSD therefore still has a place in the treatment of partial thickness burns since there is no other treatment that meets the overall advantages of SSD. There have been attempts to reduce the cytotoxicity of silver particles in SSD in the wound bed by introducing alternate treatment with Furacine Soluble Dressing (Furacine 2mg/g ointment). In two of the three Dutch burn centres, SSD is used until the 6th post burn day. Thereafter, Furacine Soluble Dressing is used on the even post burn days and SSD on the odd post burn days. Although this treatment strategy has not been studied yet in a clinical trial, there is a trend to narrow the indications for which SSD is used in the treatment of burn wounds. For example, burn wounds of >30% TBSA are often treated with SSD-Cerium. Studies have shown that Cerium denaturizes the immunosuppressive lipid protein complex that is generated by burned skin. (67) A randomized controlled trial (RCT) of 60 patients showed that SSD-Cerium resulted in a better survival in burn patients with large life-threating burn wounds when compared with SSD alone.(68) In line with this trend, new treatment modalities are being examined. Recently, Flaminal® (Flen Pharma, Kontich, Belgium) is used to overcome the limitations of SSD. Pre-clinical studies have shown that Flaminal® was not toxic to keratinocytes and fibroblasts in vitro.(69, 70) As a result, wound healing may not be impaired. In vitro studies have also shown that Flaminal® had an antimicrobial effect against a wide range of gram-negative and gram-positive bacteria.(69, 70) Furthermore, two retrospective studies found a favourable effect on wound healing when Flaminal® was compared to Flamazine® in the treatment of partial thickness burns.(71, 72) So far, these effects had not been studied in a randomized clinical study.

Shifting focus

Due to the improvement of survival of patients with burn injuries in the last decades, the focus of burn care has shifted to other important burn outcomes such as scar formation and quality of life. Scar formation is one of the most adverse effects after burn injury with a negative impact on physical and psychological well-being of burn patients, e.g. due to pruritus, pain, contractures, movement limitations, negative body image, depression or post-traumatic stress syndrome.(73-77) Therefore, assessment of scar formation is indispensable to evaluate the effectiveness of a burn wound treatment. Ideally, assessment of scar formation includes both a subjective and objective evaluation of the scar. Two subjective scar assessment tools that have widely been used are the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS).(7, 78) With the POSAS, visual (color) and tactile properties of the scar (stiffness, thickness, irregularity) as well as pain and pruritus can be quantified. The POSAS is preferred over the VSS because with the POSAS the scar formation is not only assessed by the clinician but also by the patient. Moreover, the POSAS is superior in terms of clinimetric properties compared with the VSS.

(7) Various objective instruments are also available that measure different properties of the scar, such as elasticity (measured with a Cutometer), color and pigmentation (measured with a Dermaspectrometer). Insights into the course of different scar properties (e.g. stiffness, pruritus) after burn injury and into factors that influence these scar properties can ultimately be used in directing treatment strategies for burn scars.

The concept of quality of life is multidimensional and includes physical, social and psychological components.(79) In studies, problems with appearance were reported by up to 42% of the burn patients after discharge, while psychological distress was reported by one-third of the burn patients up to two years post-burn.(75, 80) Visible scars, physical dysfunctions because of scar formation, pain, pruritus and poor scar status have been described to have a negative effect on quality-of-life in burn patients.(81-83) Scar formation and quality of life are important aspects that are addressed in modern management of burn patients and form the next challenge in the optimization of burn care.

Costs

The health care expenditure in the Netherlands was over € 100 billion in 2018, which is expected to double by 2040.(84, 85) Burn care is undeniably expensive, because burn patients often need treatment in a specialized burn centre. It requires a multidisciplinary approach by different medical specialties during a significant length of hospital admission, which involves high medical expenses for wound treatment, intensive care and rehabilitation.(86-88) It is clear that in the era of increasing health care expenditures and limited budgets, the high quality of burn care is not affordable at any costs. Therefore, in the search for optimal treatment of partial thickness burns, the effectiveness of alternative treatment strategies should also be studied relative to their costs (cost-effectiveness analysis). The question arises which 'core set' of outcomes should be used for the economic evaluation of a treatment strategy. A review of 156 studies on costs of burn care described that hospital stay and treatment costs (healthcare costs) were used as outcomes in the majority of these studies.(88) In this review, the mean total healthcare was €64,112 per burn patient but varied widely from €512 to €521,928. It should be noted that different types of treatments and studies from low- and high-income countries were included. Furthermore, there was methodological variation between the studies and information on how the costs were calculated was often lacking. Until recently, no clear unit prices were available for important specific burn care components such as burn centre stay, surgery in the acute phase or reconstructive surgery. However, in the past years the three Dutch burn centres initiated various studies to determine price units of these care components that can be used in economic evaluation of burn care.(89, 90) Beside healthcare costs, there is also increasing evidence that non-health care costs, in particular costs due to productivity loss, are a major part of burn care costs.(87, 91). A

literature review on functional outcome after burns found that 21 - 50% of the patients had problems with return to work after a burn injury.(75) It can be concluded that in the era of increasing health care expenditures and limited budgets, comprehensive insights into both the health-care and non-health care costs (societal costs) of burn care are mandatory to assist policymakers to find a favourable balance between costs and quality of care.

AIM AND OUTLINE OF THIS THESIS

The focus of this thesis is on the optimization of burn wound treatment. Therefore, the objective of thesis is to study different aspects of wound treatment beside wound healing as important outcomes in burn wound treatment. In this light, part of this thesis evaluates modern techniques for the assessment of %TBSA, which is essential in the management of burn wounds. Another aim is to study the effectiveness of a treatment not only by focusing on the clinical outcomes such as wound infection, but also by describing the consequences of burn injury for the burn patient in terms of scar formation, quality of life as well as the economic burden of burn wound treatment. Another focus is on the period after burn wound treatment when scar formation is the next challenge for both the patient and clinician. The thesis aims to gain more insights into the course of different properties of scar formation and factors that are influencing these properties from the patient's perspective.

Part I of this thesis focuses on the clinimetric properties of three-dimensional imaging using the Artec MHT™ Scanner and software for measuring %TBSA. In general, methods to estimate %TBSA are challenging since %TBSA cannot be measured directly but is in fact the ratio of the wound surface area relative to the total body surface area (TBSA) expressed as a percentage. Therefore, **Chapter 2** investigates whether this novel method is reliable and valid to measure wound surface area before implementing this method for measuring %TBSA. In **Chapter 3**, the reliability and feasibility of the same method for measuring %TBSA is studied.

Part II evaluates treatment of partial thickness burns in paediatric patients. **Chapter 4** describes a systematic review and meta-analysis that summarizes the available evidence on clinical effectiveness for silver sulfadiazine (SSD) compared to nonsilver treatment for partial thickness burns in paediatric patients. **Chapter 5** studies the usability and clinical effectiveness of a novel biosynthetic dressing (Suprathel®) in the treatment of partial thickness burns in paediatric patients.

Part III of this thesis describes a randomized clinical trial (FLAM study) that compares two commonly used treatments for partial thickness burns in adult patients, based on modern management of burn wounds: Flaminal® Forte and SSD (Flamazine®). In this study the clinical

effectiveness of the interventions, their effect on scar formation and quality of life are compared and the cost-effectiveness is assessed. **Chapter 6** describes the study protocol of the trial. In **Chapter 7**, the results for the clinical effectiveness and scar quality of the FLAM study are presented, while **Chapter 8** addresses the results of quality of life and cost-effectiveness of the FLAM study.

Part IV of this thesis focuses on patterns of and predictors for various burn scar properties. **Chapter 9** describes patterns and predictors of burn scar properties in the first twelve months post-burn from the patient's perspective.

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Part I

Clinimetric studies on burn wound surface area estimation

Chapter 2

Three-dimensional imaging: a novel, valid, and reliable technique for measuring wound surface area

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ABSTRACT

Background: The aim of this study was to investigate the validity and reliability of a novel three-dimensional imaging technique using Artec MHT™ 3D Scanner for measuring wound surface area.

Methods: The validity was tested by measuring the surface area of 60 stickers (gold standard) on 20 volunteers. Stickers with standardized areas of 2590 mm^2, 7875 mm^2 and 15540 mm^2 were resectivley applied on the thorax, forearm and thigh. For the reliability test 58 burn wounds on 48 patients were assessed twice by two different observers with the Artec MHT™ 3D Scanner. Scanning, post-processing and surface area measurements were performed by two clinicians.

Results: The results for the validity analysis showed an intraclass correlation coefficient of 0.99 and coefficient of variation of the thorax, forearm and thigh were 1.1%, 0.9% and 0.6%, respectively. The reliability analysis showed an intraclass correlation coefficient of 0.99, a coefficient of variation of 6.3% and limits of agreement between measurements of two observers was calculated at 0 ± 0.17 x *mean surface area.*

Conclusion: Three-dimensional imaging using the Artec MHT™ 3D Scanner is a valid and reliable method for measuring wound surface area.

INTRODUCTION

A valid and reliable wound surface measurement is an essential component of wound care. From a clinical perspective, monitoring changes in wound surface area is necessary to observe wound healing and assess effectiveness of treatment.(1) An accurate measurement is also obligatory to permit a comparative assessment of wound surface area for research purposes and eventually establishing evidence-based decision making in wound management. In addition, this information can be used to support an effective communication with patients and between practitioners, particularly because nowadays wound care is managed more and more in a multidisciplinary setting.(1,2)

Essential insight on the clinimetric properties is needed before implementing a novel method for measuring wound surface area. Clinimetric properties refers to the validity (the ability of the technique to measure the actual wound surface area) and the reliability (the consistency of wound surface measurement between observers using this technique).(3)

A variety of techniques are used to measure wound surface area. The simplest method is multiplying the greatest length with the perpendicular greatest width using a rectangle or an ellipse.(4-6) An alternative method is manual planimetry by tracing the outlines of the wound on a transparent grid paper.(2,7) A modification of this method is digital planimetry by retracing the outlines of a wound from a digital photograph after manually tracing the wound boundary on a transparent grid paper. (8-10) A non-invasive method is digital photography in combination with an imaging system, whereby a ruler is photographed near the wound which allows the user to calibrate the imaging system.(11) Stereophotogrammetry is also used for wound surface measurement by assessing three-dimensional geometry of the wound using two or more cameras.(11)

Although considerable research has been devoted to innovations in techniques for measuring wound surface area, current methods have limitations. The 'length by width' technique has been shown to overestimate wound surface area by 10% to 70% (5,12,13) and is unreliable for large or irregularly shaped wounds due to the assumption that wounds are either rectangle or ellipse.(14) Manual planimetry is easy to perform and has a good reliability and validity. However this method is not suitable for large wounds and often causes discomfort for the patient.(15,16) Digital photography is non-invasive but limited as a two-dimensional photo representing a three-dimensional structure results in discrepancy when tracing the margins of a wound. Stereophotogrammetry is a non-invasive, valid and reliable method but it is less suitable for extremely curved and/ or large areas.(17,18)

To overcome the limitations of the previously described studies, we introduce a novel class of technique for measuring wound surface area that uses a portable and light-weighted, three-dimensional scanner which creates a coloured, three-dimensional reconstruction of the wound using flash bulb. This technique is non-invasive for the patient, suitable for curved body parts and larger wounds. The wound surface area can be obtained from the three-dimensional image by using a special software program.

Therefore, the main objective of this study was to evaluate the validity and reliability of three-dimensional scanning using Artec MHT™ 3D Scanner for measuring wound surface area.

PATIENTS AND METHODS

Patients and volunteers

Burn patients and volunteers were included from August 2012 until January 2013. Volunteers were recruited from the Red Cross Hospital staff, Beverwijk, the Netherlands. They were asked to allow application of stickers, that resembled burn wounds, on their body for the reliability part of the study. Burn patients were included from the outpatient clinic and ward of the Burn Center of the Red Cross Hospital, Beverwijk, the Netherlands. Burn patients of all ages were eligible for the inclusion as long as no surgical intervention was performed yet. The local ethics committee approved this study.

Artec 3D

The Artec MHT™ 3D Scanner (The Artec Group, San Diego, USA) was used to make a three-dimensional reconstruction of a wound. This device is a non-invasive, handheld measurement tool that projects structured light flashes on a surface and subsequently detects the deformations in the grid of the reflecting light. Using this method, the scanner can detect differences in texture and height that results in a realistic three-dimensional reconstruction of human body curvature. The device also adds a coloured image of the surface scanned by making regular photos every 15 frames. This results in a full-coloured three-dimensional reconstruction of the wound.(19)

With a distance of 40 cm to 60 cm, scanning is performed perpendicular to the skin surface and the device is manually rotated around the patient until the wound is fully visualized. During this process, the patient should remain still to prevent artefacts in the three-dimensional reconstruction. In addition, the patient or the volunteer can take any position during the scanning procedure as long as the device is perpendicular to the wound. Next, the laptop that is connected to the scanner uses a specially designed software program (Artec 3D Studio 9.0) which immediately generates a three-dimensional image (Figure 1). The scanning process usually takes approximately one minute.

In this same software program, it is possible to calculate the area scanned in mm^2 (measurement of the wound surface area). However, the clinician has to mark the boundaries of the wound on the software program to calculate the wound area in mm^2. This process, depending on the wound size, takes between 15 - 60 minutes. An ideal scan condition is an examination room with slightly subdued light. In our study, this setting was constantly maintained.

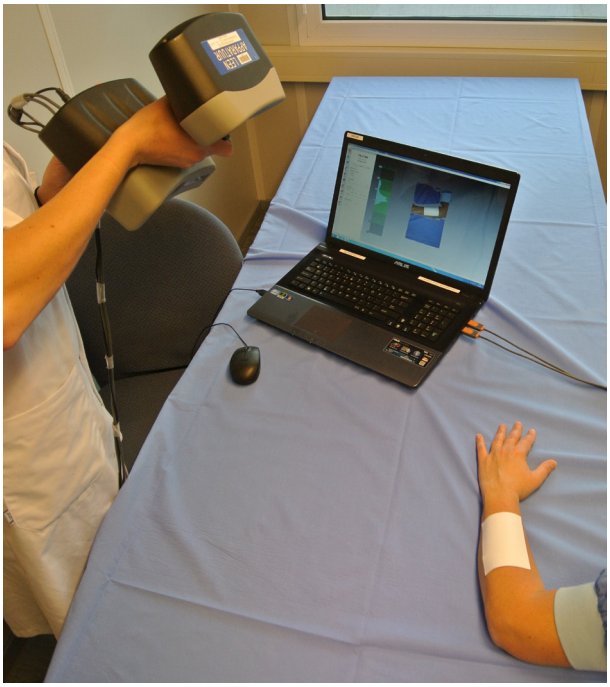

Figure 1. An example of three dimensional scanning of the left arm.

Standardized stickers

In the absence of a gold standard for measuring wound surface area, standardized stickers of known sizes were used to measure the validity of this device. Three different stickers were applied on three different body parts with different curvatures, respectively from a low to a high curvature: the thorax (size: 2590 mm^2), the ventral side of the upper right leg (15540 mm^2) and the dorsal side of the right forearm (size: 7875 mm^2).

Procedure

To evaluate the validity of Artec MHT™ 3D Scanner, three different stickers were applied on the volunteers. The stickers were scanned by one observer and post-processed as mentioned above. The same observer also performed all the measurements. Finally, sticker surface

measurements were compared with the actual sticker sizes (gold standard). After the validity part of this study, scan procedure protocol was evaluated to optimise the scanning of the wounds for the reliability measurements. To test the reliability of the Artec MHT™ 3D Scanner, wounds were scanned by two observers (observer A and B). Both observers were researchers at the Burn Center of the Red Cross Hospital and received basic course in performing scan with Artec MHT™ 3D Scanner and using Artec 3D Studio 9.0. These scans were imported into Artec 3D Studio 9.0. Thereafter, observer A performed surface area measurement of the scan of observer B, and vice versa. This resulted in two measurements of each wound. No intraobserver reliability was performed because in general intraobserver reliability is considered to be higher than interobserver reliability.(3) (Figure 2)

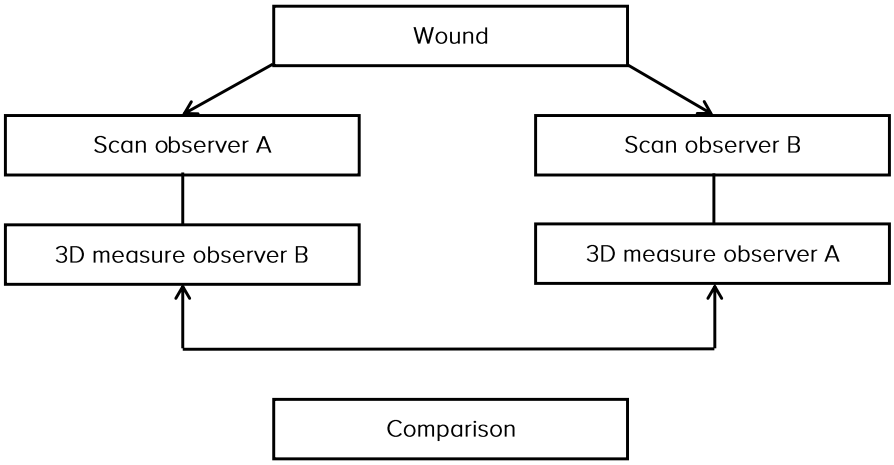

Figure 2. Schematic representation of the reliability analysis.

Statistical procedure

The data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The interobserver reliability of the Artec MHT™ 3D Scanner was assessed by comparing the patients' burn wound measurements of observer A and B as shown in figure 2. The same statistical approach was used as described in a study by Stekelenburg et al.(18) The most commonly used statistical parameter for interobserver reliability analysis is the Intraclass Correlation Coefficient (ICC) which was defined as the correlation between the surface area ratings of the same burn wound by two observers based on the scans obtained by the same observers. ICC was expressed as a ratio of the wound variance (σ^2_{wound}) and the total variance (σ^2_{tot}) which is a sum of patient's variance (σ^2_{pat}), observer variance (σ^2_{obs}) and random error variance (σ^2_{error}), resulting in the following formula: $$ICCagreement = \frac{\sigma^2 wounds}{\sigma^2 wounds + \sigma^2 observers + \sigma^2 error}$$.(3)

The values for the variance components were obtained using a linear random effects model in SPSS. Random factors were the observer number (i.e. A or B) and burn wound number. The dependent variable was the burn size measured. In addition to the ICC, the Coefficient of Variation (CV) was calculated. The CV is a normalized ratio of the standard deviation to the mean of the measurements in percentages. The CV is appropriate to use when the measurement error grows with the mean value of the measurement. A low CV indicates a more reliable measurement. Difference between two measurements (y-axis) were plotted against the mean of two measurements (x-axis) in a Bland Altman Plot to provide direct information on the absolute agreement between two observers.(20) Data were considered skewed if the differences between measurements increased with the increasing mean of pairwise measurements. If the measurements have a skewed distribution, data should be log-transformed to approximate a normal distribution in order to calculate the limits of agreement. However, log-transformed data is difficult to interpret in clinical practice. Therefore, limits of agreement were transformed back to original scale by taking anti-logs and plotted together in the clinical and untransformed data conform Euser et al.(21) In this modified Bland Altman plot the limits of agreement represents two divergent lines instead of two parallel lines. To analyze the validity, the ICC and CV per body part were calculated. Differences between the measurement of observer A and the gold standard (actual size of the stickers) on the y-axis were plotted against the gold standard on the x-axis in a Bland and Altman Plot.

RESULTS

Volunteers and patients characteristics

A total of 20 healthy adult volunteers (8 males and 12 females) were enrolled for the validity analysis. The median age was 33 years (range 24 to 61). Eighteen volunteers of Caucasian, one of Asian/Mediterranean, and one of Negroid race, were included. For the reliability analysis, a total of 58 burn wounds from 48 patients were enrolled in this study. Patient characteristics are summarized in Table 1.

Validity

Mean differences and its standard deviation (SD) between measurements of observer A and the gold standard for the thorax, forearm and thigh were 10 mm^2 (41), -44 mm^2 (69) and 20 mm^2 (79), respectively. The ICC was 0.99. The Coefficient of Variation (CV) for the measurement of the stickers on the thorax, forearm and tigh were 1.1%, 0.9% and 1.0%, respectively. However, after evaluating the scan procedure we found that two scans of the forearm were not completely scanned. Thereafter, we amended our scan procedure by confirming that all the scans were completely visible on the monitor before saving them and using them for the reliability measurements. After removing these incomplete scans from our analysis, the CV

for the forearm was 0.6% (Table 2). These data were also plotted in a Bland and Altman plot, with the gold standard on the x-axis and the difference between measurements of observer A and the gold standard on the y-axis (Figure 3).

Table 1. Patient and wound characteristics.

Number of burn wounds	58
Number of patients	48
Gender	
Male	32
Female	16
Age (years)	
Median (range)	29 (0.8 - 71)
Burn surface area in mm²	
Median (range)	5965 (442 - 57742)
Burn wounds depth, n	
2nd degree	
- Superficial	10/ 58
- Deep	14/ 58
- Mixed	18/ 58
3rd degree	10/ 58
Mixed 2nd/3rd degree	6/ 58
Burn wound location, n	
Head and neck	6/ 58
Trunk (anterior)	8/ 58
Trunk (posterior)	6/ 58
Upper extremities	20/ 58
Lower extremities	18/ 58

Table 2. Results for validity.

	Thorax	**Forearm**	**Thigh**
Gold standard, mm^2	2590	7875	15540
Mean value observer A mm^2, (SD)	2600	7831	15560
Mean difference mm^2, (SD)[1]	10 (41)	-44 (69)	20 (79)
ICC	0.99	0.99	0.99
CV (%)	1.1	0.9	0.6

ICC: Intraclass Correlation Coefficient, CV: Coefficient of Variation. [1] Mean difference between measurements of observer A and the gold standard.

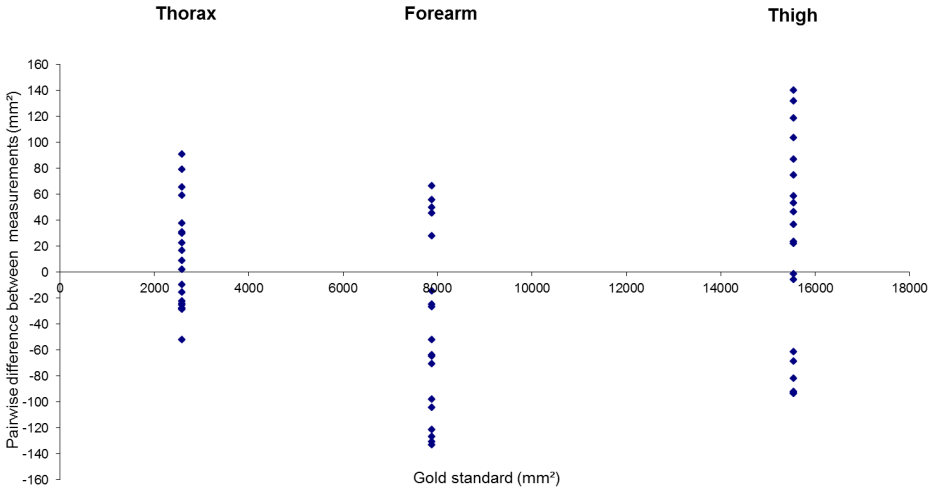

Figure 3. A modified Bland and Altman plot presenting agreement between an Artec measurement by one observer and the actual size of the stickers (without incomplete scans).

Reliability

Our results showed that the ICC was 0.99, which in this study is the correlation between the wound surface area measurement of the same burn wound by two observers based on the scans obtained by the same observers. All mean differences between measurements of both observers was < 251 mm². The CV was approximately 6.1%. The estimation of all variance components can be found in Table 3.

Table 3. Results for reliability.

ICC	0.99
CV	6.3%
Variance (Random effect)	
- Wound variance (σ^2_{wound})	1.332
- Observer variance (σ^2_{obs})	0.000
- Random error variance (σ^2_{error})	0.004

ICC: Intraclass Correlation Coefficient, CV: Coefficient of Variation.

A Bland and Altman plot is presented in figure 4 that showed a skewed distribution of the data indicating that the measurement error increased with the size of the wound. A log transformation was performed to obtain an approximately normal distribution in order to calculate the limits of agreement as a function of the mean of the burn surface area. The limits of agreement were 0 ± 0.17 x *mean surface area* and increased with the wound size (Figure 4). In figure 4 the backtransformed limits of agreement were plotted in the clinical and untransformed data.

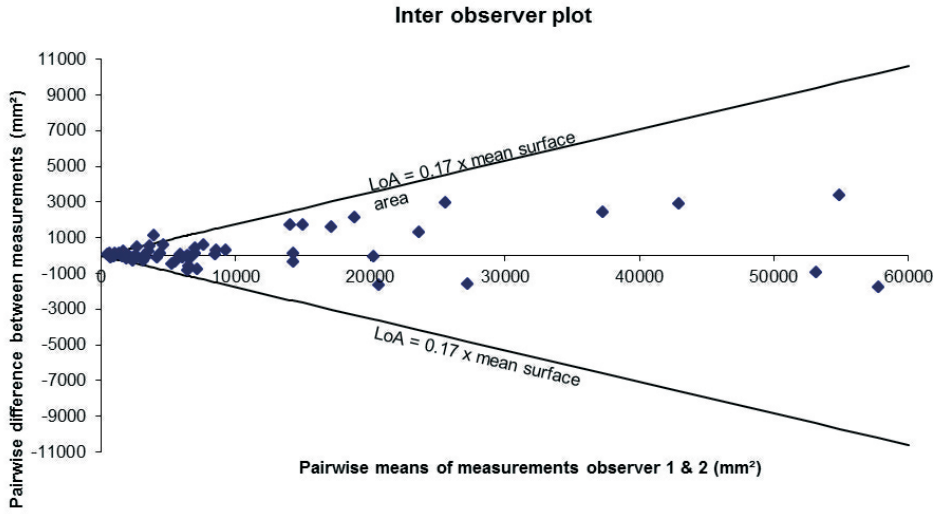

Figure 4. A Bland and Altman plot presenting the inter-observer agreement between the two observers.

DISCUSSION

This study has shown that this novel three-dimensional method using Artec MHT™ 3D scanner and software is a valid and a reliable method for measuring wound surface area.

An excellent ICC of 0.99 found for the validity indicates the 3D method using the Artec MHT™ 3D scanner to be a valid method for measuring wound surface area. In general, an ICC of >0,90 is considered to be acceptable in clinical practice, whereas an ICC >0,7 is recommended for use in research settings(3). Furthermore, the standard deviation of the mean difference increased with the size of the sticker. This finding that is supported by our reliability analysis. We also found that the largest mean difference to be in the forearm, which is the most curved body part in this study. Difficulties in measurement of wound surface area of curved body parts is a well-known problem.(22,23) However, the mean differences in the present study were all negligibly small. The coefficient of variation was found to be very low for all body parts and also decreased with wound size. This finding indicates an acceptable error for the validity analysis. In absence of a 'gold standard' to measure wound surface area, stickers with a standard and known-size were used for the validity analysis. However, a limitation of this setting is that these stickers do not represent wounds in patients.

For the reliability part of this study, a high ICC of 0.99 indicated an excellent reliability of this novel method in both research and clinical practice. Several factors explain the high ICC and the CV in our study. The high quality colour three-dimensional reconstruction of the wound

allowed observers to make an accurate digital tracing of the wounds. Also, the Artec 3D Studio software contains important features for a precise tracing, for example enlarging the wound and interaction with the 3D wound model. The agreement between observers for measuring the wound surface area of the same wound were displayed by using Bland and Altman plots and calculating their limits of agreement. As illustrated in figure 3, this analysis has shown that the limits of agreement of 0 ± 0.17 x *mean surface area* were narrow. Narrow limits of agreement indicate an acceptable variation in measurements values between observers.

To our knowledge, there are no other studies using a 3D scanner, by measuring distortions in a beam of structured light and creating a full coloured 3D reconstruction of the wound, for the purpose of wound surface area measurements. Therefore, a comparison with other 3D methods using different methods for measuring wound surface area is not entirely objective. However, the single-measure interobserver ICC of 0.99 in our study was higher than a study using stereophotogrammetry for measuring wound surface area (ICC = 0.747).(24) In contrast, the high ICC and CV in our study are comparable with a similar study on measuring scar surface area with 3D-stereophotogrammetry.(18) Recently, a wound imaging and measurement system called SilhouetteMobile (ARANZ Medical, Christchurch, New Zealand) was introduced. This technique consists of a mobile computing device and camera that captures wound surface area and uses laser technology to estimate wound depth. An interobserver ICC of single-measurement of 0.901 was reported.(25) Another combination of laser projector and a digital camera system by Kecelj-Leskovec et al. showed a standard error of measurement of 9.7% for wound surface area measurement.(26) However, the authors concluded that this device was less suitable for very flat wounds and wounds with irregularity of the surrounding skin.(26)

The Artec MHT™ 3D Scanner is a portable, very easy to handle and light weighted device that can be used at any clinical setting including the operating theatre. Performing a scan requires no wound contact and takes only seconds. The accompanying Artec 3D software guides the user through a phased plan for post-processing of the scans. The obtained scans are highly detailed and full-colour representation of the wound. This 3D representation of the wound provides important visual information regarding the depth, volume and signs of infection of the wound. Also, these scans have a valuable potential to be used for telemedicine. Despite the advantage of this novel 3D system, there are a few limitations that need to be mentioned. The measurement procedure of performing a scan, post-processing of the data and measuring wound surface area takes in the majority of the wounds approximately 15 minutes. However, larger wounds (i.e. > 50 cm^2) could take up to one hour. It should be noted that Artec 3D software is still under development and a newer version provides significant improvements in terms of reducing post-processing time which is the most time consuming process of the measurements. In order to perform a scan, the patient should remain still during scanning. This could be an issue in paediatric patients. However, we were able to scan 10 paediatric patients < 5 years in our study without any limitations.

CONCLUSION

This study shows that three-dimensional imaging using Artec MHT™ Scanner and software is a non-invasive, valid and reliable technique for the measurement of wound surface area. However, further research is warranted to explore the possibilities of this promising technique in clinical practice and research setting and its possible limitations.

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Chapter 3

Three-dimensional imaging is a novel and reliable technique to measure total body surface area

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ABSTRACT

Objective: The aim of this study was to explore the diverse clinimetric aspects of three-dimensional imaging measurements of TBSA in clinical practice compared with the methods currently used in clinical practice (i.e., the rule of nines and palm method) to measure TBSA in clinical practice.

Method: To assess reliability, two independent researchers measured the TBSAs of 48 burn patients using Artec MHT™ Scanner and software. Subsequently, a resident and burn specialist estimated the TBSA of the same wounds using the rule of nines and palm method.

Results: Three-dimensional imaging showed excellent inter-observer reliability, with an intra-class correlation coefficient (ICC) of 0.99, standard error of measurement (SEM) of 0.054, and limits of agreement (LoA) of ± 0.15 x the mean TBSA (between the measurements of two researchers). The inter-observer reliability of the methods used in current clinical practice was less reliable, with an ICC of 0.91, SEM of 0.300 and LoA of ± 0.78 x the mean TBSA. The inter-observer reliability was least reliable between three-dimensional imaging and the residents compared with the Burn specialists for the estimated TBSA, with an ICC of 0.68, SEM of 0.69 and LoA of ± 1.49 x the mean TBSA.

Conclusion: The inter-observer reliability of three-dimensional imaging was superior compared with the rule of nines and palm method.

INTRODUCTION

A correct estimation of burn wound size, which is defined as total body surface area (TBSA), is essential for adequate burn wound management in acute care setting. TBSA determines the need for intravenous fluid resuscitation and whether the patient must be transferred to a specialized burn unit.(1) Moreover, an accurate TBSA estimation is important to manage nutritional support and evaluate treatment efficacy, as well as for research purposes.

In current clinical practice, the rule of nines(2), palm method(3) and Lund and Browder chart(4) are used to estimate TBSA. However, these methods have some limitations. The rule of nines tends to overestimate TBSA.(5) The definition of the palm method is not always clear to the clinicians, and the area of the palm, including the fingers, does not resemble 1% of the body surface area (BSA) in adults, which could lead to overestimation of the burn area. (3, 6-10) The Lund and Browder chart is based on a two-dimensional model, and it does not consider the three-dimensional aspect of the body. However, the inter-rater reliability of this method is better compared to the rule of nines.(5) Moreover, digital Lund & Browder charts showed high reproducibility and fewer estimation errors compared to the paper Lund & Browder chart. (11-13) In general, the reliability of each described method is highly dependent on the size and irregularity of the wound, the body mass index (BMI) of the patient, and the experience of the physician.(6, 14-16)

Recent research indicates that computerized techniques are a promising and likely more accurate method of estimating TBSA. Three-dimensional imaging of the wound surface area is a novel technique that has the potential to overcome the limitations of the described methods to estimate TBSA. With this technique, a full-coloured three-dimensional reconstruction of the burn wound can be performed. TBSA is then obtained from the measured wound surface area and body surface area (BSA).

To assess the applicability of three dimensional imaging in clinical practice, the clinimetric properties, such as reliability, of this method must be investigated first.

In a previous study, we found that three-dimensional imaging using the Artec MHT™ Scanner and software to be a non-invasive and reliable technique for measuring burn wound surface area. The objective of this explorative study was to investigate the inter-observer reliability of three-dimensional imaging for measuring the TBSA in clinical practice compared with methods currently used (rule of nines and palm method).

PATIENTS AND METHODS

Study population

Data were obtained from our validation study.(17) In short, burn patients were included consecutively from the Burn Center of the Red Cross Hospital, Beverwijk, from August 2012 to January 2013. The Red Cross Hospital is one of the three tertiary burn centres in the Netherlands. All burn patients were eligible for study inclusion, except those who had undergone surgical intervention. Informed consent was obtained from all patients before they were included in the study. The local ethics committee approved this study.

Three-dimensional imaging

To measure the burn wound surface area, the Artec MHT™ 3D Scanner, a non-invasive, handheld device (the Artec Group, San Diego, CA, USA), was used. This device projected structured light flashes on a burn wound and then reconstructed the three-dimensional view of the scanned area. This device also provided a coloured image of the scanned area every 15 frames. As a result, a full-coloured three-dimensional reconstruction of the burn wound was obtained. Scans were performed perpendicular to the burn wound at a distance of 40 - 60 cm. Then the software program (Artec 3D Studio 9.0) generated a three-dimensional image of the wound. Thereafter, the clinician had to mark the boundaries of the burn wound on a full-coloured, three-dimensional reconstruction of the wound. Finally, the software program calculated the surface area of the burn wound in mm^2, as marked by the boundaries determined by the clinician. We comprehensively described the technique and procedure of this novel technique in our validation study.(17)

TBSA

To determine the TBSA, the burn surface area measured with three-dimensional-imaging was divided by the body surface area (BSA). The BSA was calculated using the DuBois and DuBois formula (BSA (m^2) = 0.20247 x Height(m)$^{0.725}$ x Weight(kg)$^{0.425}$)(18) for adults and the Haycock formula (BSA (m^2) = 0.024265 x height (cm)$^{0.3964}$ x weight (kg)$^{0.5378}$)(19) for children. To determine the TBSA in clinical practice, a resident and a burn specialist used the rule of nines and palm method to estimate the TBSA. The TBSA estimate performed by a resident and a burn specialist was thought to be most relevant, as for most burn patients, the TBSA is first determined by a resident from a general hospital. When referred to a specialized burn centre, the TBSA is estimated again by a burn specialist.

Study design

Inter-observer reliability of three-dimensional imaging

To assess the inter-observer reliability of determining the TBSA using Artec MHT™ 3D scanner, the TBSAs of all burn wounds were independently calculated by two researchers (A and B). Researcher A and B were researchers at the Burn Centre of Red Cross Hospital and had the

clinical experience of a resident. Both used the Artec MHT™ 3D Scanner to scan the burn surface area. Next, researcher A measured the burn surface area of the scan of researcher B with the Artec 3D software program, and vice versa. This design most accurately reflects clinical practice with divided task and shifts. Finally, TBSAs were calculated by dividing the measured burn surface area by the BSA times a hundred.

Inter-observer reliability of current clinical methods

To put the results of the reliability of three-dimensional imaging in perspective with the reliability of methods used in current clinical practice, the inter-observer reliability of the rule of nines and palm method in estimating the TBSA was determined. Therefore, using the rule of nines and palm method, a resident and a burn specialist also estimated the TBSA of the same series of burn wounds. Four residents and four burn specialists participated in the study.

Inter-observer reliability of three-dimensional imaging and current methods

To study the inter-observer reliability of three-dimensional imaging and current methods, the TBSA of researcher A (measured with an Artec MHT™ 3D scanner), was compared to the TBSA estimated by a resident and a burn specialist using rule of nines and palm method.

Statistical analysis and clinimetrics

The data were analysed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Different statistical outcomes were used to study the inter-observer reliability in this study.

Intraclass Correlation Coefficient (ICC)

ICCs were used to estimate the correlation between the TBSAs of the same burn wound estimated by different observers. Wound variance (σ^2 wounds), observer variance (σ^2 observer) and error variance (σ^2 error) were calculated using a linear random-effect model in SPSS to calculate the ICC. The ICC was defined as follows: σ^2wounds / (σ^2 wounds + σ^2 observer + σ^2 error). This ICC measures agreement, as the sample of observers in the study is representative of a large (future) population of observers. (20, 21)

Standard Error of Measurement (SEM)

The standard error of measurement (SEM) was calculated using the following formula: SEM = $\sqrt{}$(σ^2 observer + σ^2 error).

Bland and Altman plot with limits of agreement (LoA)

A modified Bland and Altman plot with the limits of agreement (LoA) was obtained to measure the absolute agreement between the observers and to provide an informative graphical representation of reliability.(20) In this plot, the mean of two estimated TBSA's (x-axis) was plotted against the difference between two estimated or calculated TBSA (y-axis). The LoA

indicated the 95% confidence interval (CI) of the difference between the TBSA estimations or calculations of two observers. Log-transformation of the data was performed when the data were considered to be skewed. Skewed data were considered when the difference between two estimated TBSA increased with the increasing TBSA. However, data were transformed back to the original scale for a better interpretability of the modified Bland and Altman plot in clinical practice, as described by Euser et al.(22) Finally, the LoA was obtained through back transformation of the data (X) and derived from the formula: LoA = $(^2\sqrt{X}+X\pm1.96\sqrt{2}\text{ x SEM})^2$.

RESULTS

Patient characteristics

Forty-eight burn patients were included in this study, 34 adults, and fourteen children < 18 years. Patient characteristics are shown in Table 1.

Table 1. Patients characteristics.

Number of patients	48
Gender, Male (n)	32
Adults	34
Age (years)	
Median (range)	29 (0.8 - 71)
TBSA[1]	
Median (range)	7.0 (0.1 - 7.0)
Burn wounds depth, n	
Partial thickness	34
Full-thickness burns	8
Mixed	6
Burn wound location, n	
Head and neck	6
Trunk (anterior)	8
Trunk (posterior)	6
Upper extremities	20
Lower extremities	18

TBSA: Total body surface area. [1]Estimated at admission by burn specialist.

Three-dimensional imaging

The agreement between the measurement of TBSA between researcher A and B using three-dimensional imaging had an inter-observer ICC of 0.99. The SEM was 0.054. (Table 2) The absolute agreement between both researchers are visually shown in a Bland and Altman plot (Figure 2). The LoA increased with increasing TBSA and the LoA was calculated at 0 ± 0.15 x the mean TBSA. (Figure 1)

Current clinical practice

The agreement between the TBSA measurements of the resident and burn specialist using the rule of nines and palm method had an inter-observer ICC of 0.91. The SEM was 0.30 (Table 2). The LoA increased with increasing TBSA and the LoA was calculated at 0 ± 0.78 x the mean TBSA. Only the LoA is shown in Figure 1.

Table 2. Reliability.

	Three-dimensional imaging[2]	**Current clinical practice**[1]	**Three-dimensional imaging vs current clinical practice**	**Three-dimensional imaging vs current clinical practice**
	Researcher A vs Researcher B	Resident vs Burn specialist	Researcher A vs Burn specialist	Researcher A vs Resident
ICC (range)	0.998	0.91	0.743	0.680
SEM	0.054	0.300	0.437	0.686
LoA	± 0.15 x mean TBSA	± 0.78 x mean TBSA	± 1.08 x mean TBSA	± 1.49 x mean TBSA

ICC: Intraclass Correlation Coefficient, SEM: Standard Error of measurement, LoA: Limits of Agreement. [1]Both rule of nines and palm method were used to estimate percentage of TBSA, [2]Artec MHT™ 3D Scanner was used to measure TBSA.

Three-dimension imaging vs current clinical practice

The agreement between researcher A using three-dimensional imaging and the burn specialist using the rule of nines and palm method had an inter-observer ICC of 0.74. The SEM was 0.44 (Table 2). The agreement between researcher A and the burn specialist is shown in a Bland and Altman plot (Figure 2). The LoA increased as the TBSA increased, and the LoA was calculated at ± 1.08 x the mean TBSA. (Figure 2).

The agreement between researcher A using three-dimensional imaging and resident using the rule of nines and palm method had an inter-observer ICC of 0.68. The SEM was 0.69 (Table 2) The agreement between researcher A and the resident is shown in a Bland and Altman plot (Figure 2). The LoA increased with as the TBSA increased, and the LoA was calculated at ± 1.49 x the mean TBSA. (Figure 2) The agreement between the measurements of researcher B using three-dimensional imaging and the clinicians was comparable with the results of researcher A.

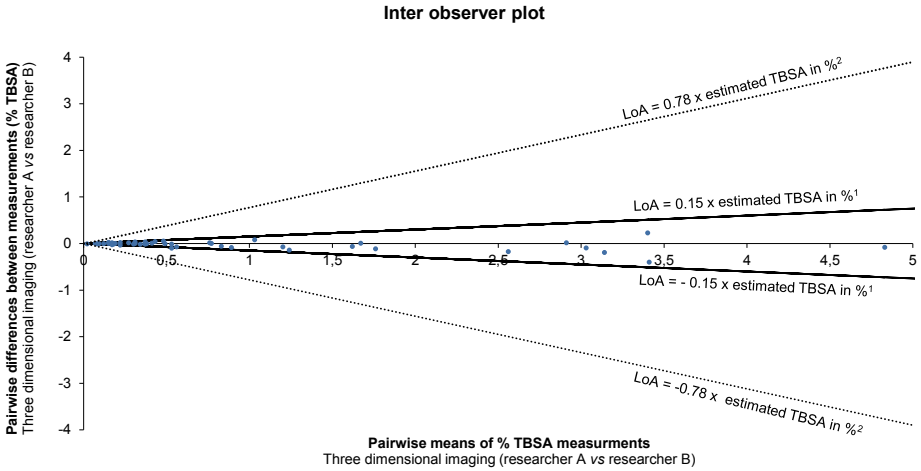

Figure 1. Bland and Altman plot presenting the inter-observer agreement between two researchers using three-dimensional imaging for means % TBSA. [1] Limits of agreement (LoA) between two researchers using three-dimensional imaging method, [2] Limits of agreement (LoA) between resident and burn specialist using rule of nines and palm method.

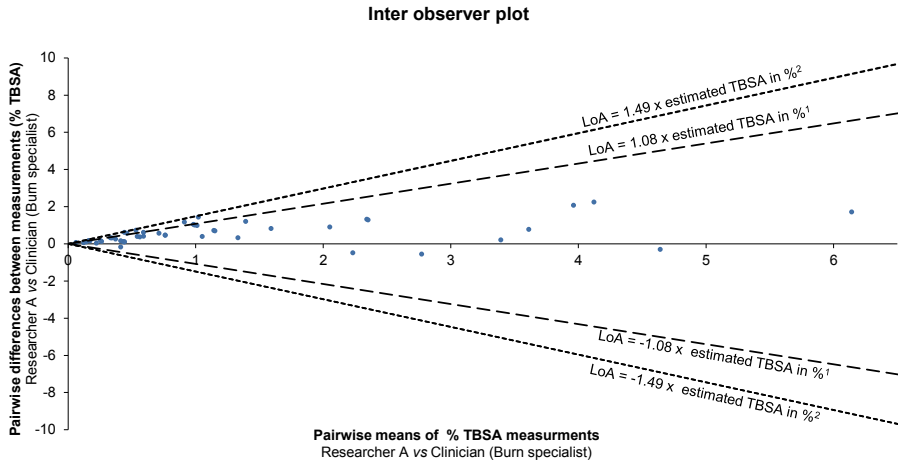

Figure 2. Bland and Altman plot presenting the inter-observer agreement between researcher A using three-dimensional imaging and burn specialist using the rule of nines and palm method for means percentage of TBSA. [1] Limits of agreement (LoA) between researcher A and burn specialist, [2] Limits of agreement (LoA) between researcher A and resident.

DISCUSSION

In this explorative study, three-dimensional imaging, using an Artec MHT™ Scanner and software, was found to be a reliable method for measuring TBSA of burn wounds in clinical practice. The inter-observer reliability of three-dimensional imaging was considerably better than that of a resident and a burn specialist using the rule of nines and palm method to measure TBSA. The inter-observer reliability between three-dimensional imaging and methods used in current clinical practice by a resident was less reliable compared with three-dimensional imaging and methods used in current clinical practice by a burn specialist in determining TBSA.

Strength and limitations

This study is the first study that describes three-dimensional imaging for measurement of the TBSA. An important advantage of three-dimensional imaging is the direct full-coloured three-dimensional reconstruction of the wound without any pre-specified three-dimensional model. A pre-specified three-dimensional model is a potential source of bias. While exploratory, this study aimed to investigate clinimetric properties of three-dimensional imaging in more detail by calculating not only ICC but also SEM and LoA to measure inter-observer reliability. ICC is a popular parameter for measuring reliability, however, it has two important limitations. First, by increasing the range of measurements and, thus, the variation between wounds, ICC can be artificially inflated. Second, ICC does not provide information on the absolute size of the measurement error, which is important in the clinical setting.(23) Therefore, estimating several different clinimetric properties of a method, for example a Bland and Altman plot with LoA in which the absolute measurement error is shown, is essential.

Our study had several limitations. First, we cannot specify the variation in reliability if researcher A and B measured their own scans instead of measuring one another's scans. Nevertheless, introducing this uncontrolled source of variation was justified in the current study design because this study was aimed toward clinical practice, in which case, it would be most likely that one physician performs the scan and another physician measures the TBSA. However, excellent reliability was obtained despite the current study design. In theory, the reliability would be greater if the observers performed and measured their own scans. Second, no intra-observer reliability was performed because in general, intra-observer reliability is higher than inter-observer reliability. (24) Third, for practical reasons, no validity study was performed for the TBSA measurements. However, in a previous study, three-dimensional imaging was found to be both valid and reliable for measuring the burn wound surface area. Fourth, in a recent study, a close correlation ($r > 0.95$) and no significant difference were observed between the mean BSA values calculated by Ct-scan (gold standard) and the formulas used in this study (DuBois & DuBois and Haycock) for BSA measurements.(25) These results suggests that the formulas used in our study to calculate BSA are acceptable. In addition, while not

objectively assessed, the measurement procedure of performing a scan took no longer than two minutes per patient. However, post-processing the data and measuring the wound surface area took between 15 minutes and one hour. Note that the Artec 3D software is constantly under development, and newer versions provides significant improvements regarding the post-processing time. Finally, given the range of the studied TBSA (< 6% TBSA) in this study, the results might not be generalized to higher TBSA.

Comparison with literature

To the best of our knowledge, three-dimensional reconstruction of a burn wound for the purpose of measuring TBSA has not been previously described. Therefore, there could be no direct comparison with the characteristics of comparable methods. However, two studies have described using software with pre-defined three-dimensional models to measure TBSA (BurnCase 3D and BAI).(26, 27) Only one study (BurnCase 3D) has investigated the inter-rater reliability of their method, with an ICC of 0.98.

Our results confirmed the finding from various studies describing poor correlation between TBSA estimates between referring physicians (comparable with the estimation made by the resident in our study) and burn specialists.(28-30) An LoA of 0 ± 0.78 x the mean TBSA between the residents and burn specialists in our study could lead to serious under- or overestimation of TBSA. Errors in estimating TBSA could result in a miscalculation of the need for intravenous fluid resuscitation and uncertainty whether the patient should transferred to a specialized burn unit.

To put the reliability of three-dimensional imaging in perspective, comparison with the reliability of current methods in clinical practice is obligatory. Interestingly, the inter-observer ICC of three-dimensional imaging and methods used in current clinical setting were both > 0.90, which indicates high reliability. However, as previously described, ICC has limitations. In this study, three-dimensional imaging showed superior results, as indicated by smaller SEM and much smaller LoA compared with methods currently used in clinical practice.

In the literature, no comparisons were found between three-dimensional imaging and current methods used in clinical practice to estimate TBSA. However, Prieto et al. have compared BAI with the rule of nines. The ICCs of BAI for the estimation of TBSA for the superficial and deep burns were 0.55 and 0.77, respectively.(27) Furthermore, in another study, the rule of nines and palm method were found to overestimate the TBSA by 38% and 37%, respectively, compared with BurnCase 3D.(31)

Future perspective

Future study on three-dimensional imaging should concentrate on more critical appraisals of the clinimetric properties of the method. Our results are encouraging, and validation studies should be performed. Finally, the implication of using Artec MHT™ Scanner and software in clinical practice for the clinical decisions, such as correct measurement of TBSA and subsequent patient outcomes (e.g., wound healing and mortality) should be studied and compared with the results of current methods.

CONCLUSION

In this explorative study three-dimensional imaging, using Artec MHT™ Scanner and software, was found to be superior compared with methods currently used in clinical practice (i.e., the rule of nines and palm method) for measuring TBSA. The inter-observer reliability between three-dimensional imaging and methods used in current clinical practice by residents was less reliable compared with three-dimensional imaging and methods currently used in clinical practice by burn specialists to determine TBSA.

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Part II

Partial thickness burn wounds in paediatric patients

Chapter 4

Non-silver treatment versus silver sulfadiazine in treatment of partial thickness burn wounds in children: a systematic review and meta-analysis

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ABSTRACT

The evidence for application of silver containing dressings and topicals in the treatment of partial thickness burns in pediatric patients is largely based on clinical trials involving adult patients despite the important differences between the skin of children and adults. A systematic review and meta-analysis was performed of all randomized controlled trials comparing non-silver treatment with silver containing dressings and silver topical agents in children with partial thickness burns in the acute stage. Endpoints were wound healing, grafting, infection, pain, number of dressing changes, length of hospital stay and scarring. Seven randomized controlled trials were included involving 473 participants. All trials used silver sulfadiazine as control in comparison with five different non-silver treatments. Most trials were of moderate quality with high risk of bias. Use of non-silver treatment led to shorter wound healing time (weighted mean difference -3.43 days, 95% confidence interval -4.78, -2.07), less dressing changes (weighted mean difference -19.89 dressing changes, 95% confidence interval -38.12, -.1.66) and shorter length of hospital stay (weighted mean difference -2.07 days, 95% confidence interval -2.63, -1.50) compared to silver sulfadiazine treatment, but no difference in the incidence of wound infection or grafting was found. In conclusion, non-silver treatment may be preferred over silver sulfadiazine but high-quality randomized controlled trials are needed to validly confirm the effectiveness of silver containing preparations, in particular silver containing dressings, above non-silver treatments.

INTRODUCTION

The treatment of partial thickness burns focuses on promoting rapid wound healing, preventing infection and systemic illness, decreasing pain, and minimizing long-term negative effects such as scarring and functional impairment.(1-6) Treatment modalities include silver containing topicals and other topical products, silver containing dressings, biological and (semi)synthetic dressings, enzymatic debridement, and surgical treatment.(6) Despite the wide range of treatment options, there is no consensus on the optimal treatment of partial thickness burns in children.(4-8) Yet, silver containing dressings and topical silver agents are widely used in this age group for treating partial thickness- and minor full thickness burns, and prior to grafting.(8-13) The action of silver treatments is caused by binding of the silver ions to the DNA of bacteria and bacterial spores in an aqueous environment which results in a reduced ability to replicate.(14-16) Its bactericidal properties include both gram-positive and gram-negative organisms, though resistance has been reported.(16-20)

Several reviews have evaluated the efficacy of silver treatment, but the available evidence is largely based on clinical trials involving adult patients. Various reviews found insufficient evidence that silver containing dressings and topical silver agents promote wound healing or prevent wound infection in burn patients.(8,10-12,21) These reviews as well as the majority of other reviews and clinical studies on acute burn treatment, do not specify treatment by age.

Translating this evidence to pediatric patients should be done with great caution as there are important differences between the skin of children, especially infants, and adult skin. In children, the stratum corneum (epidermis layer) and supra-papillary epidermis are respectively 30% and 20% thinner than adult skin and is yet under-keratinized compared to that of adults.(1,4,22) (23,24) Infants' skin is further characterized by a not fully developed palmar planter epidermis, decreased subcutaneous fat store, high surface hydration, high acidity, high desquamation and high keratinocyte proliferation rates. As a result, it is much more vulnerable to burn injury and subsequently more susceptible to bacterial colonization and infection due to the compromised epidermal barrier function.(25) Children also have a larger body surface area (BSA) to body weight ratio that makes them prone to hypothermia, and their metabolic systems have not yet fully developed.(1,26) Consequently, the bioavailability and absorption of an applied treatment in pediatric burn patients are greater than in adults burn patients.

We performed a systematic review of the available literature on the acute treatment of pediatric partial thickness burns, and compared outcomes after silver containing dressings and topical silver treatments versus non-silver treatments in a meta-analysis.

MATERIALS AND METHODS

Study protocol

The systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 Guideline.(27) The objective, inclusion and exclusion criteria, primary and secondary outcomes, and methods of synthesis were prespecified in a study protocol according to the recommendations of the Cochrane Collaboration.(28)

Search strategy

A literature search was conducted with the help of a trained medical librarian in the databases MEDLINE, EMBASE, Cochrane Library and CINAHL. The original search was conducted in October 2012, and was updated on September 2013. The search strategy combined various terms and synonyms for child(ren) and partial thickness burns. The complete search strategy is shown in supporting information 1.

Study selection

Two authors (RK and ZR) independently screened title and abstract of retrieved articles. Randomized Controlled Trials (RCT) were selected if they compared silver containing dressings and/or silver topical agents with a non-silver treatment and included pediatric patients aged 0-18 years with partial thickness burns randomized within 48 hours after injury. Studies that were not reporting on any of the primary outcomes of the review (wound healing and need for grafting) were also excluded. Full-text articles of the selected studies were obtained. Primary outcome measures were defined as time to wound healing (not predefined) and need for grafting. Secondary outcome measures were infection or colonization (predefined), number of dressing changes, pain, length of hospital stay (LOS) and scarring. If some of included patients were >18 years and age-specific results were not reported in the original publication, the authors were contacted and asked to provide additional information. If this information was not provided the study was not included. Disagreement between reviewers on study selection were resolved by discussion.

Data extraction

Two reviewers independently extracted information from each included trial on: (1) characteristics of trial participants including number of participants, age, type of partial thickness burn, method of burn assessment, percentage total body surface area (TBSA), follow-up of the patients, and the trial's inclusion and exclusion criteria; (2) type of interventions; (3) outcome measures: time to wound healing, need for grafting, infection or colonization, number of dressing changes, pain, length of hospital stay (LOS) and scarring. When the outcomes were not reported in a form suitable for meta-analytic calculation, we derived these data from graphical representation

of the outcomes, or by estimation based on the available information in the publication (for example recalculating a standard error from an exact p-value).(29) If needed we contacted the authors for additional information. When outcomes were presented for superficial and deep partial thickness burns separately, a pooled mean difference or pooled OR was computed for that single study (fixed-effect meta-analysis) summarizing the outcome in the total group with partial thickness burns.

Risk of bias assessment

The risk of bias of the individual randomized controlled trials was assessed as 'low', 'high' or 'unknown' independently by the two reviewers according the Cochrane Collaboration's tool for assessing risk of bias.(28) Discrepancies were resolved by discussion.(28)

Meta-analysis

Meta-analysis of study outcomes was performed using Review Manager (RevMan), version 5.2 (Cochrane Collaboration, Copenhagen: The Nordic Cochrane Centre).

We performed a meta-analysis calculating a pooled mean difference (continuous outcomes) or odds ratio (OR, for binary outcomes) and its corresponding 95% confidence interval (CI) in a random effects model.

Meta-analysis of binary outcomes was based on the crude numbers in both study arms. If in a study the number of events was equal to zero for binary outcomes, all cell counts were increased by one for all the studies to enable the computation of the pooled OR. For continuous variables calculations were performed based on mean estimates and accompanying standard deviations (SD) in both groups. In case of missing SD but a known p-value, the standard deviation was obtained by calculating the z-value and standard error of the mean (SEM), a method described by Altman et al.(29)

To assess heterogeneity between studies the Cochran's chi-squared test and the I^2 statistic were used. Heterogeneity was assumed for Cochran's chi squared test P-values < 0.1 or $I^2 > 50\%$.(30)

Finally, sensitivity analysis was performed to assess the robustness of the results if heterogeneity was detected, by excluding studies with outlying results.

RESULTS

Study selection

The search identified 1128 potentially relevant studies in the literature databases, of which 593 were screened after removal of duplicates (Figure 1). A total of 156 articles were retrieved for full text assessment. Of these, 131 studies were not randomized and therefore excluded. Eighteen randomized studies were excluded because no age-specified results were reported. Authors of these studies were contacted, of whom only two replied but did not provide the requested information because the numbers of pediatric patients were insufficient to be analysed separately. The remaining seven studies with age-specific results were included.

Study and patient characteristics of the seven included studies are summarized in Table 1. The RCT's compared silver sulfadiazine (SSD) to collagenase ointment and Polymyxin (bacteriostatic)(31), Amniotic membrane(32), Biobrane® / TransCyte® (biosynthetic skin substitute dressings)(33-35) or Mepitel® (silicon coated nylon dressing).(36,37) All seven RCTs were open label and single-center studies. The study populations differed with respect to the percentage TBSA. Two studies reported on patients with a mean TBSA < 5% (33,36) and five studies on patients with a mean TBSA <15%. (31,32,34,35,37) No RCTs including silver based dressings comparing with non-silver treatment among children were found.

The time between trauma and presentation at the hospital varied from 24 hours to a maximum of 48 hours post-burn between the studies. Five studies included patients with partial thickness burns**,** whereas one study also included superficial burns(32) and another only reported on superficial partial thickness burns(34). Only two studies reported the length of follow-up.(31,32)

Risk of bias assessment

The assessed risk of bias in the included studies is presented in Table 2.(28) In general, risk of bias was considered to be high, and important information was often lacking. In three studies the method of randomization was not described. Lal et al.[33] included seven patients (9%) that were not randomized but for whom treatment choice was based on the preferences of the resident on-call. In all studies allocation concealment was unclear and none of the studies were blinded. Three studies reported incomplete outcome data(33,34,36) and in one study it was unclear in how many patients the outcomes were measured or how many participants were lost to follow-up.(37) Selective reporting was difficult to judge since authors do not present the original study protocol.

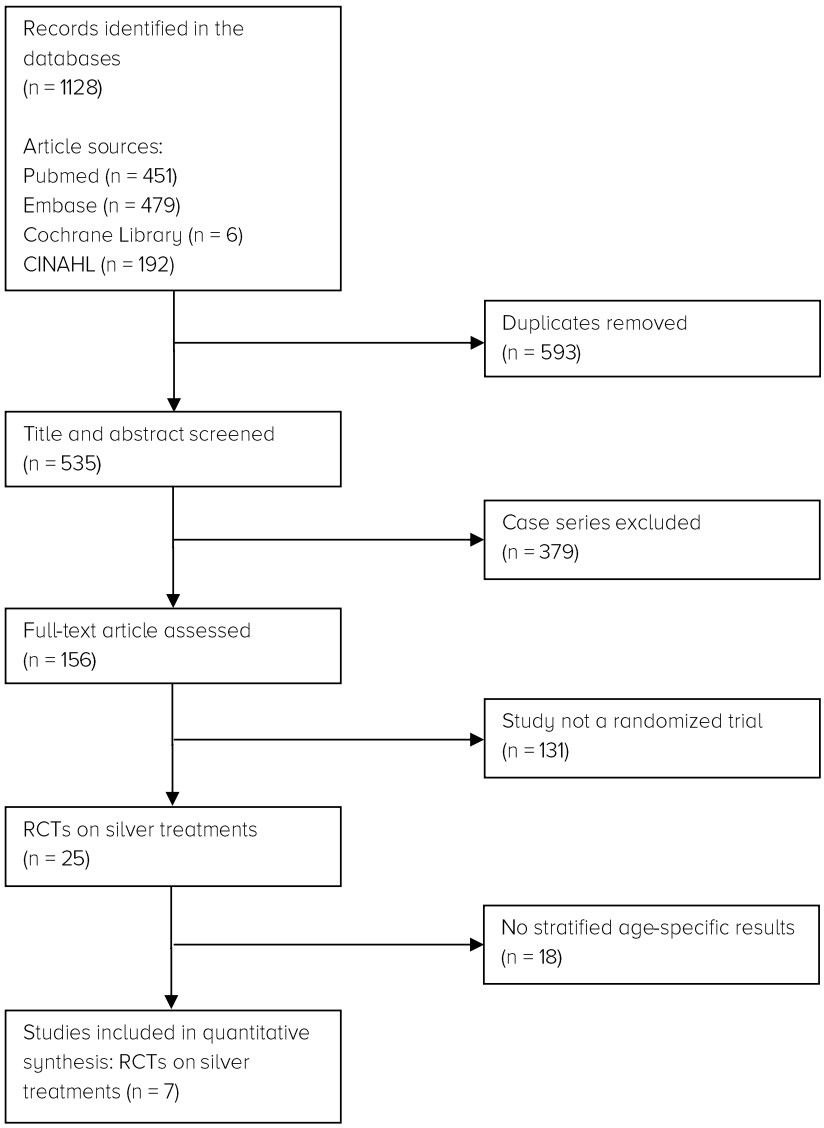

Figure 1. Flow chart of study selection.

Table 1. Characteristics of included trials.

Study	Participants	Age in years (Mean (SD))	Study design (Country)	Intervention (I)	Controle (C)	follow-up in months (mean (SD))
Ostlie et al. 2012	100 patients with partial thickness burns TBSA: I = 9.4% (SD = 6.1) C = 9.9% (SD = 6.8) Assessment: Clinical	2 months – 18 yr. I = 4.8 (NR) C = 5.1 (NR)	Open label, single center RCT (USA)	Collagenase Santyl Ointment (CO) + Polymixin (n = 50)	SSD (n = 50)	I = 8.0 (8.9) C = 5.8 (7.5)
Mostaque et al. 2011	102 patients with partial thickness burns TBSA < 15% Assessment: Clinical	1 day - 12 yr. I = 3.6 (2.3) C = 4.0 (2.4)	Open label, single center RCT (Bangladesh)	Amniotic membrane (AM) (n = 51)	SSD (n = 51)	Up to 6 months, no data provided
Kumar et al. 2004	33 patients (58 wound sides) with partial thickness burns TBSA: average 5% Assessment: LDI	Average age: 3.6 yr.	Open label, single center RCT (Australia)	Biobrane® (n = 17) TransCyte® (n = 20)	Silvazine® (n = 21)	NR
Barret et al. 2000	20 patients with partial thickness burns TBSA: 8.9% (SD = 4.9) Assessment: Clinical	NR	Open label, single center RCT (USA)	Biobrane® (n = 10)	SSD (n = 10)	NR
Lal et al. 2000	79 patients with superficial partial thickness burns TBSA: I = 11.5 (SD = 0.9) C = 11.8 (SD = 1.1) Assessment: Clinical	I = 2.8 (SEM = 0.5) C = 3.4 (SEM = 0.6)	Open label, single center RCT (USA)	Biobrane® (n = 34)	SSD (n = 45)	NR

Table 1. Continued.

Study	Participants	Age in years (Mean (SD))	Study design (Country)	Intervention (I)	Controle (C)	follow-up in months (mean (SD))
Gotschall et al. 1998	63 patients with partial thickness burns TBSA: I = 6.8% (SD = 3.4) C = 5.1% (SD = 2.2) Assessment: Clinical	NR	Open label, single center RCT (USA)	Mepitel® (n = 33)	SSD (n = 30)	NR
Bugmann et al. 1998	76 with partial thickness burns TBSA: I = 2.3 (SD = 2.0) C = 1.9 (SD = 2.1) Assessment: Clinical	I = 3.29 (3.1) C = 3.43 (3.7)	Open label, single center RCT (Switzerland)	Mepitel® (n = 41)	SSD (n = 35)	NR

I: intervention, C: control, SD: standard deviation, SEM: standard error of the mean, SSD: Silver sulfadiazine, LDI: Laser Doppler Imaging, LOS: length of stay, NR: Not reported, PBD: post-burn day, RCT: Randomized Controlled Trial, TBSA: total body surface area.

Table 2. Risk of bias assessed according to the criteria as described by Higgins et al.[27]

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ostlie et al 2012	-	?	+	?	-	?	+
Mostaque et al 2011	-	?	+	+	-	+	-
Kumar et al 2004	-	?	+	+	+	?	-
Barret et al 2000	?	?	+	?	-	?	-
Lal et al 2000	+	+	+	+	+	?	-
Gotschall et al 1998	?	?	+	+	?	?	+
Bugman et al 1998	?	?	+	?	+	+	-

?: unclear, +: high risk of bias, -: low risk of bias.

META-ANALYSIS: PRIMARY OUTCOMES

Time to wound healing

Wound healing was clinically assessed in five studies,[31,33-36] and by Laser Doppler Imaging (LDI) in combination with clinical judgment in one study.(33) Wound healing was defined as >90% re-epithelialisation(33), as complete closure(36), as covering of the moist and red granulation tissue with pale epidermis(32), or was not defined (31,34,35,37).

All six studies (419 patients in total) that reported wound healing, found significantly longer healing times for burns treated with SSD compared to burns treated with other non-silver dressings (Amniotic Membrane(32), Biobrane®(33-35), TransCyte®(33) or Mepitel®(36,37)). (Table 3). In a meta-analysis, the weighted mean difference (WMD) in healing time between non-silver treatments and SSD was -3.43 days (95% CI -4.78, -2.07, $p < 0.0001$) (Figure 2). Statistical heterogeneity was detected ($I^2 = 78\%$, $p = 0.0002$).

The study of Gotschall al. was a clear outlier for this outcome. After exclusion of this study in a sensitivity analysis, no significant changes in the direction and magnitude of the estimates were seen (WMD -3.26 days, 95% CI: -4.53, -.2.00, p = 0.0005).

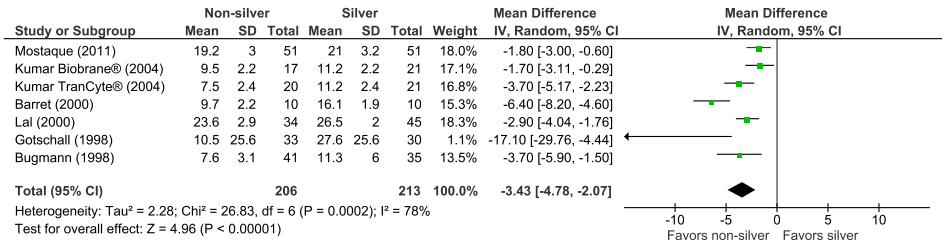

Figure 2. Forest plot for time to wound healing.

Need for grafting

Five of the seven studies reported on the need for wound grafting.(31,33-36) In none of the individual studies a statistically significant difference in the need for grafting was found between SSD and non-silver treatment (Table 3). The meta-analysis also showed no significant difference in the need for grafting between patients that were treated with SSD and those treated with non-silver (Odds Ratio [OR] 0.71, 95% CI: 0.40, 1.24, p = 0.23), and this trend was consistent in the sensitivity analysis (Figure 3). No statistical heterogeneity between the studies was detected (I^2 = 0%, p = 0.79).

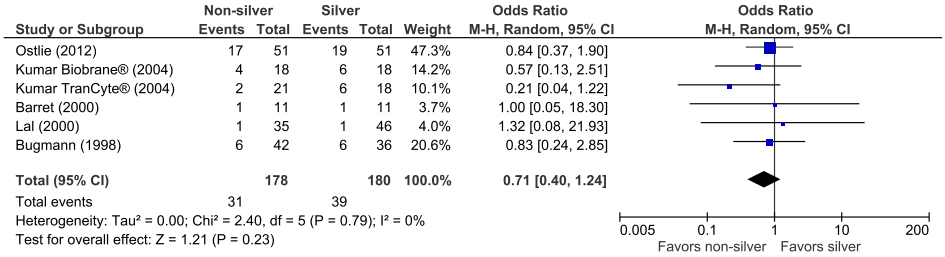

Figure 3. Forest plot for wound grafting.

Meta-analysis: Secondary outcomes

Infection/colonization

Six of the seven studies reported infection rate, although four studies neither provided a definition of infection, nor taken swabs to determine wound colonization. Kumar et al. took wound swab and defined infection as loss of product due to an inflammatory response, while only results on infection were reported.(33) Gotschall et al. stated no definition of infection

but wound swabs were taken, while no results on colonization were reported.(37) In the separate studies, no statistically significant differences in infection rate were found between the treatment groups (Table 3). The meta-analysis also did not show a significant difference in wound infection between patients that were treated with SSD vs. those treated with non-silver. (OR: 0.87, 95% CI: 0.37, 2.04, p = 0.76). Statistical heterogeneity was not detected (I^2 = 21%, p = 0.27) (Figure 4).

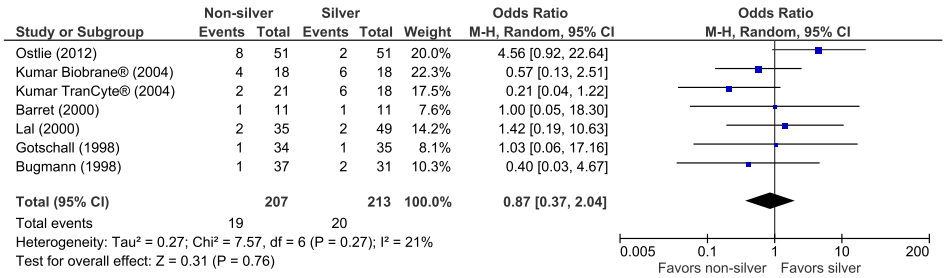

Figure 4. Forest plot for infection.

Dressings change

Four studies reported on this outcome. Gotschall et al. reported that the time required for dressings change was shorter when Mepitel® was used than with SSD.(37) Three studies reported a reduced number of dressing changes with Amniotic Membrane, Biobrane®, TransCyte® and Mepitel® treated burns compared with SSD.(32,33,36,37) (Table 3) The meta-analysis of these three studies showed that significantly less dressings changes were needed in patients treated with non-silver vs. those treated with SSD (Weighted mean difference [WMD] -19.89 dressing changes, 95% CI: -38.12, -.1.66, p = 0.03). Statistical heterogeneity between the studies was detected (I^2 = 99%, p < 0.00001) (Figure 5).

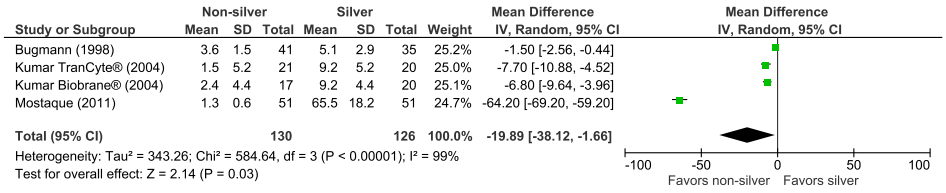

Figure 5. Forest plot for number of dressing changes.

The study of Mostaque et al. was a clear outlier for this outcome. After exclusion of this study in a sensitivity analysis, the meta-analysis showed a smaller but still significant difference in dressing changes favoring non-silver treatment. (WMD -5.15, 95% CI: -9.63, -.0.68, p = 0.02).

Pain

Four studies reported on pain, but this was not measured in a uniform manner, so no meta-analysis was performed for this outcome (Table 3). Gotschall et al. presented an overall significant pain reduction with Mepitel® compared to SSD(37) and in another study Biobrane® was found to significantly reduce pain at the first- and second day after admission compared to SSD.(35) Amniotic Membrane also led to significantly lower pain scores during and in between dressings changes compared to treatment with SSD.(32) Kumar et al. reported that patients who were treated with Biobrane® required significantly less pain medication compared to patients treated with Silvazine®(33) (Table 3).

Length of hospital stay (LOS)

Four studies reported LOS, three of which reported significantly reduced LOS after treatment with Amniotic Membrane and Biobrane® compared to SSD. (32,34,35) Ostlie et al. found no difference in LOS between Collagenase Ointment and Polymyxin and SSD treated burn wounds.(31) Our meta-analysis showed the weighted was -2.07 days (95% CI -2.63, -1.50, p < 0.00001) shorter in non-silver treatments compared to SSD (Figure 6). No statistical heterogeneity between the studies was detected (I^2 = 35%, p = 0.20).

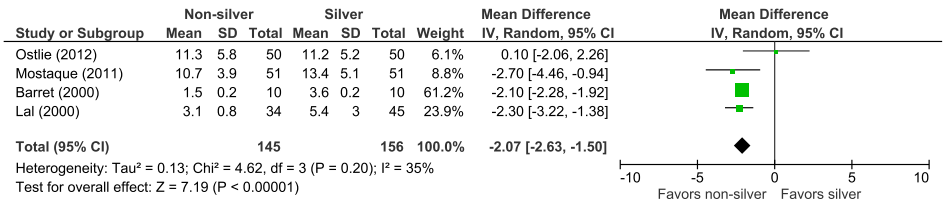

Figure 6. Forest plot for number of Length of hospital stay (LOS).

Scar formation

None of the selected studies reported on scar formation.

Table 3. Outcome results.

Study	**Wound healing** Definition. Mean (SD)	**Need for grafting** Number (%)	**Infection** Method. Definition Infection number (%)	**Number of dressings change** Mean (SD)	**Pain**		**LOS (mean (SD))**
Ostlie et al. 2012	NR	I = 16 / 50 (32%) C = 18 / 50 (36%)	Clinical judgment. No definition. No swab taken. I: 7 (14%) C: 1 (2%)	NR	NR		In days I = 11.3 (5.8) C = 11.2 (5.2)
Mostaque et al. 2011	Number of days until the moist and red granulation tissue is covered with pale epidermis. Superficial partial thickness burns I = 13.3 (1.0) C = 14.2 (1.0) Deep partial thickness burns I = 21.6 (1.4) C = 23.7 (1.5)	NR	NR	I = 1.3 (0.6) C = 65.5 (18.2)	During application Painless[3] I = 43 (84.3%) C = 11 (21.6%) Painful I = 8 (15.7%) C = 40 (78.4)	In-between application No pain I = 17 (33.3%) C = 6 (11.8%) Some pain I = 34 (66.7%) C = 12 (23.5) Persistent pain I = 0 (0%) C = 33 (64.7%)	In days I = 10.7 (3.9) C = 13.4 (5.1)
Kumar et al. 2004	Number of days until >90% reepithelialization. I Biobrane® = 9.5 (NR) I TransCyte® = 7.5 (NR) C: 11.2 (NR)	I Biobrane® = 3 / 17 (17%) I TransCyte® = 1 / 20 (5%) C = 5 / 17 (24%)	Clinical judgment. Loss of product due to an inflammatory response and exudate. Swab taken. I Biobrane® = 3 / 17 (5.6%) I TransCyte® = 1 / 20 (1,9%) C = 5 / 17 (9.3%)	I Biobrane® = 2.4 (NR) I TransCyte® = 1.5 (NR) C = 9.2 (NR)	Less pain medication with non-silver treatment than with Silvazine® (p = 0.0001)		NR
Barret et al. 2000	In days. (Wound healing not defined) I = 9.7 (SEM = 0.7) C = 16.1 (SEM = 0.6)	I = 0/ 10 (0%) C = 0/ 10 (0%)	Clinical judgment. Definition not reported. No Swab taken. I: 0/ 10 (0%) C: 0/ 10 (0%)	NR	Pain at second day[4] I = 2.6 (SEM = 0.3) C = 3.8 (SEM = 0.4)	Pain medication (doses/ person/ day) I: 2.6 (SEM = 0.3) C: 3.8 (SEM = 0.4)	In days I = 1,5 (SEM = 0.2) C = 3,6 (SEM = 0.2)

Table 3. Continued.

Study	Wound healing Definition. Mean (SD)	Need for grafting Number (%)	Infection Method. Definition Infection number (%)	Number of dressings change Mean (SD)	Pain	LOS (mean (SD))
Lal et al. 2000	In days. (Wound healing not defined) Data derived from graphical representation	I = 0 / 34 (0%) C = 0 / 45 (0%)	Clinical judgment. Definition not reported. No Swab taken. I: 1 / 34 (2,9%) C: 1 / 48 (2.2)	NR	NR	< 3 yrs old[6] I = 0.5 (SEM = 0.08) C = 0.2 (SEM = 0.08) p < 0.05 3 - 17 yrs old I = 0.4 (SEM = 0.02) C = 0.2 (SEM = 0.02)
Gotschall et al. 1998	In days. (Wound healing not defined) I = 10.5[1] (NR) C = 27.6[1] (NR)	NR	Clinical judgment. Definition not reported. Swab taken. I: 0 / 30 (0%) C: 0 / 33 (0%)	I = 22 minutes[2] C = 31 minutes[2]	I = 3.8 (NR)[5] C = 4.6 (NR)	NR
Bugmann et al. 1998	Number of days until complete closure I = 7.6 (3.1) C = 11.3 (6.0)	I = 5 / 41 (12.2%) C = 5 / 35 (14.3%)	Clinical judgment. Definition not reported. No Swab taken. I: 0 / 36 (0%) C: 1 / 30 (3.3%)	I = 3.6 (1.5) C = 5.1 (2.9)	NR	NR

I: intervention, C: control, NR: not reported, SEM: Standard Error of the Mean. [1] Median, [2] Mean time required for dressings change, [3] Number of patients (%), [4] Mean score on Visual Analog Scale (VAS) and faces scale with grading zero to four, [5] Mean score on objective pain scale, [6] Days/ % TBSA burned (no exact data was given; values derived from the diagram).

DISCUSSION

This study is the first systematic review and meta-analysis of RCT's comparing the outcomes of non-silver treatments with SSD that focuses only on pediatric patients with partial-thickness burns. In our meta-analysis we found that wounds treated with non-silver treatments healed more rapidly, required less dressing changes and shorter LOS than SSD. In addition, there are indications that non-silver treatments cause less pain than SSD treatments in burn wounds. However, there is no evidence to support the use SSD in treatments for prevention of wound infection and lesser grafting in pediatric patients with partial-thickness burns. Unfortunately, none of the included studies reported results on scar formation which is one of the most important outcomes in burn patients.

The methodological quality of the included RCTs was moderate and the risk of bias was high. In general, bias cannot be avoided when writing a review due to language bias and publication bias. We were unable to assess the extent hereof, but the 'file drawer problem' should not be underestimated, since there is a tendency that significant results are published more readily than non-significant results, leading to overestimation of the true treatment effect. Another limitation of this review was that the available information on study results was limited. Although authors were requested to provide us with missing data, none of the authors provided the requested information.

For some study outcomes (wound healing time and number of dressing changes) statistical heterogeneity between studies was detected. This statistical heterogeneity might reflect underlying clinical heterogeneity with respect to age range, percentage TBSA, type of included burn wounds or different non-silver treatments. However, different non-silver treatments were pooled in our meta-analysis because all the individual studies had similar outcome in respect to wound healing, grafting, infection and pain compared to SSD.

Our finding that non-silver treatment is associated with more rapid wound healing compared to SSD is in line with several other literature reviews on this topic in pediatric patients. Dorsett-Martin reported inconclusive results after analysis of comparative studies from 1997-2007, though for TransCyte®, Biobrane®, beta-clucan collagen and Mepitel® often superior results were reported compared to SSD with respect to healing times and pain reduction in peediatric patients.(38) Mandal et al. reported on the basis of scanty prospective comparative studies that Biobrane® seemed to be more effective with regard to wound healing, pain control and LOS than conservative treatment, including SSD in pediatric patients.(39) A recent Cochrane review, based mainly on adult patients, found also that SSD was consistently associated with poorer healing outcomes.(8) Finally, a similar systematic review of 7 RCT's comparing silver-dressings and topical silver to

non-silver dressings found a longer healing time for partial thickness burns when silver-dressings were compared to non-silver treatment in adults [WMD 3.96 days; 95% CI 2.41, 5.5].(10) A mean difference of 3.4 days in healing time, as found in our meta-analysis, between wounds that are treated with non-silver treatment versus SSD, could be of a great important. Hospital stay, in particular dressing changes, could be traumatic for a child. Furthermore, hospital admission of a child requires that at least one parent has to stay in the hospital during that time.

Regarding wound infection and grafting, our findings are also in agreement with other studies. Different reviews conclude that there is insufficient evidence that SSD prevent wound infection. (21) (8,10,12) This despite the fact that several vitro studies have shown that silver has an antimicrobial activity against a wide range of gram positive and gram negative microorganisms, including resistant forms such as MRSA and VRE, and fungi and anaerobes. (17,18,40) Some studies found that organisms do not develop resistance to silver, but recent studies suggest that resistance does occur. (19,20) However, in vitro studies of the antimicrobial efficacy of SSD do not necessarily reflect their performance in a wound due to the complexity of the wound environment.

There have been conflicting studies regarding the workings of silver on wound healing in adults. A review by Atiyeh et al. concluded that silver-based products used as a topical antimicrobial strategy in treatment of superficial partial thickness wounds should be avoided if possible because of the cytotoxicity of silver to the wound bed.(9) In a study by Burd et al. it was found that five silver-based preparations in a tissue explant culture model, in which the epidermal cell proliferation was evaluated, resulted in a significant delay of reepithelialisation. (41) It was also found that SSD in animal models (pig and mice) lead to strong inhibition of wound reepithelialisation on the 7 Post Burn Day.(42) Another study by Poon et al. supported these findings and found that silver is cytotoxic on keratinocytes and fibroblasts in vitro models by using MTT and BrdU assays.(43) Lee et al. also found that SSD in collagen sponge was cytotoxic to fibroblasts and caused a significant impairment in the wound healing process and a decrease in wound tear strength.(42) Conversely, different studies found some silver preparation not to be toxic and suggested that silver promotes wound healing.(44,45)

It should be noted that we only found RCTs that compared SSD with non-silver treatments in our search of the literature, despite the fact that our search strategy designed to compare all silver containing dressings and/or silver topical agents with a non-silver treatment. Meanwhile, “next generation” silver containing preparations are widely used in the treatment of partial thickness burns.(9) In particular, silver containing dressings have potential advantages over SSD. These dressings contain a silver releasing compound or a sustained release of nanocrystalline silver which is covering the outer layer of the dressing, impregnated within

the structure of the dressing or as a combination of these.(3) The dressing usually consist of activated charcoal, hydrofiber, polymer film, polyacrylate matrix, nylon fabric that has been silver-plated or high-density polyethylene mesh.(9) These silver containing dressing, depending on the type of dressing, are designed to require less dressing changes, easier to apply on the wound, allow a better autolytic debridement and at the same time sustenance moist wound environment to promote wound healing, and provide sustained release of silver ion into the wound compared to SSD.(46) Various studies in adults suggests that burn wounds that are treated with nanocrystalline silver had a shorter healing time, lower incidence of infection, decreased pain level, less wound dressings and costs compared to older silver formulations such as silver nitrate or SSD.(47) On the other hand a recent Cochrane review found only a shorter haling time and less dressing changes for silver containing dressing compared to SSD in partial thickness burns. Overall there is evidence that silver containing dressing is preferable to SDD in terms of wound healing. Therefore, future studies could focus on comparison of silver containing dressing with non-silver treatments.

Some recommendations for future studies follow from this review. We would like to emphasize the importance of presenting age-specific study results as the skin of adults and children are different and may, therefore, react differently to treatment. Consequently, inclusion of patients of all ages or presenting results as if patients form one homogenous group, may mask underlying effect heterogeneity. In addition, studies on burn patients should focus on adequate randomization methods, allocation concealment and blinding of outcome assessment, and most importantly, the presentation of complete outcome data. Uniform outcome measurements should be chosen, e.g. for measuring pain, and uniform and clear definitions of wound healing and infection should be used. LDI is an accurate and reliable way to estimate wound healing in burn patients by evaluation of the differences in perfusion of the microvascular blood flow of the wound. (48,49) Lastly, future studies could focus more on comparison of silver containing dressing with non-silver treatments.

CONCLUSION

Our systematic review and meta-analysis suggests that non-silver treatment may be preferred over SSD in terms of wound healing time, dressing changes, pain and LOS, while no treatment differences were found regarding infection and grafting rates. However, we emphasize the lack of high-quality RCTs that are needed to validly confirm the effectiveness of non-silver treatments above silver containing preparations, in particular silver containing dressings, in pediatric patients with partial thickness burns.

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Appendix A. The search strategy.

For Pubmed

(("child"[mesh] OR "child"[all fields] OR "children"[all fields] NOT "child"[au]) OR "schoolchild"[all fields] OR "schoolchildren"[all fields] OR "infant"[all fields] OR "infants"[all fields] OR "adolescent"[all fields] OR "adolescents"[all fields] OR "pediatric"[all fields] OR "paediatric"[all fields] OR "neonatal"[all fields] OR "neonate"[all fields] OR "neonates"[all fields] OR "youth"[all fields] OR "youths"[all fields] OR "baby"[all fields] OR "babies"[all fields] OR "toddler"[all fields] OR "toddlers"[all fields] OR" teen"[all fields] OR "teens"[all fields] OR "newborn"[all fields] OR "newborns"[all fields]OR "puberty"[all fields] OR "suckling"[all fields] OR "sucklings"[all fields] OR "juvenile"[all fields]) AND ("burns"[MesH] OR "burns"[all fields] OR "burn"[all fields] OR "burned"[all fields] OR "burnt"[all fields] OR "burning"[all fields] OR "burnings"[all fields]) AND ("silver sulphadiazine"[all fields] OR "SSD"[all fields] OR "Flammazine"[all fields] OR "Flamazine"[all fields] OR "Silver Sulfadiazine"[MESH] OR "Sulfadiazine"[all fields] OR "Sulfafdiazine"[all fields] OR "Dermazin"[all fields] OR "Sicazine"[all fields] OR "Thermazene"[all fields] OR "silverderma"[all fields] OR "Sulfargen"[all fields] OR "Brandiazin"[all fields] OR "Silvadene"[all fields] OR "sulfazin"[all fields] OR "silver"[all fields])

For Embase

((exp child/ OR "child".mp. OR "children".mp. NOT "child".au.) OR "schoolchild".mp. OR "schoolchildren".mp. OR "infant".mp. OR "infants".mp. OR "adolescent".mp. OR "adolescents".mp. OR "pediatric".mp. OR "paediatric".mp. OR "neonatal".mp. OR "neonate".mp. OR "neonates".mp. OR "youth".mp. OR "youths".mp. OR "baby".mp. OR "babies".mp. OR "toddler".mp. OR "toddlers".mp. OR "teen".mp. OR "teens".mp. OR "newborn".mp. OR "newborns".mp.OR "puberty".mp. OR "suckling".mp. OR "sucklings".mp. OR "juvenile".mp.) AND ("exp burn/" OR "burns".mp. OR "burn".mp. OR "burned".mp. OR "burnt".mp. OR "burning".mp. OR "burnings".mp.) AND ("silver sulphadiazine".mp. OR "SSD".mp. OR "Flammazine".mp. OR "Flamazine".mp. OR "exp sulfadiazine silver/" OR "Sulfadiazine".mp. OR "Sulfafdiazine".mp. OR "Dermazin".mp. OR "Sicazine".mp. OR "Thermazene".mp. OR "silverderma".mp. OR "Sulfargen".mp. OR "Brandiazin".mp. OR "Silvadene".mp. OR "sulfazin".mp. OR "silver".mp.)

For CINAHL

((MH child+) OR (TX child*) OR (TX schoolchild*) OR (TX infant*) OR (TX adolescent*) OR (TX pediatric*) OR (TX paediatric*) OR (TX neonatal*) OR (TX neonate*) OR (TX youth*) OR (TX baby*) OR (TX babie*) OR (TX toddler*) OR (TX teen*) OR (TX newborn*) OR (TX pubert*) OR (TX suckling*) OR (TX juvenil*)) AND ((MH burns+) OR (TX burn*)) AND ((MH silver sulphadiazine) OR (TX SSD) OR (TX Flammazine*) OR (TX Flamazin) OR (TX Sulfadiazine) OR (TX Sulfafdiazine) OR (TX Dermazin) OR (TX Sicazine) OR (TX Thermazene) OR (TX silverderma*) OR (TX Sulfargen) OR (TX Brandiazin) OR (TX Silvadene) OR (TX sulfazin*) OR (TX silver*))

For Cochrane

(silver or silversulphadiazine or Flammazine) and (child or schoolchild or infant or adolescent or pediatric or paediatric or neonatal or neonate or suckling) and burn

Chapter 5

Usability and effectiveness of Suprathel® in partial thickness burns in children

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ABSTRACT

Purpose: Evaluation of usability and effectiveness of Suprathel® in the treatment of partial thickness burns in children.

Methods: A prospective, observational study to evaluate adherence of Suprathel® to the wound bed, reepithelialization time, grafting, wound colonization and infection, pain, dressing changes, length of hospital stay (LOS) and scar formation.

Results: Twenty-one children (median age 2.4 years, range 5 months - 14 years) with a median total body surface area (TBSA) of 4% (range 1 - 18) were included. Median LOS was 10 days (range 3 - 20). Median outer layer dressing changes was 3 (range 1-14). Suprathel® was only adherent in wounds debrided with Versajet®. Median reepithelialization time was 13 days (range 7 - 29). Three patients needed a split skin graft. There were 7 (33%) patients with wound colonization before application of Suprathel®. This increased to twelve (57%) patients during treatment. One patient developed a wound infection. Median Visual Analogue Scale (VAS) scores for background and procedural pain in patients > 7 years were 3.2 (range 2 - 5) and 3.5 (range 2 - 5), respectively. In younger patients, median background was and median procedural COMFORT-B scores were 13.8 (range 10 - 23) and 14.8 (range 13 - 23, p = 0.03) respectively. *Patient and Observer Scar Assessment Scale (*POSAS) scores were favorable after 3 and 6 months post burn.

Conclusions: Suprathel® provides potential advantages regarding pain and scar formation, but extensive wound debridement is needed to achieve adequate adherence.

INTRODUCTION

Although partial thickness burns are the most common burn injuries among children, there is no 'gold standard' for the optimal treatment of this type of burn injury.(1, 2) The treatment of partial thickness burns focuses on undisturbed wound healing by providing a moist wound environment, removal of exudate, prevention of infection, and minimization of pain, scar formation and functional impairment.(1, 3, 4)

In the last few decades significant progress has been made in the field of (semi)synthetic wound dressings to meet the above requirements. One of the latest innovations in this field is the development of Suprathel®. Suprathel® (PolyMedics Innovations GmbH, Filderstadt, Germany) is a biosynthetic, non-animal derived wound dressing that imitates the protective properties of the human epithelium by adhering to the wound bed at body temperature. (5, 6) The microporous membrane of Suprathel®, which has an elongation capacity of up to 250%, is water-soluble and composed of a co-polymer (terpolymer) of poly-DL-lactide, trimethylene carbonate and ε-caprolactone.(5, 7) The porous property of Suprathel® is intended to prevent accumulation of wound exudate and thereby wound infection. Also, a moist wound environment is supposed to be established, which may contribute to an optimal wound healing. Suprathel® is transparent after application to the wound bed which enables inspection of the wound without removing the dressing.(8)

Literature on effectiveness of Suprathel® in pediatric burn patients is scarce. Only two recent non-comparative studies reported good results in terms of wound healing in children with partial thickness burns.(6, 9) However, no studies reported validated data on the wound colonization, scar formation and pain after application of Suprathel® on the wound and before and after each outer layer dressing changes.

This study evaluates the usability and effectiveness of Suprathel® in the treatment of partial thickness burns in children.

PATIENTS AND METHODS

This observational, prospective study was conducted in the Juliana Children's Hospital, The Hague and in the Beverwijk Burn Centre of the Red Cross Hospital, Beverwijk, The Netherlands.

Patients

Between November 2011 and January 2013 all consecutive patients younger than 18 years with partial thickness burns who were seen in these hospitals within 48 hours after injury, were eligible for this study. Patients were excluded if they had only facial burns, if they previously had been treated elsewhere for their burn wounds or if they were expected to be non-compliant with their treatment, for example because of a profound language barrier.

Ethical approval

The local ethics committees approved our study (Reference number: 2012-346). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Parents of the included pediatric patients gave informed consent prior to the inclusion in the study.

Treatment protocol

All included patients underwent the same treatment protocol. Suprathel® was applied to the wound after administrating oral analgesics in the outpatient department or under general anesthesia (propofol, fentanyl) in the operating theatre within 48 hours after injury. The burn wounds were cleaned by rinsing and superficial debridement of loose skin remnants and blisters or by using a Versajet® hydrosurgery system for surgical wound debridement.(10) Thereafter, a Suprathel® film was cut to adequate dimensions in order to cover the complete burned area, whereupon a multilayer Vaseline gauze dressing was applied in order to keep the Suprathel® separated from the outer absorbing dressings. Depending on the extension of the burns, patients were then either admitted to the ward or discharged and regularly seen in the outpatient clinic until complete wound healing. Thereafter, patients were seen at three and six months after injury. Suprathel® was left in situ until 95% reepithelialization had been achieved, while the outer dressings were changed routinely every three to five days. During these dressing changes only outer layer dressings were removed, adherent Suprathel® was left untouched and loose Suprathel® over the healed area was trimmed. If the Suprathel® was completely detached from the unhealed wound bed, it was removed after which the exposed wound was treated with a topical agent. At the 10^{th} – 14^{th} day post burn it was decided whether a skin graft was needed. Reasons for grafting were expected absence of progressive wound healing in the next 7 to 11 days and full thickness burns.

Swabs for semi-quantitative analysis of wound microbial flora were taken on admission, before the application of Suprathel® and during each outer layer dressing change. Wound colonization was defined as at least one positive bacterial culture from the wound.(11) Infection was defined as a combination of skin redness, pain, swelling, tenderness, warmth, fever or pus draining

from the skin with a positive wound colonisation.(12) If infection occurred, Suprathel® was removed from the wound. Based on the outcome of the swabs, infected wounds were treated with an appropriate local antiseptic.

Data

Baseline characteristics were recorded including gender, age, cause and location of the burn, depth of the burns (superficial or deep partial thickness), time from burn to start of treatment in days, and percentage of affected total body surface area (TBSA). Superficial partial thickness burns (SPTB) were clinically defined at the acute stage as painful burn wounds that had a moist pink colored appearance, with intact or disrupted blisters and with a capillary refill within less than seconds. Deep partial thickness burns (DPTB) were defined as painful wounds with a dry and red to pale appearance with pale blotchy patches, with intact or disrupted blisters and a capillary refill after more than 3 seconds.(13)

Usability of Suprathel® was evaluated by its adherence to the wound bed and the number of (outer layer) dressing changes. Effectiveness of Suprathel® was evaluated in terms of reepithelialization time, need for skin grafting, wound colonization and infection, pain, length of hospital stay (LOS) and scar formation.

Reepithelialization time was defined as the number of days until at least 95% reepithelialization of the wound, judged by an experienced burn surgeon. The number of burn wounds that were treated with Suprathel® and required secondary (surgical) intervention was also determined. Pain was measured before each outer layer dressing change to measure background pain and after each outer layer dressing change to evaluate procedural pain. Patients older than seven years scored pain on a Visual Analogue Scale (VAS), a continuous horizontal 10 cm line ranging from 0 (no pain) to 10 (worst possible pain). The COMFORT-Behaviour scale was scored by trained pediatric nurses to measure pain in younger patients. This COMFORT-B scale contains six behavioral items including alertness, calmness, respiratory response or crying, muscle tone, physical movement, and facial tension. For each item, the response categories range from 1 (‘no distress) to 5 (severe distress) leading to an overall score ranging from of 6 to 30.(14)

Scar formation was assessed at three and six months post burn, using the Patient and Observer Scar Assessment Score (POSAS(15, 16)). The POSAS consists of an observer scale, which is scored by an experienced burn specialist, and a patient scale, which is scored by the patient. The observer scale includes items on vascularization, pigmentation, thickness, relief and pliability while the patient scale measures pain, itching, color, stiffness, thickness and irregularity of the scar. The items on both scales are scored on a 10-point scale, ranging from 1 (‘normal skin’) to 10 (‘worst imaginable scar’). Patients above 13 years of age score the patient scale themselves whereas parents or caregivers fulfil this task for younger patients.

Statistical analysis

For this observational study no formal sample size calculation was performed. A sample size of about twenty patients was considered sufficient to obtain insight into the usability and effectiveness of Suprathel® during the inclusion period. Data were stored in an SPSS database version 17 (SPSS Inc., Chicago IL) and described using summary statistics (median/range or number). Categorical data were compared between groups using the Fisher's exact test. Comparison of the time to reepithelialization between SPTB and DPTB or wounds with/without bacterial colonization was performed using the log-rank test. Pain scores before and during application of Suprathel® on the wound bed were compared within patients using the Wilcoxon signed-rank test for paired data. Two-sided *P*-values < 0.05 were considered as statistically significant.

RESULTS

Patients

Twenty-one patients (10 male, 11 female) with a median age of 2.4 years (range 5 months - 14 years) were treated with Suprathel® during the inclusion period (Table 1). All patients were in good general health without comorbidities. Most burns were caused by scalding (n = 19) and affected the anterior trunk (n = 10) or the extremities (n = 17). Eleven (52%) patients were treated in an outpatient setting and ten (48%) patients were admitted to hospital. Median TBSA at admission was 4% (range 1.0 - 18.0). Median TBSA of the patients that were treated in outpatient settings was 2.5% (range 1.0-5.0), while median TBSA of admitted patients was 6.0% (range 3.5 - 18.0). At the initial assessment, the burns of twelve (57%) patients were classified as SPTB and as DPTB in nine (43%) patients as DPTB. Median LOS of the admitted patients was 10 days (range 3 - 20).

Usability of Suprathel®

Adherence to wound bed

In most patients with SPTB (11/12, 92%) a superficial wound debridement was performed, while the wounds of patients with DPTB were mostly debrided by Versajet® hydrosurgery (7/9, 78%) (Table 2). The median time to application of Suprathel® on the wound was 1 day (range 0-2) post burn. In nine (43%) patients Suprathel® was completely detached from the wound surface at the first outer layer dressing change (Table 2). All cases of complete detachment occurred in the group in which only superficial wound debridement had been performed (9/13, 69%). In contrast, no detachment of Suprathel® from the wound was seen in the group in which debridement had been performed by Versajet® hydrosurgery (0/8, p = 0.005).

Table 1. Patient characteristics of 21 children with partial thickness burns.

Age, median (range)	2.4 years (5 months - 14 years)
Gender, n (%)	
- Male	10 (48)
- Female	11 (52)
Burn cause, n (%)	
- Scald	19 (90)
- Flash	1 (5)
- Flame	1(5)
Location of burn, n (%)	
- Head and neck	2 (7)
- Trunk (anterior)	10 (33)
- Trunk (posterior)	1 (3)
- Upper extremities	9 (30)
- Lower extremities	8 (27)
Treatment, n (%)	
- in outpatient clinic	11 / 21 (52)
- admitted	10 / 21 (48)
% TBSA, median (range)	
- in patients treated in outpatient clinic	2.5 (1.0 - 5.0)
- in admitted patients	6.0 (3.5 - 18.0)
- total	4.0 (1.0 - 18.0)
Depth of burn, n (%)	
- SPTB	12 (57)
- DPTB	9 (43)

TBSA: Total Body Surface Area, SPTB: Superficial Partial Thickness Burns, DPTB: Deep Partial Thickness Burns.

Dressing changes

The median number of outer layer dressing changes was 3 (range 1 - 14) in patients in whom Suprathel® was adherent. However, in nine (43%) patients in whom Suprathel® did not adhere to the wound bed, another dressing was applied. The median number of these dressings changes was 2 (range 0 - 7) (Table 2).

Effectiveness of Suprathel®

Reepithelialization time and need for skin grafting

The median reepithelialization time was 13 days (range 7 - 29). No significant difference in time to reepithelialization was found between SPTB and DPTB, 11 days (range 7 - 29) and 15 days (12 - 19; p = 0.26), respectively. The median time to reepithelialization was 15 days (range 9 - 29) for wounds with bacterial colonization, and 13 days (range 7 - 18) for non-colonized wounds (p = 0.45). One patient, who suffered a wound infection healed in 29 days. All SPTB healed without surgical intervention, whereas three of the patients with DPTB needed a split skin graft.

Table 2. Measures of usability and effectiveness of Suprathel® in 21 children with partial thickness burns.

Debridement, n (%)	
SPTB	
- Superficial debridement	11 / 12 (92)
- Versajet® hydrosurgery	1 / 12 (8)
DPTB	
- Superficial debridement	2 / 9 (22)
- Versajet® hydrosurgery	7 / 9 (78)
Time until application of Suprathel® in PBD, median (range)	1 (0 - 2)
TBSA of wound area treated with Suprathel®, median (range)	4 (1 - 18)
Adherence till wound healing, n (%)	
- Yes	12 (57)
- No	9 (43)
Number of dressings changes, median (range)	
- during Suprathel® adherence	3 (1 - 14)
- after detachment Suprathel®	2 (0 - 7)
Time to reepithelialisation in days, median (range)	
Total	13 (7 - 29)
Wound without bacterial colonisation	13 (7 - 18)
Wound with bacterial colonisation	15 (9 - 29)
Split skin graft, n (%)	3 (14)
Length of hospital stay, median (range)	10 (3 - 20)

SPTB: Superficial Partial Thickness Burns, DPTB: Deep Partial Thickness Burns, PBD: Post burn day, TBSA: Total Body Surface Area.

Colonization and infection

Seven (33%) patients showed wound colonization before application of Suprathel® to the wound. During treatment with Suprathel® the number of patients with wound colonization increased to twelve (57%). Various microorganisms were found in the colonized wounds: *Staphylococcus aureus*, *Pseudomonas* and *group B streptococcus*, and *Acinetobacter baumannii*. One patient in the DPTB group showed signs of infection with *Staphylococcus aureus*.

Pain

Patients younger than 7 years had a median background COMFORT-B score of 13.8 (range 10 - 23), while their median procedural score was 14.8 (range 13 - 23, p = 0.03). There was no difference between pain scores given by the older patients before (median 3.5, range 2 - 5) and during (median 3.2, range 2 - 5) outer layer dressing changes (p = 1).

Scar formation

Table 3 presents the median POSAS scores at 3 and 6 months post burn. Most of the POSAS scores by observers and patients/ parents were mainly in the lower third of the range, reflecting a good scar quality after 6 months post burn.

Table 3. Scores on the Patient and Observer Scar Assessment Score (POSAS) for evaluation of scar formation in 21 children with partial thickness burns treated with Suprathel®.

	3 month post burn	**6 month post burn**
Observer		
Vascular, median (range)	3 (2 - 6)	2.5 (1 - 7)
Pigmentation, median (range)	3 (2 - 7)	2.5 (2 - 8)
Thickness, median (range)	3 (1 - 6)	2.5 (1 - 4)
Relief, median (range)	2 (1 - 6)	2.5 (1 - 4)
Pliability, median (range)	2 (1 - 8)	2 (1 - 5)
Surface, median (range)	2 (1 - 7)	2 (1 - 3)
Overall opinion, median (range)	3 (1 - 7)	2.5 (1 - 5)
Patient/ parents		
Pain, median (range)	1 (1 - 8)	1 (1 - 2)
Itching, median (range)	3 (1 - 8)	2.5 (1 - 5)
Colour, median (range)	6 (3 - 8)	6 (2 - 9)
Pliability, median (range)	2 (1 - 6)	2.5 (1 - 8)
Thickness, median (range)	2 (1 - 8)	3 (1 - 8)
Irregularity, median (range)	2 (1 - 9)	3 (1 - 8)
Overall opinion, median (range)	4.5 (2 - 9)	3.5 (1 - 7)

DISCUSSION

Suprathel® is a potentially good alternative for biological wound dressing, because it is not derived from animals and therefore acceptable for all patient groups. To the best of our knowledge, this study is the only detailed prospective study including long-term results on the usability and effectiveness of Suprathel® in the treatment of partial thickness burns in children. The data resulting from this study, which obtained by validated measurement tools if possible, provide more insight into the usability and effectiveness of this treatment in daily practice and can be used to design future comparative studies with other types of dressings in the treatment of partial thickness burns in children.

The lack of adherence of Suprathel® to the wound bed seems to be attributable to the extent of debridement technique. Adherence of Suprathel® was achieved when the Versajet® system had been used, while no adherence was seen in most cases when superficial debridement had been performed. Three studies reported on the adherence of Suprathel® to the wound bed in the treatment of partial thickness wounds and found excellent material adherence.(6, 7, 9) However, the effect of the extent of wound debridement on the adherence is not clear in these studies because either different debridement techniques were used or no information was reported on the debridement technique. Our study suggests that extensive wound bed debridement might be a requirement for adequate adherence of Suprathel® to the wound.

The results regarding time to reepithelialization in our study were comparable to those of a previous non-comparative study on the treatment of partial thickness burns in children with Suprathel®.(6, 9) In two recent systematic reviews on the treatment of partial thickness burns in children the mean time to reepithelialization in randomized controlled trials (RCT) that used other (semi)synthetic dressings varied between 7.5 and 23.6 days.(1, 17) In adults, no difference in reepithelialization was found when Suprathel® was compared to other (semi)synthetic dressings (Biobrane®(18) and Omiderm®)(19) or split-thickness skin graft (STSG)(8) in the treatment of partial thickness burns. In pediatric patients, a short reepithelialization time is important as other studies have shown a low risk of developing hypertrophic scars and contractures in burn wounds that healed within 21 days.(20, 21) Our study seems to confirm this finding as healing of the burn wound in one patient took more than 21 days, due to wound infection, after which this patient developed a hypertrophic scar and had the worst POSAS score in our study.

Three children (14%) in our study received a skin graft because no spontaneous wound healing was expected within 21 days after the burn injury. In other studies, the need for skin grafting varied between 0% and 17% in children with partial thickness burns that were treated with other (semi)synthetic dressings than Suprathel®.(22-25) However, comparing these results with the current study should be done with caution, because in these studies no indication for and timing of skin grafting were reported. In our hospital the standard care for the partial thickness burns is aimed to achieve reepithelialization, with or without skin grafting, within 21 days. The aims of relatively early skin grafting are to allow the superficial area to heal, to reduce the risk of infection and inflammatory syndrome and to improve the functional result by minimizing the risk of scar formation.(26) This approach may have led to a relatively high number of skin grafts in our study.

Scar formation is one of the most important outcomes that is evaluated rarely in children with partial thickness burns.(1) Adequate follow-up and evaluation of the scars with validated measurement tools is vital to manage scar formation. Cubison et al. demonstrated that hypertrophic scars had developed four months post burn in children with a TBSA of

more than 5%.(27) Therefore, we evaluated our patients at 3 and 6 months post burn. To our knowledge, no previous study evaluated the scar formation with a validated method in pediatric patients with partial thickness burns that were treated with Suprathel®. In adults, treatment with Suprathel® has shown a better scar quality compared to STSG in the treatment of partial thickness burns after 90 days post burn.(8) On the other hand, two other studies have shown no difference in hypertrophic scar formation when Suprathel® was compared to Omiderm® or Biobrane® in the treatment of partial thickness burns in adults.(18, 19) We found favorable scar quality in our study after 6 months post burn according to the POSAS scores.

Suprathel® forms a surrogate, natural barrier for microorganisms, that is intended to prevent accumulation of wound exudate and contains polylactic acid which reduces the local wound pH.(28) These properties may theoretically minimize the risk of wound colonization and wound infection and may therefore support optimal reepithelialization. However, an in vitro study by Ryssel et al. showed insufficient evidence for an antiseptic effect of Suprathel®.(28) Our study seems to support these results since the number of patients with a colonized wound did not decrease after application of Suprathel®. Nevertheless, the current study found no apparent difference in reepithelialization between wounds with and without bacterial colonization. The role of microorganisms in delayed wound healing is not clearly established(29). Some studies found that the concentration of microorganisms is an important determinant for wound healing process(30-32), while other studies found the role of microorganisms less important in delayed wound healing.(33-35) On the contrary, the only patients with wound infection in our study had delayed reepithelialization. In the literature, the association of burn wound infection and delayed reepithelialization is well established.(36, 37)

This study found minimal changes between background pain and procedural pain. There was a statistically significant increase in COMFORT-B scores in the youngest children, but the difference in scores was minimal and may not be clinically relevant. Everett et al. also found minimal pain levels after application of Suprathel® on the wound in the treatment of partial thickness burns in children.(9) An explanation for these minimal changes between background pain and procedural pain might be that no manipulation of the wound bed occurs when Suprathel® adheres to the wound bed. Manipulation of the wound bed is the main cause of the procedural pain which is the most intense pain in burn patients. (38, 39) Inadequate management of burn injury pain increases patients' anxiety for the dressing changes, reduces the effectiveness of analgesia and, in the long-term, changes pain perception and related behaviours.(40-42) Thus, novel burn treatments focus on reducing burn injury pain for instance by reducing the number of dressing changes. One study described analgesic response of the outer layer dressing changes as "very good" to "excellent" in children with partial thickness burns that were treated with Suprathel®.

However, pain was not scored with a validated measurement tool in this study.(6) Studies in adult patients have shown lower pain scores for patients that were treated with Suprathel® compared to Omiderm® and Mepilex® in the treatment of partial thickness burns and donor sites of skin grafts, respectively.(7, 43)

Since Suprathel® is porous and permeable to fluid it requires an outer layer absorbing dressing to absorb the extensive amount of wound exudate. The number of outer layer dressing changes is not previously described in studies in patients with partial thickness burns that were treated with Suprathel®. The number of outer layer dressing changes in our study is comparable with the mean number of dressing changes between 1.5 and 7.5 in RCTs that used (semi)synthetics dressings in the treatment of partial thickness burns in children.(23, 24, 44, 45)

A limitation of this study is the small sample size so that the power of the study was too low to detect clinically relevant differences between subgroups of patients. Another limitation of this study is that the burn depth was evaluated only by clinical assessment. It has been demonstrated that the combination of the clinical assessment and Laser Doppler Imaging (LDI), that evaluates the difference in perfusion of the microvascular blood flow of the wound, is more accurate and reliable way to evaluate the burn depth than clinical evaluation only.(46) Finally, no comparison with other (semi) synthetic wound dressing is performed in this study due to the non-comparative nature of this study.

CONCLUSION

Our study on the usability and effectiveness of Suprathel® in the treatment of partial thickness burns in pediatric patients found potential advantages of Suprathel® treatment regarding pain and scar formation as compared to published results on (semi)synthetic dressings in the literature. No clear advantages were found regarding reepithelialization, need for grafting, wound colonization and infection and dressing changes. In addition, extensive wound debridement is needed to achieve adequate Suprathel® adherence. Randomized controlled trials are needed to evaluate the efficacy of Suprathel® compared to other (semi)synthetic dressings in the treatment of partial thickness burns in pediatric patients.

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Part III

Partial thickness burn wounds in adult patients

Chapter 6

Clinical effectiveness, quality of life and cost-effectiveness of Flaminal® versus Flamazine® in the treatment of partial thickness burns: study protocol for a randomized controlled trial

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ABSTRACT

Background: Partial thickness burns are painful, difficult to manage and might have a negative effect on quality of life through scarring, permanent disfigurement and loss of function. The aim of burn treatment in partial thickness burns is to save lives, stimulate wound healing by creating an optimumly moist wound environment, to have debriding and analgesic effect, protect the wound from infection and be convenient for the patient and caregivers. However, there is no consensus on the optimal treatment of partial thickness wounds. Flaminal® and Flamazine® are two standard treatment options that provide the above mentioned properties in burn treatment. Nevertheless, no randomized controlled study yet compared these two common treatment modalities in partial thickness burns. Thus, the aim of this study is to evaluate the clinical effectiveness, quality of life and cost-effectiveness of Flaminal® versus Flamazine® in the treatment of partial thickness burns.

Methods/Design: In this two-arm open multicenter randomized controlled trial, 90 patients will be randomized between Flaminal® and Flamazine® and followed for 12 months. The study population will consist of competent or temporary non-competent (because of sedation and/or intubation) patients, 18 years of age or older, with acute partial thickness burns and a total body surface area (TBSA) of less than 30%. The main study outcome is time to complete re-epithelialization (greater than 95%). Secondary outcome measures include need for grafting, wound colonization/infection, number of dressing changes, pain and anxiety, scar formation, health-related quality of life (HRQoL), and costs.

Discussion: This study will contribute to the optimal treatment of patients with partial thickness burn wounds and will provide evidence on the (cost-)effectiveness and quality of life of Flaminal® versus Flamazine® in the treatment of partial thickness burns.

BACKGROUND

Partial thickness burn wounds are painful, difficult to manage, and susceptible to infection.(1) The aim of burn treatment in partial thickness burns is to promote rapid wound healing, decrease pain and suffering, protect the wound from infection, minimize scar formation and functional impairment, and to enable patients to return to normal daily activities as soon as possible.(2, 3) Thus, an ideal dressing should stimulate wound healing by creating an optimum moist wound environment, but also have a debriding and analgesic effect. Moreover, an ideal dressing should protect the wound from infection and be convenient for the patient and caregivers.

Nowadays, many topical dressing materials are available for the treatment of superficial and deep partial thickness burns, while there is no strong evidence to support their use.(4) In clinical practice, silver-containing dressings and topicals, in particular silver sulfadiazine (SSD), have been the most commonly used burn wound dressing in the treatment of partial thickness burns for over 30 years.(4-8)

The popularity of SSD can mainly be explained by its antimicrobial effect in vitro against a wide range of gram-positive and gram-negative microorganisms including resistant forms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE), and against fungi and anaerobes.(9-11) However, a Cochrane review of 26 randomized controlled trials (RCTs) found insufficient evidence to establish whether silver-containing dressings or topical agents prevent wound infection more effectively compared to non-silver containing treatments.(12)

Several studies have shown that silver is highly toxic to both keratinocytes and fibroblasts in in vitro models.(7, 13-15) Other studies found that SSD will form a pseudoeschar which can promote bacterial proliferation and requires frequent removal or debridement on a daily basis to facilitate re-epithelialization and the optimal assessment of the wound state. In contrast, two other studies found that some silver preparations are not toxic and suggest positive effects of silver on wound healing.(16, 17) A number of systematic reviews of clinical trials showed that SDD is consistently associated with poorer wound healing than non-silver treatment for superficial and partial thickness burns.(4, 18, 19) However, the results of these reviews should be interpreted with caution because of the high risk of bias in these clinical trials. With regard to costs, a number of studies suggested that SDD is less cost-effective than Mepilex® Ag, Aquacel® Ag and Acticoat®.(20-24)

Recently, Flaminal® (Flen Pharma, Kontich, Belgium) was introduced onto the market. Flaminal® consists of hydrated alginates polymers in a polyethyleneglycol (PEG) matrix embedded with a biologic enzyme system based on glucose oxidase and lactoperoxidase that are stabilized by guaiacol.(15) This enzyme system forms free radicals which destroy the cell wall of absorbed bacteria. Furthermore, short chain PEG dissolves dry scab and necrotic material which results in lysed material. Wound exudate, including bacteria, and lysed material are absorbed by alginates in hydrated form. These two steps result in continuous debridement.(25, 26)

Pre-clinical data by Vandenbulcke et al. and de Smet et al. showed that Flaminal® Forte is not toxic to keratinocytes and fibroblasts in vitro.(15, 27) In effect, Flaminal® Forte may not damage skin cells which will finally result in undelayed wound healing. Two studies have indicated a faster wound healing when a partial thickness burn wound was treated with Flaminal® Forte compared to SSD.(28, 29) But these results should be interpreted with caution due to the retrospective design of these studies. However, a shorter wound healing time would not only reduce length of hospital stay (LOS) but probably also scar formation since Deitch et al. and Cubison et al. demonstrated that burn wounds which heal within 21 days have less risk of developing hypertrophic scars and contractures.(1, 30)

There are studies showing conflicting data with respect to bacterial growth under Flaminal® Forte; with some demonstrating count reductions(15, 27) while others show increases.(29)

Dressings with SSD should be changed every 24 hours, and removing the pseudoeschar, which is a result of the SSD base drying out, is usually painful. In contrast, Flaminal® Forte can be applied every other day after the third post-burn day (PBD) and can be removed easily from the wound. However, the effect on pain perception and anxiety during dressing changes between these treatments have not yet been compared. Also, the effect of both treatments on LOS, scarring and Health-related quality of life (HRQoL) are not known.

Finally, medical costs including those for medical staff, materials for wound care, surgical procedures, hospital stay, HRQoL, and productivity loss due to the burn injury are unknown for both treatments. A cost-effectiveness analysis is thus mandatory to evaluate the long-term health economic outcomes of the studied treatments and justify the application of both treatments in clinical practice.

Objectives

The aim of this study is to evaluate the clinical effectiveness, quality of life and cost-effectiveness of Flaminal® versus Flamazine® (SSD) in the treatment of partial thickness burns.

METHOD/ DESIGN

This investigator initiated, open label, multi-center, RCT compares the effects of treatment and cost-effectiveness of Flaminal® Forte versus Flamazine® in the treatment of partial thickens burns.

Study population

The study will be performed in two of the three burn centers (Beverwijk and Rotterdam) in the Netherlands. In these burn centers, both Flaminal® and Flamazine® are therapeutic options for treating partial thickness burns. Patients who are admitted to the Beverwijk or Rotterdam Burn Centre and who meet the following inclusion criteria will be eligible for this study: competent or temporarily non-competent (because of sedation and/or intubation); partial thickness burns of minimally 1% total body surface area (TBSA) (possibly in combination with full thickness burns); hospital admission within 48 hours of burn injury; written informed consent by the patient. Patients meeting one or more of the following criteria are excluded: age below 18 years; TBSA more than 30%; burns caused by chemicals, electricity or radiation; if local therapy with a topical agent has already started; patients who are expected (according to the treating medical physician) to be non-compliant with the study protocol.

Recruitment, consent and randomization

All patients who are admitted to the burn center undergo standardized screening and baseline procedures according to the local protocol. The local investigator will check the inclusion and exclusion criteria of the study and will inform the participant about the study. If the participants are willing to participate in this study, they must provide written informed consent. If an eligible patient is temporarily non-competent because of sedation and/or intubation, a legal representative of the patient, according to the Dutch Medical Treatment Act (WGBO), will be informed about the study and will provide written informed consent. After the sedation or intubation has ended, the patient will be asked to confirm willingness to participate in the study in writing, otherwise the participation is discontinued and the collected study data will be destroyed.

After informed consent has been obtained, the largest partial thickness area will be assigned as the study area. Thereafter, the patient will be randomly assigned to one of the two study arms using TenALEA (Trans European Network for Clinical Trials Services), an online randomization program (www.flam-studie.nl). The online-randomization is stratified by center and uses variably sized blocks in a 1:1 ratio. In both participating hospitals the local trial coordinator will receive a username and password for online randomization. After randomization the local trial coordinator of that center and the central trial coordinator will receive an email with the inclusion number and the randomization outcome. The outcome will also be displayed on the website, only visible for the randomizing local and central trial coordinators. Then, all the burn wounds will be treated with the treatment that is assigned by the randomization.

When the study area that was initially assessed as a partial-thickness burn, turns out to be a full-thickness burn area after performing Laser Doppler Imaging (LDI), then the study area will be replaced: the second largest partial-thickness area (confirmed by LDI) will then be chosen as the study area.

For practical reasons it is not possible to blind the patients. It is also impossible to blind the medical staff who provide the burn wound care, because they are involved in all aspects of the care and are able to recognize each treatment from its appearance. No blinding of other outcomes is also possible for the same reasons.

Interventions

The patient will be allocated to one of the following treatments.

Flaminal® Forte

Treatment with Flaminal® Forte (glucose oxidase-lactoperoxidase guaiacol complex of 50 g in 5.5% alginogel) will be initiated within 24 hours after admission. Before applying Flaminal® Forte on the wound, pain medication must be given. Paracetamol, Oxynorm and Oxycontin will be used as standard pain medication. The usage and doses of pain medication will be monitored. The burn wound will be cleaned and rinsed with Prontosan® followed by careful dabbing and drying of the wound. The wound will then be covered with a non-adhesive dressing on which a sufficiently thick layer (4-5 mm) of Flaminal® Forte has been applied. A net bandage/ dressing will be used to keep the dressing in place. Dressing changes will be performed daily during the first three days post burn and thereafter every other day. If an infection is suspected, or in case of leaking or insufficient gel, the dressing with Flaminal® Forte may be changed daily after three days post burn. In case of wound colonization or infection, treatment with Flaminal® Forte will be changed to another relevant treatment based on the results of the wound culture.

Flamazine®

Treatment with Flamazine® (silver sulfadiazine 10 mg/g in hydrophilic crème base) will consist of daily washing and application of Flamazine®. Before applying Flamazine® on the wound, pain medication must be given. Paracetamol, Oxynorm and Oxycontin will be used as standard pain medication. The usage and doses of pain medication will be monitored. The burn wound will be cleaned and rinsed with Prontosan® followed by carefully dabbing and drying of the wound. A sufficiently thick layer (at least 2-3 mm) of Flamazine® will be applied directly on the wound. The cream will be covered with a non-adhesive dressing. A net bandage/dressing will be used to keep the dressing in place. This procedure is repeated once every 24 hours until the sixth day post burn. Thereafter, the treatment of all patients in this study arm will consist of Furacine Soluble Dressing (Furacine 2mg/g ointment) on the seventh day post-

burn, and Flamazine® on the eighth day post-burn. Treatment with Furacine Soluble Dressing and Flamazine® will be alternated until complete wound healing/operation because of the cytotoxicity of the silver particles in Flamazine® on the wound bed when used continuously. In case of wound colonization or infection the treatment will be replaced with another relevant treatment based on the results of the wound culture.

After discharge, patients in both group will be treated in an outpatient setting, according to the local protocol

Outcome measures

Primary outcome

Primary endpoint is time to complete re-epithelialization (greater than 95%) of the study area, in days, judged by two experienced burn specialists during each dressing change. Complete re-epithelialization of the study area is only affirmed when the two burn specialists agree with each other.

Secondary outcomes /study parameters

Clinical outcomes

- Need for operation which is evaluated between 10 and 14 days post burn. Reasons for operation are that the experienced burn specialist expects no further wound healing in the next 7 to 11 days of the partial thickness area or a full thickness burn. If the decision to graft is made before 10 to 14 days post-burn then the operation will still performed before 10th day post-burn day. The only indication for operation before the tenth post-burn day is when partial thickness burn becomes a full partial thickness burn. The treatment of full thickness burns is split skin graft in an early stage.
- Percentage TBSA of the study area that covered with skin graft
- Colonization: twice a week a wound swab will be taken from the study area. The wound swab will then be sent for laboratory investigation. In brief, the analysis of the wound swab will include the following steps. The microscopic examination will entail gram staining. Thereafter, a quantity of the specimen will be cultured to obtain a pure single specimen culture. Finally, the sensitivity of the organisms to specific local therapy will be determined. In case of wound colonization the treatment will be changed to another relevant treatment based on the results of the wound culture.
- Infection: infection is suspected if a combination of skin redness, pain, swelling, tenderness, warmth, fever or pus draining from the wound is present. Infection is a clinical evaluation of the wound, in presence of absence of positive wound culture, and is judged by a physician at the burn center during each dressing change.
- Number of dressing changes
- Use of systemic antibiotics

Patient-reported outcomes

- Pain will be measured during the application and removal of the wound dressing (procedural pain, measured directly after dressing change) and background pain (measured in the morning and evening). Pain will be measured twice daily during hospital admission by use of a Visual Analogue Thermometer (VAT), which is a numeric scale from 0 (no pain) to 10 (worst imaginable pain).
- Itching will be measured daily in the evening during hospital admission by use of a VAT.(31)
- Anxiety: the Burn Specific Pain Anxiety Scale (BSPAS) will be scored on day 7 ± 2 post-burn and on the day of discharge. The BSPAS is a valid and reliable nine-item self-report scale for the assessment of pain-related and anticipatory anxiety in burned patients.(32, 33)
- Health-related quality of life (HRQoL) will be measured using the following questionnaires, in the week before discharge and at 3, 6 and 12 months post-burn:
    - Burn-specific quality of life (QoL) will be measured using the Dutch version of the Burn Specific Health Scale (BSHS)–Brief.(34, 35) The BSHS-Brief is a valid and reliable self-administered questionnaire that covers nine domains (heat sensitivity, affect, hand function, treatment regimens, work, sexuality, interpersonal relationships, simple abilities, and body image). The questionnaire takes 10–15 minutes to complete and 5 minutes to score. Responses are scored by the patient on a five-point scale from 0 (extreme) to 4 (none/not at all) for each of the 40 items. Mean scores are calculated for each of the domains.
    - General HRQoL will be measured using the EuroQol-5D (EQ-5D) questionnaire.(36) This simple and generic description of health status is widely used in studies on clinical and economic appraisal. The EQ-5D outcomes will be converted in utility scores between 0 (death) and 1 (perfect health) based on empirical valuations. (37) From the area under the utility curve during the 12 months of follow-up quality adjusted life years (QALYs) will be calculated.

Scar formation

The following aspects of scar formation will be measured after 3, 6 and 12 months post burn:

- Scarring will be measured using the Patient and Observer Scar Assessment Score (POSAS), a valid and reliable scale that is designed for the evaluation of all types of scars by professionals and patients. It consists of two numeric scales: the Patient Scar Assessment Scale which is completed by the patient and the Observer Scar Assessment Scale which is completed by the medical staff. The variables scored by the patient are pain, itching, color, stiffness, thickness and irregularity.(38, 39)The variables scored by the medical staff include vascularization, pigmentation, thickness, relief and pliability.

- Elasticity will be measured using a Cutometer (Courage& Khazak), a validated instrument to measure the vertical deformation of the skin in millimetres when the skin is pulled by means of a controlled vacuum into a circular aperture.(40)
- Scar colour and pigmentation will be measured using the DSM II colorimeter (Dermaspectrometer).This is a validated instrument to measure scar colour by a narrow-band simple reflectance meter.(40)

Total (medical and non-medical) costs

Total costs in this study represent direct health care costs (inpatient and outpatient medical costs), direct non-healthcare costs and indirect non-health care costs (productivity loss). Personnel time and used materials for wound care and surgical procedures, hospital days for initial stay and re-admittance and outpatient visits during the first year will be measured prospectively as part of the case record form. Health resource use outside the hospital, travel costs and productivity losses will be recorded by questionnaires filled out by the patients at 3, 6 and 12 months post burn. Cost of dressing changes and surgical procedures will be assessed by translating the personnel time and used materials into costs by means of gross salaries and market prices. The costs of hospital stay and outpatient care in burn centers will be calculated by multiplying the number of hospital days respectively outpatient visits with their cost prices(41). Other healthcare use will be translated into costs by standard prices(42). Productivity losses will be valued using the friction cost method.(43)

Baseline parameters

Age, gender, skin type, wound aetiology, bacterial contamination at admission, location of the wound, type of wound, TBSA% and co-morbidities. In all patients, the burn depth of the study area will be accurately determined on day 2-5 post burn day by clinical evaluation and LDI scan using the MoorLDI2-Burn Imager™ (Moor Instruments, Amnixter, UK) and, based on pre-defined criteria (Table 1), be classified as superficial, intermediate or deep partial thickness injury. The size of each burn wound is then estimated in TBSA.

In a LDI the low intensity laser beam is scanned across a tissue surface in a raster fashion using a moving mirror. There is no direct contact with the tissue being assessed. The wounds are scanned by a trained research physician or nurse, after removal of topical medication (during regular wound treatment). All research physicians and nurses in both burn centers have followed the same training sessions and have the same experience. The scanning will take 1 – 5 minutes.

A schedule with baseline and outcome measurements during the study is presented in Table 2.

Table 1. Clinical assessment and LDI results.

Classification	Clinical properties						LDI colour
	Blisters	**Colour/ appearance**	**Pliability**	**Capillary refill**	**Pain**	**Healing time**	
Superficial partial thickness burns	Small blister: intact and open	Pink-red, shiny	Supple	< 2sec	++	Within 14 days	Red
Intermediate partial thickness burns	Blisters: intact and open	Pink-red, shiny and dry	Mix of supple and stiff	< 2 sec	+	14-21 days	Yellow
Deep partial thickness burns	Blisters: intact and open	Red, shiny and dry	Mix of supple and stiff	>2 sec	+/-	>21 days or even no spontaneous healing	Blue
Full thickness burns	Non	White-yellow, red, brown and black	Stiff	>2 sec	-	No spontaneous healing	Blue

Sample size calculation

The study is designed to demonstrate a clinically relevant difference regarding time to complete epithelialization between the treatment arms. Based on a retrospective study of 70 patients with superficial and deep partial thickness burns of the hand, we expect wounds to heal in 11 days on average with Flamazine® and in 6 days on average with Flaminal® (pooled standard deviation 7.5 days).(28) With alpha set at 5%, 41 patients are needed in both intervention arms to detect a difference in wound healing time with 80% power. To allow for 10% attrition, a total of 90 patients will be included in the study.

Statistical analysis

The analysis will be performed according to the intention-to-treat principle. The baseline patient characteristics will be described as mean ± standard deviation for normally distributed continuous variables, as median (range) for skewed continuous variables, and as number (proportion) for categorical variables. Differences in time to complete re-epithelialisation will be compared in both treatment groups will be analyzed with Kaplan-Meier curves and log rank test. If the baseline characteristics seem unbalanced despite randomization, a multivariable Cox regression analysis will be performed to correct for potentially confounding variables to confirm the primary analysis.

The secondary clinical and patient-reported outcomes on specific follow-up moments will be compared between the treatment groups using the two-sided t-test or Mann-Whitney test for continuous data, and a two-sided Chi-square test or Fisher's exact test for categorical data. Repeatedly measured study parameters such as pain and quality of life will be also analyzed using a linear mixed model with treatment as fixed effect and patient as random effect. In the analyses, p-values < 0.05 will be considered statistically significant.

Economic evaluation

The economic analysis will be performed from the societal perspective. The follow-up period is 12 months. Due to this short time frame, no discounting will take place. Cost-effectiveness ratios will be calculated by dividing the difference in average costs per patient between both intervention groups by the difference in primary outcome (time to complete re-epithelialisation). Dressing changes are reported to be one of the most painful and traumatic aspects of burn treatment. This impact is not measured in the primary outcome measure (time to greater than 95% re-epithelialization). In a sensitivity analysis, therefore, the difference in costs will be related to the difference in dressing changes between both treatments.

Table 2. Time schedule for study procedures and assessments.

Procedure/ assessment	**Admission**	**Treatment phase**	**Follow-up (month)**		
			3	6	12
Standard screening, baseline procedures	x				
Check eligibility (inclusion criteria)	x				
Provide patient Information	x	x (confirmation by patients who were initially			
Obtain written informed consent	x	incompetent)			
Randomization (Flaminal® vs Flamazine®)	x				
Baseline parameters	x				
LDI		x			
Wound colonisation	x	x			
Wound healing		At each dressing change			
Need for surgery of partial and/or full thickness burns and % of study area requiring skin graft		10-14 PBD			
Colonization	x	Swabs on Mondays and Thursday			
Infection	x	Clinical judgment during dressing changes			
Dressing changes	x				
Use of systemic antibiotics	x				
Pain and Anxiety	x				
- Visual analogue thermometer **(VAT)** and	x	- Daily, before and after dressing change and			
Itching	x	in the evening			
- Burn Specific Pain and Anxiety Score		- On the day of discharge			
(BSPAS)					
Health-related quality of life (HRQoL)					
- Burn Specific Health Scale Brief **(BSHS-B)**		In the last week of hospitalization	x	x	x
- EuroQol5D **(EQ-5D)**			x	x	x
Scarring					
- POSAS			x	x	x
- Cutometry			x	x	x
- Dermaspectrometry			x	x	x
Costs		Daily	x	x	x

Ethical consideration and safety

This study has been approved by the Medical Research Ethics Committee of Noord-Holland (NL43671.094.13). EudraCt number: 2013-000901-21. This study is also registered in the Netherlands Trial Registry (NTR), trial number 4486 and will be conducted in agreement with the Declaration of Helsinki, version Fortaleza (Brazil), October 2013, concerning the Ethical Principles for Medical Research Involving Human Subjects, and in accordance with the International Conference on Harmonization (ICH) of Good Clinical Practice (GCP) Guidelines and the valid Dutch laws. Adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) are documented and reported to the competent authorities. All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. There is no additional risk or discomfort for the patients in this study compared to daily practice. Since most of the measurements and questionnaires used in the study are also implemented in daily care of burn patients in the Dutch burn centres, participation does not involve a large extra burden for the patients.

DISCUSSION

This randomized controlled study will enable a comparison of the effectiveness, cost-effectiveness and quality of life of Flaminal® and Flamazine®, two common treatment modalities for partial thickness burns.

An accurate diagnosis of the partial thickness burns is essential in our study. Several studies have shown that clinical evaluation of burn depth is highly dependent on the experience of the clinician and that experienced clinicians are accurate in about 50-75% of the cases.(44-48) Therefore, we use LDI, which has an accuracy of 95% in combination with clinical evaluation of the wound, for measuring burn depth. (48-50) Furthermore, in our study two experienced wound specialists must agree on the time to complete re-epithelialization in order to optimize the accuracy of wound re-epithelialisation. Bloemen et al. have shown that experienced observers are able to evaluate the re-epithelialization rate in a reliable and effective way.(51) No digital analysis is required to evaluate wound re-epithelialization since clinical evaluation by an experienced burn specialist is as equally effective as digital analysis.(52)

This study will contribute to optimize the treatment of patients with partial thickness burn wounds from both the clinical and economical perspective.

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Chapter 7

Flaminal® versus Flamazine® in the treatment of partial thickness burns: a randomized controlled trial on clinical effectiveness and scar quality (FLAM study)

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ABSTRACT

Although partial thickness burns are the most frequently reported burn injuries, there is no consensus on the optimal treatment. The objective of this study was to compare the clinical effectiveness and scar quality of Flaminal® Forte to silver sulfadiazine (Flamazine®) in the treatment of partial thickness burns. In this two-arm open label multi-center randomized controlled trial, adult patients with acute partial thickness burns and an affected *total body surface area* of less than 30% were randomized between Flaminal® Forte and Flamazine® and followed for 12 months. Dressing changes in the Flamazine® group were performed daily, and in the Flaminal® group during the first three days post burn and thereafter every other day until complete wound healing or surgery. Forty-one patients were randomly allocated to Flaminal® Forte and 48 patients to Flamazine®. The primary outcome was time to wound healing, which did not differ between the groups: median 18 days with Flaminal® Forte (range 8 - 49 days) versus 16 days with Flamazine® (range 7 - 48 days; $p = 0.24$). Regarding the secondary outcomes during hospital admission, there were no statistically significant differences between the groups concerning need for surgery, pain scores, pruritus, or pain-related and anticipatory anxiety. More patients in the Flaminal® group developed wound colonisation (78% versus 32%, $p < 0.001$), but the treatment groups did not differ regarding the incidence of local infections and use of systemic antibiotics. In terms of scar quality, no statistically significant differences between both treatment groups were found regarding subjective scar assessment (Patient and Observer Scar Assessment Scale (POSAS)), scar melanin and pigmentation (DermaSpectrometer®) and scar elasticity and maximal extension (Cutometer®) during 12 month post-burn. In conclusion, time to wound healing did not differ, but the use of Flaminal® Forte seemed favourable because less dressing changes are needed which lowers the burden of wound care.

INTRODUCTION

Although various treatment modalities are available for partial thickness burns none of these are generally accepted as standard or optimal care.(1) Since decades, silver sulfadiazine (SSD), such as Flamazine®, has been used for treatment of partial thickness burns.(1-5) The widespread use of SSD may be explained by its broad antimicrobial effect in vitro.(4, 6, 7) However, a Cochrane review of clinical studies showed that SSD does not prevent wound infection better than non-silver containing comparators.(8) Several studies have also shown considerable disadvantages of SSD despite its popularity. SSD is highly toxic to the wound bed, forms a pseudoeschar that can lead to bacterial proliferation and impaired wound assessment, requires daily dressing changes and is consistently associated with poorer wound healing of partial thickness burns compared to non-silver treatments.(1, 3, 9-11)

To overcome the limitations of SSD, various local therapies have been developed. Several systematic reviews showed that in more than half of the studies that wound healing time was shorter with viscous dressings (e.g. Flammacerium®, honey based wound dressings, Silvazine®), solid dressings (e.g. Acticoat®, Aquacell®, Mepitel®, Biobrane® and Trancyte®) and biologicals dressings (e.g. Xenoderm, Amnion) compared with SSD.(1, 9, 12-14) However, only studies with honey based wound dressings showed consistently better results for wound infection compared with SSD.(13) In general, solid dressings needed less dressing changes, while their application was found to be more difficult in some anatomical locations compared to SSD. (12) These results should be interpreted in light of the paucity of high-quality evidence, high risk of bias, limited number of included patients and unclear role of sponsorship in the majority of the included clinical trials. Therefore, no firm conclusion regarding the effectiveness of the studied local treatments of partial thickness burns can be drawn based on these systematic reviews.

In recent years, Flaminal® Forte (Flen Pharma, Kontich, Belgium) used for the treatment of burn wounds, has gained popularity, in particular because Flaminal® Forte does not requires daily dressing change. Flaminal® Forte is composed of hydrated alginate polymers with a biologic enzyme system that is based on glucose oxidase and lactoperoxidase stabilised by guaiacol. Due to its composition, Flaminal® Forte is expected to have an antimicrobial and continuous debriding effect.(15-17) In vitro studies have shown that Flaminal® Forte is not toxic to keratinocytes and fibroblasts,(15, 18) and that it reduces wound colonization by a wide range of Gram-negative and Gram-positive micro-organisms.(15, 18) However, one retrospective clinical study found significantly more bacterial growth in partial thickness burns when treated with Flaminal® compared to SSD.(19) Furthermore, two retrospective studies showed faster wound healing when partial thickness burns were treated with Flaminal® compared to SSD. (19, 20)

To the best of our knowledge, there is a paucity of evidence for Flaminal® Forte in the treatment of partial thickness burns. Available evidence is based on retrospective studies with a limited number of studied patients and relevant outcomes. Despite the limitation of these studies, Flaminal® Forte might have advantages such as faster wound healing and less dressing changes compared to Flamazine®, while the preventing effect on wound colonisation and infection remains unclear.

Therefore, we performed a multicentre randomized controlled clinical trial in which the clinical effects, quality of life and cost-effectiveness of Flaminal® Forte and Flamazine® in the treatment of partial thickness burns were compared. This first part of the paper reports on the clinical effectiveness and scar quality of Flaminal® Forte and Flamazine® during the clinical treatment phase of partial thickness burns with a follow-up of 12 months.

MATERIALS AND METHODS

Study design and randomization

In this investigator-initiated, open label, multi-centre, randomized controlled trial (RCT) we compared the clinical effectiveness of Flaminal® Forte versus Flamazine® in the treatment of partial thickness burns. An extensive description of the study protocol was published previously.(21) The results are reported following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.(22) The study was conducted in compliance with the ethical rules for human experimentation that are stated in the 1975 Declaration of Helsinki and approved by the Medical Research Ethics Committee Noord-Holland (NL43671.094.13). The study was registered in the European Clinical Trials Database (*EudraCT number*: 2013-000901-21) and the Netherlands Trial Registry (trial number 4486).

Patients

Patients were enrolled in this study from February 2014 until September 2015 in two burn centres in the Netherlands (Red Cross Hospital, Beverwijk and Maasstad Hospital, Rotterdam). In these burn centres, both Flaminal® and Flamazine® are already commonly used for treating partial thickness burns. Patients were eligible for the study if they had partial thickness burns of minimally 1% affected total body surface area (TBSA) based on clinical evaluation and Laser Doppler Imaging (possibly in combination with full thickness burns); were admitted to the hospital within 48 hours of the burn injury; were mentally competent or temporary incompetent (because of sedation and/or intubation) and provided written informed consent. The exclusion criteria were age < 18 years; TBSA of > 30%; burns caused by chemicals, electricity or radiation; if local therapy had already started; or if the treating physician expected that the patient would not comply with the study protocol.

Study procedure and randomization

Either the local investigator or the on-call burn physician/ -surgical resident informed the eligible patients about the study and randomized the participants after they had provided informed consent. If a patient was temporarily incompetent, a legal representative of the patient was informed about the study and provided informed consent. In these cases, informed consent was obtained from the patient as soon as possible. If these patients did not confirm the consent provided by their legal representative, they were withdrawn from the study. Their collected study data was deleted and the allocated treatment was continued as usual care.

Patients were randomly assigned to treatment with either Flamazine® or Flaminal® Forte, using the online randomization program TenALEA (Trans European Network for Clinical Trials Services). The randomization was stratified by centre and used variably sized blocks in a 1:1 ratio. The patients and medical staff who provided the burn wound care could not be blinded because both treatments can be recognised by their appearance. Also, the observers could not be blinded because they were involved in the clinical care of the participants.

Interventions

The patients received treatment with either Flaminal® Forte (Glucose oxidase-Lactoperoxidase Guaiacol complex of 50 g in 5.5% alginogel) manufactured by Flen Pharma, Belgum or Flamazine® (containing silver sulfadiazine 10 mg/g in hydrophilic crème base) manufactured by Sinclair Pharmaceuticals, Surrey, United Kingdom.

Treatment with Flaminal® Forte consisted of cleaning and rinsing the burn wound with Prontosan® (containing 0.1% Polyaminopropyl Biguanide (Polihexanide), Betaine Surfactant and purified water) manufactured by B. Braun, Switzerland. Thereafter, a sufficiently thick layer (4 - 5 mm) of Flaminal® Forte was applied on a non-adhesive dressing and applied on the burn wound. A net bandage was used to keep the dressing in place. Dressings were changed daily during the first three days post burn and thereafter every other day until complete wound healing or surgery.

Treatment with Flamazine® also started with cleaning and rinsing the burn wound with Prontosan®, followed by application of Flamazine® on the burn wound and coverage with a net bandage to keep the dressing in place. This procedure was repeated once every 24 hours until the sixth day post burn. Thereafter, Furacine Soluble Dressing (Furacine 2mg/g ointment) was applied on the burn wound on the even post-burn days and Flamazine® on the odd post-burn days until complete wound healing or operation. The alternation of treatment in this study arm was justified because of the cytotoxicity of the silver particles in Flamazine® in the wound bed when used continuously.

In case of wound colonization or infection, the treatment with either Flaminal® Forte or Flamazine® was changed to the relevant treatment based on the results of the wound culture. Treatment of colonized wounds required daily dressing changes, which could influence the number of daily dressing changes in both treatment groups. Need for split skin graft was evaluated between 10 and 14 days post-burn. Partial thickness burn wounds that were not expected to heal within 21 days, were excised and skin grafted, as this leads to a lower risk of hypertrophic scar formations. (23, 24) This treatment strategy is standard approach of treatment of partial thickness burns at the Dutch Burn Centres. After discharge, patients in both groups were treated in an outpatient setting according to the local protocol.

Baseline characteristics and outcome measures

The following baseline parameters were collected for both study arms: age, gender, wound aetiology, bacterial contamination at admission, location and type of the wound, TBSA and co-morbidities. The burn depth of the study area was accurately determined on day 2 - 5 post burn by clinical assessment and Laser Doppler Imaging (LDI), using a MoorLDI2-Burn Imager™ (Moor Instruments, UK) and based on pre-defined criteria.(21) Studies demonstrated that LDI has an accuracy of 95% in combination with clinical estimation, for assessing burn wound depth.(25, 26)

The primary outcome was time to wound healing, defined as the number of days until complete (defined as >95%) re-epithelialisation of the study area, as judged by two experienced burn specialists during each dressing change. Secondary outcomes were: The need for operation, performed between 10 - 14 days post-burn if the burn wound was not expected to heal; percentage TBSA of the study area that was covered with skin graft; post-surgical complications; number of dressing changes; length of hospital stay; wound colonisation; wound infection; use of systemic antibiotics; pain; anxiety; and pruritus. A wound swab was taken from the study area at admission and twice weekly. Infection was defined as a combination of skin redness, pain, swelling, tenderness, warmth, fever or pus draining from the wound in presence or absence of wound colonisation (established by wound culture). Pain of the study area was assessed every day in the evening (background pain) and before and during dressing change (procedural pain) using a Visual Analogue Thermometer (VAT) on a scale from 0 (no pain) to 10 (worst imaginable pain). Pruritus was assessed daily in the evening during hospital admission by use of a VAT on a scale from 0 (no pruritus) to 10 (worst imaginable pruritus).(27) The Burn Specific Pain Anxiety Scale (BSPAS) was used to assess pain-related and anticipatory anxiety in burn patients on the day of discharge.(28, 29) BSPAS consists of a nine-item self-report scale from 0 (not at all) to 100 (the worst imaginable way).

Scar quality

The scar quality of the study area was assessed at 3, 6 and 12 months post-burn in the outpatient clinic using different measurement instruments. First, the Patient and Observer Scar Assessment Scale (POSAS) was used on a scale from 1 (resembles normal skin) to 10 (worst imaginable scar). The POSAS is a reliable and validated scar assessment scale, which is designed to evaluate scars by both professionals and patients. The questionnaire consists of two separate six-item scales: the Patient Scar Assessment Scale (patient scale) and the Observer Scar Assessment Scale (observer scale). The six items scored by the patient are pain, itching, colour, stiffness, thickness and irregularity. The six items scored by the observer are vascularization, pigmentation, thickness, relief, pliability, and surface area. (30, 31)

Second, the DermaSpectrometer® (Cortex Technology, Hadsund, Denmark) was used to measure the scar erythema (color) and melanin (pigmentation). It is a validated instrument to measure scar vascularization (erythema) and pigmentation (melanin) by a narrow band simple reflectance meter. Results were calculated as absolute difference between scar tissue and the nonaffected skin. (32) Finally, scar elasticity (Ue) and maximal extension (Uf) in mm were measured with the Cutometer® (Courage & Khazaka GmbH, Cologne, Germany). Cutometer® is a validated instrument to measure the vertical deformation of the skin in millimetres when the skin is pulled by means of a controlled vacuum into a circular aperture. Results represent the ratio between scar tissue and nonaffected skin.(33)

Sample size calculation

Based on a retrospective study of 70 patients with partial thickness burns(20), we expected wound healing in 11 days on average with Flamazine® and 6 days on average with Flaminal® (pooled standard deviation 7.5 days). To identify such a clinically relevant difference regarding time to complete epithelialization between the treatment arms (with 80% power and alpha 5%), it was calculated that 41 patients per arm were needed. Assuming a 10% attrition rate, the sample size was fixed at 45 patients in each arm.

Statistical analysis

The data analysis was performed according to the intention-to-treat principle using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). The baseline patient characteristics were described as mean ± standard deviation for normally distributed continuous variables, as median (range) for skewed continuous variables, and as number (proportion) for categorical variables. The difference in time to complete re-epithelialisation was compared in both treatment groups and analysed with Kaplan-Meier curves and log rank test. To correct for potentially confounding variables, a multivariable Cox regression analysis was performed to confirm the primary analysis.

The secondary clinical and patient-reported outcomes on specific follow-up moments was compared between the treatment groups using a two-sided t-test or Mann-Whitney test for continuous data, and a two-sided Chi-square test or Fisher's exact test for categorical data. Repeatedly measured study parameters (pain, pruritus and scar quality) were analysed using a linear mixed model with treatment as fixed effect and patient as random effect. To check for effect-modification of the treatment differences by time, an interaction term (treatment*time) was added in de models. In the analyses a p-value < 0.05 was considered statistically significant.

RESULTS

Inclusion and baseline characteristics

From February 2014 until September 2015, 135 patients were eligible for the study, of whom 90 were randomized (Figure 1). Twelve patients were withdrawn from the study within two weeks after randomization for the following reasons: Five patients who had been intubated due to inhalation injury did not confirm the consent provided by their legal representative after detubation, two patients did not sufficiently speak the Dutch language, two patients lived outside of the Netherlands and could therefore not take part in the follow-up, two patients had TBSA of > 30% after reassessment of the wound during admission and one patient received other treatment than the allocated study treatment. The Medical Research Ethics Committee gave permission to randomize twelve more patients to replace the withdrawn patients and meet the required sample size. Eventually, 90 patients were included in the study, of whom 42 were randomized for treatment with Flaminal® Forte and 48 for treatment with Flamazine®. The imbalance in patient numbers between the study groups was caused by the additional inclusion of 12 patients replacing the patients who were excluded after randomization. A major protocol violation occurred in one patient who was randomized for Flaminal® Forte but crossed over to treatment with Flamazine® because of high pain levels with Flaminal® Forte during dressing changes.

The baseline characteristics of the analyzed patients are presented in Table 1. The patients in the Flaminal group were on average 7.6 years older compared with the Flamazine® group. The treatment groups were comparable regarding gender, percentage TBSA of the study area, trauma mechanism, anatomical location of the study area, comorbidity and wound colonisation at admission.

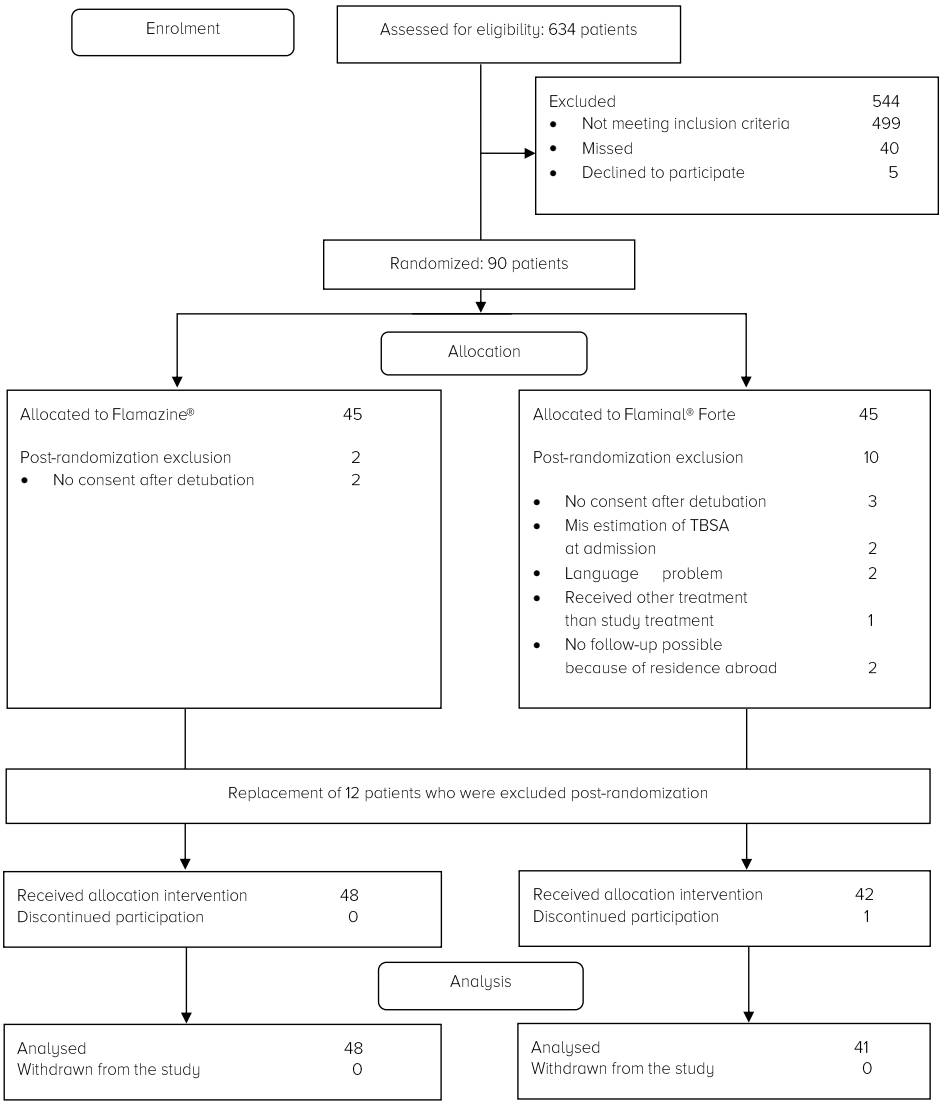

Figure 1. Flowchart of patients.

According to the protocol, dressing changes were less often performed during hospital admission in the Flaminal® group compared to the Flamazine® group ($p < 0.0001$): while the dressings of the patients in the Flamazine® group were changed every day, the dressings of the patients in the Flaminal group were changed on median 85% of the days admitted in hospital (range 52 - 100%).

Table 1. Baseline characteristics.

Characteristic	Flaminal® Forte (n = 41)	Flamazine® (n = 48)
Age in years, mean (SD)	50.2 (15.4)	42.6 (16.2)
Male gender, n (%)	32 (78)	39 (81)
Smoking, n (%)	12 (29)	16 (34)
%TBSA study area, median (range)		
- Partial thickness burns	3 (0.75 - 10)	3 (0.5 - 16)
- Superficial	1 (0 - 9)	1 (0 - 4)
- Intermediate	0.5 (0 - 3.5)	0.8 (0 - 7)
- Deep	0.25 (0 - 4)	0.18 (0 - 15)
On ventilation, n (%)	6 (15)	8 (17)
Duration in days, median (range)	3 (1 - 19)	3.5 (1 - 10)
Trauma mechanism, n (%)		
- Scald	4 (10)	7 (15)
- Flame	20 (49)	21 (44)
- Flash	12 (29)	16 (33)
- Hot grease	2 (5)	4 (8)
- Hot steam	3 (7)	0 (0)
Location of study area, n (%)		
- Head and neck	1 (2)	1 (2)
- Trunk (anterior)	10 (24)	6 (13)
- Trunk (posterior)	6 (15)	2 (4)
- Upper extremities	16 (39)	24 (50)
- Lower extremities	8 (20)	15 (31)
Comorbidity, n (%)		
- Diabetes	2 (5)	3 (6)
- Cardiovascular	8 (20)	3 (6)
- Renal disease	0 (0)	1 (2)
- Obesity	2 (5)	1 (2)
- Psychiatric disorder	6 (15)	2 (4)
- Malignancy	2 (5)	0 (0)
Colonization on admission, n (%)	4 (10)	8 (17)

Primary outcome: Wound healing

The median time to wound healing in the Flaminal® group was 18 days (range 8-49 days) compared with 16 days (range 7 - 48 days, Mann-Whitney test p = 0.24) in the Flamazine® group. Figure 2 shows the Kaplan-Meier curves of time to wound healing for the Flaminal® group and the Flamazine® group (log-rank test, p = 0.44). Given that the patients in the Flaminal group were on average more than 7 years older, a Cox proportional hazards model was performed to adjust for age, showing no difference in time to wound healing (hazard ratio 0.89 for Flaminal compared to SSD, 95% confidence interval [CI] 0.58-1.35,

p = 0.58). In the model, age was not associated with time to wound healing (hazard ratio per one-year increase 0.99, 95% CI 0.98 to 1.00, p = 0.19). Furthermore, no difference was found between the treatment groups with respect to time to wound healing of the non-operated study area.

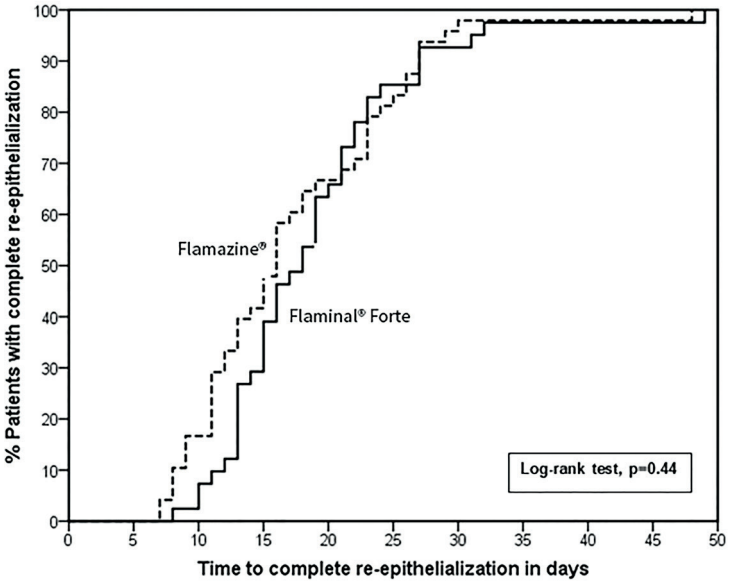

Figure 2. Kaplan-Meier curves for time to wound healing of partial thickness burn in the Flaminal® Forte and Flamazine® group.

Surgical outcomes

No difference was found between the treatment groups regarding need for operation, percentage of the study area covered with skin graft, complications after surgery and length of hospital stay (Table 2).

Wound colonisation and infection

At admission, four patients in the Flaminal® group and eight in the Flamazine® group already had colonized burn wounds. Of the initially not colonized wounds, 29 (78%) in the Flaminal group developed wound colonization during admission compared to 13 (33%) in the Flamazine® group (p < 0.0001; Table 3). The number of days until wound colonisation did not differ between treatment groups, nor did the local infection rate and the use of systemic antibiotics between the treatment groups (Table 3). The microbiology of the colonized burn wounds is described in Table 3. The studied burn wounds were mainly colonized by Gram+ microorganisms, mostly *Staphylococcus aureus*.

Table 2. Outcome measures – Intention-to-treat analyse.

Outcome measure	**Flaminal® Forte (n = 41)**	**Flamazine® (n = 48)**	***p***
Time to wound healing (days)[1], median (range)	18 (8 - 49)	16 (7 - 48)	0.24[2]
Time to wound healing of non-operated study area, median (range)	14.5 (8 - 27)	11 (7 - 29)	0.07[2]
Length of hospital stay, median (range)	16 (1 - 33)	17 (2 - 102)	0.79[2]
Need for operation, n (%)	21 (51)	24 (50)	0.91[3]
%TBSA of study area covered with skin graft, median (range)	1.5 (0 - 5)	0.9 (0 - 6)	0.20[2]
Complication after surgery, n	3 / 21	4 / 24	(not
- Hematoma	1 / 21	0 / 24	tested)
- Graft migration	1 / 21	0 / 24	
- Graft loss	1 / 21	3 / 24	
- Wound infection	0 / 21	1 / 24	
- Allergic reaction	0 / 21	1 / 24	
- Re-operation	0 / 21	1 / 24	

[1] Defined as reepithelialisation >95%, [2] Mann-Whitney test, [3] Chi-square test.

Pain, anticipatory anxiety and pruritus

Pain before and during dressing changes decreased significantly over time during hospital admission in both treatment groups (Figure 3A and 3B). In the model, the mean decrease in pain score before dressing change was 0.10 points per day (95% CI 0.08 to 0.12, $p < 0.0001$) and the mean decrease in pain score during dressing change was 0.13 points per day (95% CI 0.11 to 0.15, $p < 0.0001$). No difference in procedural pain was seen for the Flaminal® group compared to the Flamazine® group for pain before dressing change (mean difference 0.10, 95% CI -0.56 to 0.77, $p = 0.76$), nor for pain during dressing change (mean difference 0.26, 95% CI -0.45 to 0.97, $p = 0.47$). Scores for background pain (measured in the evening) also decreased over time during hospital admission by an average of 0.07 points per day (95% CI 0.05 to 0.09, $p < 0.0001$), but did not differ between the treatment groups ($p = 0.89$; Figure 3C).

Pain-related and anticipatory anxiety during admission was comparable in the treatment groups: the median BSPAS score in the Flaminal® group was 35 (range 0 - 78) compared with 26 (range 0 - 82) in the Flamazine® group (Mann-Whitney test $p = 0.45$).

The scores for pruritus of the study area increased slightly over time during hospital admission by on average 0.02 points per day (95% CI 0.01 to 0.04, $p = 0.004$; Figure 3D). No difference in scores for itching was found between the treatment groups ($p = 0.52$).

Table 3. Wound colonisation and infection.

Outcome measure	**Flaminal® Forte (n = 41)**	**Flamazine® (n = 48)**	***p***
Colonization of study area, n (%)[1]	29 / 37 (78)	13 / 40 (33)	< 0.0001[2]
Time to colonisation of study area in days, median (range)	5 (2 - 11)	4 (2 - 19)	0.36[3]
Species, n			(not tested)
Gram +			
- *Bacillus species*	3	1	
- *Gram-postive (unspecified)*	1	0	
- *Group B streptococcus*	2	0	
- *Staphylococcus aureus*	24	9	
Gram -			
- *Acinetobacter species*	1	0	
- *Aeromonas sobria*	0	1	
- *Enterobacter Faecalis*	3	0	
- *Gram-negative bacteria (unspecified)*	0	1	
- *Klebsiella Oxytoca*	0	1	
- *Pseudomonas aeruginosa*	2	0	
Infection of study area, n (%)	4/ 41 (10)	1/ 48 (2)	0.18 [4]
Use of systemic antibiotics, n (%)	0/4	0/1	(not tested)

[1] Wounds which were colonized at admission were excluded, [2] Chi-square test, [3] Mann-Whitney test, [4] Fisher's exact test.

Scar quality

Results on subjective and objective scar quality are shown in Table 4. POSAS general impression score for both patient and observer score showed statistically significant decrease during the first 12 months post-burn ($p < 0.0001$), while no statistically significant difference was found between both treatment groups during the first 12 months post-burn (POSAS patient general impression $p = 0.32$; POSAS observer general impression score $p = 0.73$). A complete overview of POSAS individual items for patients and observers are shown in supplement A.

The absolute difference between scar tissue and the non-affected skin for erythema and melanin, as assessed by the DermaSpectrometer®, showed a statistically significant decrease ($p < 0.0001$) during the first 12 months post-burn. However, no statistically significant difference was found between both treatment groups in respect to erythema ($p = 0.68$) or melanin ($p = 0.97$).

Table 4. Subjective and objective scar assessment.

	Flaminal® Forte			Flamazine®			
	No. (Valid)	**Median**	**Range**	**No. (Valid)**	**Media**	**Range**	***p*[1]**
Subjective scar assessment							
POSAS patient score[2]							
General impression							
3 months post burn	35	5	1 - 10	42	4	1 - 10	0.70
6 months post burn	34	4	1 - 10	41	3	1 - 10	0.30
12 months post burn	35	3	1 - 10	38	2	1 - 10	0.09
POSAS observer score[3]							
General impression							
3 months post burn	35	5	1 - 10	42	4	1 - 10	0.70
6 months post burn	34	4	1 - 10	41	3	1 - 10	0.30
12 months post burn	35	3	1 - 10	38	2	1 - 10	0.09
Objective scar assessment							
Scar color (Erythema)[4, 6]							
3 months post burn	35	11.0	0.24 - 27.9	42	9.5	0.66 - 37.1	0.65
6 months post burn	35	5.8	0 - 28.3	41	5.3	0.43 - 27.7	0.37
12 months post burn	35	3.2	0.07 - 17.4	35	3.3	0.5 - 10.5	0.24
Scar pigmentation (Melanin)[5, 6]							
3 months post burn	35	6.7	0.3 - 28.5	42	8.0	0.1 - 25.0	0.53
6 months post burn	35	3.3	0.4 - 15.0	35	4.2	0.07 - 12.8	0.84
12 months post burn	39	3.7	0 - 17.4	39	2.6	0.3 - 18.4	0.59

Table 4. Continued.

	Flaminal® Forte			Flamazine®			
	No. (Valid)	**Median**	**Range**	**No. (Valid)**	**Media**	**Range**	***p*** [1]
Scar extension (Uf)[7, 9]							
3 months post burn	35	0.70	0.35 - 1.58	40	0.70	1.40 - 1.60	0.86
6 months post burn	35	0.73	0.20 - 1.28	41	0.74	0.06 - 1.31	0.86
12 months post burn	35	0.84	0.29 - 1.35	40	0.79	0.47 - 1.60	0.75
Scar elasticity (Ue)[8, 9]							
3 months post burn	35	0.62	0.22 - 1.36	35	0.60	0.20 - 1.94	0.50
6 months post burn	35	0.62	0.09 - 1.27	41	0.60	0.35 - 1.33	0.86
12 months post burn	35	0.78	0.19 - 1.35	40	0.70	0.36 - 1.57	0.71

[1] Mann-Whitny U test, [2] Patient and Observer Scar Assessment Scale (POSAS) general impression score provided by the patient, [3] Patient and Observer Scar Assessment Scale (POSAS) general impression score provided by the observer, [4] Scar color (Erythema) obtained by the DermaSpectrometer, [5] Scar pigmentation (Melanin) obtained by the DermaSpectrometer, [6] Values were calculated as absolute difference between scar tissue and the nonaffected skin, [7] Scar extension results (Uf) obtained by the Cutometer, [8] Scar elasticity (Ue) obtained by the Cutometer, [9] Values represent the ratio between scar tissue and nonaffected skin.

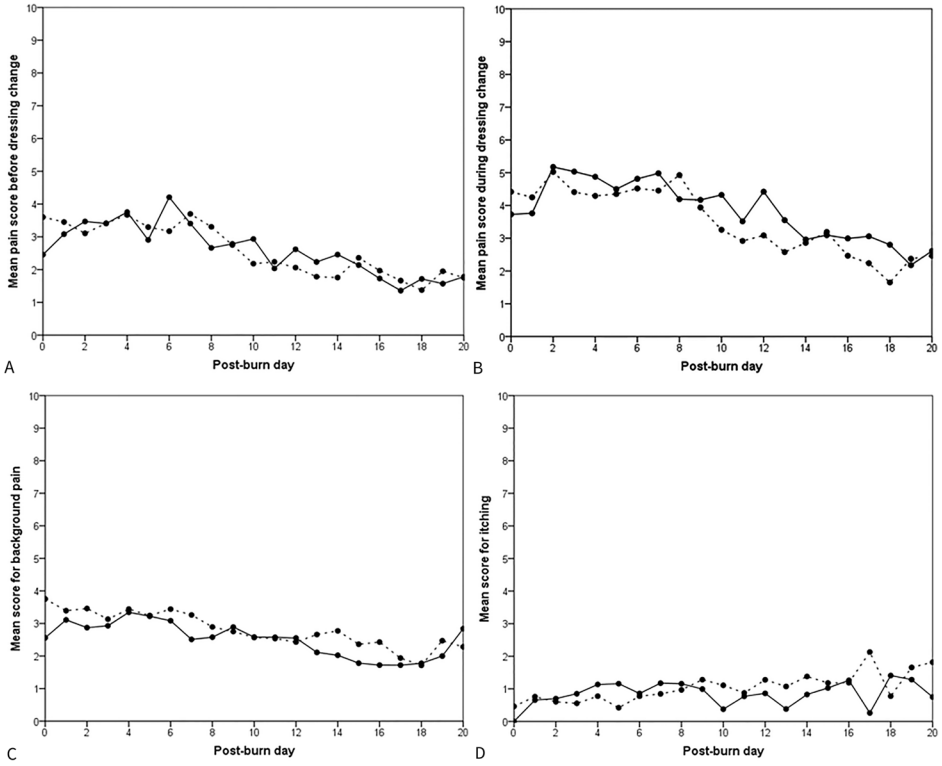

Figure 3. Mean scores for (A) pain before dressing change, (B) pain during dressing change, (C) background pain and (D) pruritus of the study area in the Flaminal group (solid line) and Flamazine® group (dotted line). Scores are presented up to 20 days post-burn; scores thereafter are not shown as these were considered too variable due to the small numbers of observations.

The ratio between scar tissue an non-affected skin for maximal scar extension (Uf) and scar elasticity (Ue), as assessed by Cutometer®, showed a statistically significant decrease during the first 12 months post-burn ($p < 0.00001$). No statistically significant difference was found between both treatment groups in respect to Uf ($p = 0.97$) or Uf ($p = 0.90$) during the first 12 months post-burn.

DISCUSSION

This study is the first randomized controlled trial comparing the clinical effectiveness of Flaminal® Forte with Flamazine® in the treatment of partial thickness burns. No statistically significant or clinically relevant differences were found between the interventions with respect to the wound healing. Furthermore, the need for surgery, pain during dressing changes, pain-related and anticipatory anxiety or pruritus did not differ significantly between the treatment groups. In the Flaminal® group, there were twice as many wound colonisations during treatment than in the Flamazine® group. Although the incidence of wound infection seemed higher in the Flaminal® group, the difference was not statistically significant. Noteworthy, patients treated with Flaminal® Forte required less dressing changes than the patients treated with Flamazine®.

Interestingly, time to wound healing was not significantly different between both treatment groups. This finding is in contrast with previous retrospective studies that described a better wound healing of partial thickness burns that were treated with Flaminal® Forte in comparison with SSD.(19, 20) Selection bias in these retrospective studies may have contributed to this finding. In the current study, the alternated treatment strategy with Furacine Soluble Dressing from 6th post burn day in the Flamazine® group may have minimized the cytotoxicity of the silver particles in the SSD on the wound bed. Silver is highly toxic to keratinocytes and fibroblasts in vitro. (3, 10, 11, 15) In effect, this treatment strategy may have limited the poor wound healing that is often seen in burn wounds treated with SSD for a longer period of time.(3, 9, 12, 34) This use of Flamazine®/ Furacine Soluble Dressing may have resulted in no difference in time to wound healing between both treatments. Overall, rapid wound healing is vital, because delayed wound healing time is found to be a risk factor for worse scar quality.(23, 24, 35) Cubison et al. concluded that the risk of developing a hypertrophic scar was high when the wound healing took more than 21 days.(23) A recent study found that the scar quality worsens with an increase in time to wound healing, as measured by the Vancouver Scar Scale (VSS).(35)

Besides a comparable time to wound healing, the treatment groups also did not differ regarding the need for surgery and size of the study area that required skin grafting. From a clinical perspective this means that both treatments equally reduce the number of operations of the deep partial thickness burns that are most likely not to heal spontaneously. At the Dutch Burn Centers burn wounds are grafted when no wound healing is expected within 21 days post-burn to minimize the risk of hypertrophic scar formation. This is likely the reason for the high percentage of grafted burn wounds in the current study. The favorable results on scar quality in the current study supports this approach. However, this treatment strategy might also have confounded results on wound healing.

Dressing changes in both treatment groups were applied according to the manufacturer recommendations. Therefore, number of dressing changes was not an outcome in this study. However, it is essential to have more insight into dressing changes and its effect on the patient because burn wound pain is most intense during dressing changes (procedural pain).(36, 37) Procedural pain is recognized to be a multidimensional experience that often induces significant anxiety and distress in burn patients.(38) The management of this type of burn pain is challenging for burn specialists, especially in absence of a consensus on treatment strategy.(39) Therefore, less dressing changes could contribute to minimize burn wound pain, anxiety and distress. In the current study, dressing changes were less often performed during hospital admission in the Flaminal® group compared to the Flamazine® group ($p < 0.0001$): while the dressings of the patients in the Flamazine® group were changed every day, the dressings of the patients in the Flaminal group were changed on median 85% of the days admitted in hospital (range 52-100%). As a result, patients in the Flaminal® group had less moments of procedural pain compared to the patients in the Flamazine® group during hospital admission. Despite the higher incidence of wound colonisation in the Flaminal® group, no significant differences in the incidence of wound infection, use of systemic antibiotics or quality of wound healing were observed compared with the Flamazine® group. This observation is in line with a previous retrospective study by Hoeksema et al.(19) There are several explanations for this finding. First, wound colonisation alone, in the absence of tissue damage, may not delay the wound healing process(40). Studies indicated that subinfective levels of bacteria may even be required for the formation of granulation tissue and collagen formation to accelerate the wound healing process.(41, 42) However, a transient stage from wound colonisation to critical colonisation or wound infection is likely to result in delayed wound healing.(40) This theory supports our results as no difference in incidence of wound infection and time to wound healing was found between the treatment groups. Second, the continuous debridement effect of Flaminal® Forte may reduce the bacterial load in the presence of wound colonisation. However, this theory was not studied in the present study and should be examined in future studies. Third, wound colonisation in our study was treated based on the results of the wound culture. This may have prevented a higher incidence of wound infection and, consequently, have prevented a delayed wound healing in colonised burn wounds in this study. Fourth, one might speculate that less wound colonisation in the Flamazine® group could be explained by the alternated treatment strategy in the Flamazine® group from the 6th post-burn day. However, the median time to first wound colonisation in the SSD group was 4 days (range 2-19). On the other hand, the statistical power of the study was insufficient to ascertain a statistically significant difference in the incidence of wound infection between the treatment groups.

In terms of scar quality, no statistical differences were found between both treatment groups. The POSAS score by both patient and observer were low and decreased during a follow-up of 12 months. In line with these findings, the melanin and the erythema indices measured by DermaSpectrometer® and scar elasticity and maximal extension measured by Cutometer® were also improved during follow-up of 12 months, which corresponds with improvement of scar quality in both treatment groups. This finding is important because scar formation negatively impacts quality of life not only in terms of physical limitations and appearance but also in terms of psychological problems including social anxiety, depression, post-traumatic stress and poor body image.(43-46)

The current study has some limitations. First, randomization would ideally have been performed after LDI for an optimal evaluation of the burn wound depth of the study area. However, in order to get reliable results LDI has to be performed between 2 and 5 days post burn.(25, 26) Local treatment could not be started before LDI was performed if randomization was performed after LDI. Consequently, burn wounds that are untreated before performing LDI are prone to delayed wound healing. Alternatively, when a local treatment other than Flammazine® or Flaminal® Forte was started before LDI, a bias was introduced to the study which may have affected the wound healing time. Moreover, the current study was designed to evaluate our daily clinical practice for the treatment of partial thickness burns in two of the three Dutch burn centres. In both centres local treatment is started directly after admission. Second, results were not stratified for superficial and deep partial thickness burns, because the study area was often partial thickness burns with different depth. This distinction is important because some authors postulate that standard operative treatment for the deep partial thickness burns minimizes poor scar quality, although, there is no consensus in the literature regarding timing and type of the operation, debridement technique, use of skin substitutes or application of growth factors and other humoral agents to enhance wound healing.(47-50) Spontaneous wound healing of deep partial thickness burns is still possible because of the surviving keratinocytes and epidermal stem cells in the remaining dermis layer.(51) Nevertheless, the re-epithelisation of deep partial thickness burns is significantly prolonged and associated with poor scar quality when treated conservatively for more than 21 days.(23, 24, 52) Therefore, in the current study partial thickness burns were operated (split skin graft) when the wound healing took more than 21 days. Moreover, the distribution of superficial, intermediate and deep partial thickness wounds was similar in the treatment groups, so we believe that the presence of deep partial thickness burns did not affect the conclusions of our study. Third, it was not possible to blind the patients and clinicians because of the characteristic appearance of both treatments. Fourth, the exclusion of psychiatric patients and children makes the sample not entirely representative. Therefore, the findings of this study should be extrapolated to psychiatric and paediatric burn patients with caution. Finally, the lack of power for our study outcome wound colonisation as mentioned above.

CONCLUSION

There was no statistically significant or clinically relevant difference in wound healing between Flaminal® Forte and Flamazine® in the treatment of partial thickness wounds. Nevertheless, Flaminal® Forte seemed favourable because of less dressing changes and therefore lower burden of wound care. More studies are needed to conform these findings.

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Supplement A. POSAS scores provided by the patients and observers.

POSAS total score	Flaminal® Forte			Flamazine®			
	No. (Valid)	Median	Range	No. (Valid)	Median	Range	*p*[1]
Patient							
Color							
3 months post burn	35	6	2 - 10	42	6	2 - 10	0.63
6 months post burn	34	5	1 - 10	41	5	1 - 10	0.57
12 months post burn	35	4	1 - 10	38	3	1 - 10	0.23
Stiffness							
3 months post burn	35	5	1 - 10	42	4	1 - 10	0.33
6 months post burn	34	4	1 - 10	41	3	1 - 9	0.17
12 months post burn	35	3	1 - 10	38	2	1 - 10	0.15
Thickness							
3 months post burn	35	3	1 - 10	42	3	1 - 10	0.68
6 months post burn	34	3	1 - 10	41	2	1 - 10	0.19
12 months post burn	35	2	1 - 9	38	1	1 - 9	0.78
Relief							
3 months post burn	35	3	1 - 10	42	3	1 - 10	0.64
6 months post burn	34	3	1 - 10	41	2	1 - 10	0.34
12 months post burn	35	3	1 - 10	38	2	1 - 10	0.10
Pain							
3 months post burn	35	1	1 - 10	42	1	1 - 10	0.83
6 months post burn	34	1	1 - 8	41	1	1 - 10	0.22
12 months post burn	35	1	1 - 7	38	1	1 - 6	**0.05**
Pruritus							
3 months post burn	35	2	1 - 10	42	3	1 - 10	0.43
6 months post burn	34	2	1 - 8	41	2	1 - 8	0.66
12 months post burn	35	1	1 - 6	38	1	1 - 7	1.0
General impression							
3 months post burn	35	5	1 - 10	42	4	1 - 10	0.70
6 months post burn	34	4	1 - 10	41	3	1 - 10	0.30
12 months post burn	35	3	1 - 10	38	2	1 - 10	0.09
Observer							
Vascularization							
3 months post burn	35	4	2 - 10	42	4	1 - 10	0.29
6 months post burn	34	3	1 - 8	41	2	1 - 8	**0.02**
12 months post burn	35	2	1 - 4	38	2	1 - 4	0.43
Pigmentation							
3 months post burn	35	4	2 - 10	42	4	1 - 10	0.64
6 months post burn	34	3	1 - 6	41	3	1 - 7	0.59
12 months post burn	35	3	1 - 6	38	2	1 - 5	0.14

Supplement A. Continued

POSAS total score		Flaminal® Forte			Flamazine®		
	No. (Valid)	Median	Range	No. (Valid)	Median	Range	*p*[1]
Patient							
Thickness							
3 months post burn	35	2	1 - 4	42	2	1 - 4	0.73
6 months post burn	34	2	1 - 6	41	1	1 - 5	0.25
12 months post burn	35	2	1 - 6	38	1	1 - 4	0.25
POSAS total score		**Flaminal® Forte**			**Flamazine®**		
	No. (Valid)	**Median**	**Range**	**No. (Valid)**	**Median**	**Range**	***p***[1]
Observer							
Relief							
3 months post burn	35	2	1 - 6	42	2	1 - 6	0.91
6 months post burn	34	2	1 - 7	41	1	1 - 4	0.13
12 months post burn	35	2	1 - 7	38	1	1 - 5	
Pliability							
3 months post burn	35	2	1 - 8	42	3	1 - 7	0.35
6 months post burn	34	2	1 - 6	41	1	1 - 7	0.25
12 months post burn	35	2	1 - 7	38	2	1 - 4	0.53
Surface area							
3 months post burn	35	1	1 - 7	42	1	1 - 4	0.88
6 months post burn	34	1	1 - 4	41	1	1 - 4	0.25
12 months post burn	35	1	1 - 5	38	1	1 - 3	0.94
General impression							
3 months post burn	35	3	2 - 6	42	2	2 - 6	0.78
6 months post burn	34	3	1 - 8	41	2	1 - 8	0.15
12 months post burn	35	3	1 - 4	38	2	1 - 5	0.26

[1] Mann-Whitny U test.

Chapter 8

Long-term quality of life and cost-effectiveness of treatment of partial thickness burns: a randomized controlled trial comparing enzyme alginogel versus silver sulfadiazine (FLAM study)

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ABSTRACT

The clinical effectiveness and scar quality of the randomized controlled trial comparing enzyme alginogel with silver sulfadiazine (SSD) for treatment of partial thickness burns were previously reported. Enzyme alginogel did not lead to faster wound healing (primary outcome) or less scar formation. In the current study, the health-related quality of life (HRQoL), costs and cost-effectiveness of enzyme alginogel compared with SSD in the treatment of partial thickness burns were studied. HRQoL was evaluated using the Burn Specific Health Scale–Brief (BSHS-B) and the EQ-5D-5L questionnaire one week before discharge and at 3, 6 and 12 months post-burn. Costs were studied from a societal perspective (healthcare and non-healthcare costs) for a follow-up period of one year. A cost-effectiveness analysis was performed using cost-effectiveness acceptability curves and comparing differences in societal costs and Quality Adjusted Life Years (QALYs) at 1 year post-burn. Forty-one patients were analysed in the enzyme alginogel group and 48 patients in the SSD group. None of the domains of BSHS-B showed a statistically significant difference between the treatment groups. Also, no statistically significant difference in QALYs was found between enzyme alginogel and SSD (difference -0.03; 95% confidence interval [CI], -0.09 - 0.03; p = 0.30). From both the healthcare and the societal perspective, the difference in costs between enzyme alginogel and SSD was not statistically significant: the difference in healthcare costs was €3210 (95% CI, €-1247 - €7667 p = 0.47) and in societal costs €3377 (95% CI €-6229 - €12982; p = 0.49). The non-significant differences in costs and quality-adjusted life-years in favour of SSD resulted in a low probability (<25%) that enzyme alginogel is cost-effective compared to SSD. In conclusion, there were no significant differences in quality of life between both treatment groups. Enzyme alginogel is unlikely to be cost effective compared with SSD in the treatment of partial thickness burns.

INTRODUCTION

The optimal treatment of partial thickness burns remains an unsolved challenge in the absence of a gold standard treatment.(1-3) The available literature is mainly based on clinical studies of poor quality that report mostly on clinical outcomes (for example wound healing) and incidentally on scar quality.(1, 4, 5) Therefore, there is a need for well-designed trials that not only evaluate clinical outcomes and scar formation but also health-related quality of life (HRQoL), costs and cost-effectiveness to help establish optimal treatment of partial thickness burns.

Two retrospective studies showed faster wound healing when enzyme alginogel which is a hydrated alginates polymers in a polyethyleneglycol (PEG) matrix embedded with a biologic enzyme system of glucose oxidase, lactoperoxidase and guaiacol was compared with SSD in the treatment of partial thickness burns, while no data was available with regard to scar formation, HRQoL, costs or cost-effectiveness.(6, 7) Therefore, our research group performed a randomized controlled trial (RCT) comparing enzyme alginogel with SSD in the treatment of partial thickness burns (FLAM study).(8) Enzyme alginogel was not found to be superior with regard to clinical outcomes such as wound healing time (primary outcome), pain, incidence of infection and scar quality, although patients in the enzyme alginogel group required significantly less dressing changes compared with the SSD group.(9) Less dressing changes in the enzyme alginogel group were expected to lead to less treatment costs compared with the SSD group. In this light, HRQoL, costs and cost-effectiveness of the treatment modalities might be decisive factors for choosing between the two treatments in clinical practice. Therefore, this study evaluated the HRQoL, costs and cost-effectiveness of enzyme alginogel compared with SSD in the treatment of partial thickness burns.

MATERIAL AND METHODS

Study design

Patients with partial thickness burns participated in an open label, multicentre RCT comparing the clinical effectiveness, quality of life and costs of enzyme alginogel with SSD. The detailed study protocol was published previously.(8) The study was approved by the Medical Research Ethics Committee Noord-Holland (NL43671.094.13) and conducted at two Dutch Burn Centres (Red Cross Hospital, Beverwijk and Maasstad Hospital, Rotterdam) from February 2014 until September 2015. Patients were eligible for the study if they were 18 years or older; had partial thickness burns of minimally 1% affected total body surface area (TBSA); presented within 48 hours of the burn injury; were mentally competent or temporary incompetent (because of sedation and/or intubation); and provided written informed consent. Patients were excluded if

they had TBSA > 30%; burns caused by chemicals, electricity or radiation; if local therapy had already started; or if the treating physician expected the patients not to be compliant with the study protocol. The patients were randomly allocated to treatment with either Flaminal® Forte (Flen Pharma, Belgium) which is an enzyme alginogel consists of 5.5% hydrated alginates and a biologic antimicrobial system (Glucose oxidase, lactoperoxidase and guaiacol) or Flamazine® (Sinclair Pharmaceuticals, Surrey, United Kingdom) which consists of silver sulfadiazine (SSD) 10 mg/g in hydrophilic crème base.

Time to wound healing and operation

In addition to previously published results on clinical effectiveness of the treatment modalities in the FLAM study,(9) of the results for time to wound healing and need for operation were analyzed in subgroups of patients with different wound depths, based on results of the Laser Doppler imager in combination with the clinical diagnosis.(10, 11) From a clinical point of view stratification of different wound depths of partial thickness wounds is important because superficial and intermediate partial thickness burns are likely to heal spontaneously in less than three weeks, while deep partial thickness burns often require operation.(11)

Health-related quality of life

HRQoL was evaluated using the Dutch version of the Burn Specific Health Scale-Brief (BSHS-B) and the EQ-5D-5L questionnaire one week before discharge and at 3, 6 and 12 months post-burn. The BSHS-B is a valid and reliable self-administered questionnaire with 40 items that cover nine domains: simple abilities, heat sensitivity, hand function, treatment regimens, work, body image, affect, interpersonal relationships and sexuality. All items are scored on a scale from 0 (extreme difficulty) to 4 (no difficulty at all). (12, 13)

The EQ-5D-5L is a generic quality of life questionnaire, which is widely used in economic evaluations, because it enables the comparison of quality of life outcomes for all kinds of interventions and different diseases. The questionnaire comprises two components.(14) The first is a descriptive system which defines health states based on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored with one item on five levels ranging from no problems to extreme problems. The combination of the scores for the five dimensions can be translated to utility values, ranging from 0 (health as bad as death) to 1 (perfect health), based on a so-called tariff which is obtained by the valuation of the Dutch population for the different health states.(15) The second component is a Visual Analogue Scale (VAS), on which the burn patients rate their health state, ranging from 0 (worst imaginable health state) to 100 (perfect health). The VAS score can also be transformed to a utility value using the power transformation $1 - (1 - VAS / 100)^{1.61}$.(16)

Quality adjusted life years (QALYs) were used to evaluate the cost-effectiveness over a period of 12 months. QALYs combine EQ-5D-5L and EQ-VAS utilities values with duration of the follow up period.(17) QALYs were calculated from the area-under-the-curve method of the utilities obtained from the EQ-5D during the 12 months of follow-up.(18)

Costs

Costs were studied from the societal perspective which included both health-care costs in and outside the hospital and non-healthcare costs (productivity loss and travel costs). Data on healthcare use were recorded prospectively by the FLAM study research team as part of the case record form during admission and by means of patient questionnaires at 3, 6 and 12 months post-burn. Costs were calculated by multiplying the volumes of healthcare use by the corresponding unit prices. Because of the 1-year time horizon, costs were not discounted. Costs were expressed in Euros and converted to the 2018 price level using the general Dutch consumer price index.(19)

Treatment

Costs of treatment were determined by micro-costing, taking into account used materials and personnel time. To assess costs of wound care, material and personnel time (ICU and non ICU nurse) needed for each dressing change, were recorded daily for each patient. The unit price for materials was obtained from the financial department of the Red Cross Hospital, Beverwijk. Subsequently, total material costs were calculated for each patient. Personnel time needed for each dressing change was recorded in hours. Costs of personnel time per hour was based on the gross salary of the nurses, increased with a surcharge for holiday allowance and social charges.(20) Personnel, material and equipment costs of surgery were obtained from a previous Dutch study by Hop et al .(21) Personnel costs were multiplied by time (surgical and anaesthesia team) needed for each operation recorded in the current study. For each patient, information on reconstructive surgery, use of blood products, pressure clothes and silicone therapy were recorded prospectively during hospital admission and the follow-up period up to 12 months post-burn. The unit price for the reconstructive surgery was derived from a previous Dutch study on this subject.(22) Unit prices of blood products, pressure clothes and silicone therapy were derived from the financial department and supplier.

Diagnostics and clinical consultations during hospitalization

Diagnostic procedures included bronchoscopy, swabs, laboratory tests and radiology, which were recorded daily during admission. Unit prices of these diagnostic procedures were obtained from the Dutch manual for costing in economic evaluation and the Dutch Healthcare Authority.(20, 23)

Burn centre stay and outpatient burn care

Length of burn centre stay in days and number of outpatient burn care visits during the follow up period of 12 months post-burn were recorded on the case record forms. Burn centre stay in days included days spent in the Intensive care Unit (ICU) of the burn centre, non-ICU burn centre days and readmittance days. Unit costs were obtained from a previous Dutch study by Hop et al.(24) Other healthcare use (rehabilitation, nursing home, visits to general practitioners and allied healthcare professionals outside the hospital) was assessed by questionnaires during follow-up period of 12 months. Unit costs were obtained from the Dutch manual for costing in economic evaluation.(20)

Non-healthcare costs

Non-healthcare costs included costs of loss of economic productivity due to absence from work (by both patients and partner) and travel costs. Data on work absence were collected by questionnaires from the patients at 3, 6 and 12 months post-burn. Productivity losses were valued using the friction cost method.(25)

Statistical analysis

All analyses followed the intention-to-treat principle. All statistical analyses were conducted with IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). BSHS results were presented as median, while utility values and costs were presented as mean. Furthermore, a two-sided t-test or Mann-Whitney test was used for comparing continuous data, and a two-sided Chi-square test or Fisher's exact test for categorical data.

For the cost-effectiveness analysis, multiple imputation by chained equations was used to reduce possible bias caused by missing data. Missing utility values or cost items were imputed using a switching regression model, that included age, gender, TBSA, location of the study area and randomisation group. Cost and QALYs were compared using the net benefit approach.(26) Depending on the willingness to pay for a QALY, a strategy is cost-effective compared with an alternative strategy if it has a higher net benefit (willingness to pay × QALYs – costs). Cost-effectiveness acceptability curves depict the probability that a strategy is cost-effective as a function of willingness to pay, given the statistical uncertainty in costs and QALYs. The threshold of willingness to pay that is commonly accepted in the Netherlands is between €20,000 and € 80,000 per QALY, depending on disease burden.(27) The base-case cost utility analysis compared QALYs at one year on the basis of the EQ-5D-5L (Dutch tariff). Sensitivity analyses were carried out using the EQ-VAS as a utility measure.

RESULTS

Study population

Of the 90 included patients, 89 patients were analysed. One patient in the enzyme alginogel group discontinued participation in the trial during the admission period. The treatment groups were comparable with regard to age, gender, percentage of TBSA of the study area, trauma mechanism and anatomical location of the study area (Table 1). Lost to follow-up were 4 / 41 (10%) patients in the enzyme alginogel group and 3 / 48 (6%) patients in the SSD group.

Table 1. Characteristics of patients.

Characteristic	**Enzyme alginogel (n = 41)**	**Silver sulfadiazine (n = 48)**
Age in years, mean (SD)	50 (15)	43 (16)
Male gender, n (%)	32 (78)	39 (81)
%TBSA study area**,** median (range)		
- Partial thickness burns	3 (1 - 10)	3 (1 - 16)
• Superficial and/ or intermediate	2 (1 - 9)	2 (1 - 9)
• Deep[1]	2 (2 - 10)	4 (1 -16)
Trauma mechanism, n (%)		
- Scald	4 (10)	7 (15)
- Flame	20 (49)	21 (44)
- Flash	12 (29)	16 (33)
- Hot grease	2 (5)	4 (8)
- Steam	3 (7)	0 (0)
Location of study area, n (%)		
- Head and neck	1 (2)	1 (2)
- Trunk (anterior)	10 (24)	6 (13)
- Trunk (posterior)	6 (15)	2 (4)
- Upper extremities	16 (39)	24 (50)
- Lower extremities	8 (20)	15 (31)

[1]Burn wounds with deep partial thickness burns as the deepest wound depth.

Time to wound healing and operation

As shown in Table 2, the median time to wound healing and need for operation did not differ between the enzyme alginogel group and the SSD group, neither within the subgroup of patients with superficial and/ or intermediate partial thickness buns nor in the subgroup of patients with deep partial thickness burns.

Table 2. Time to wound healing and need for operation based on burn wound depth of the partial thickness burns.

Outcome measure	Enzyme alginogel (n = 41)	Silver sulfadiazine (n = 48)	*p*
Superficial and/ or intermediate partial thickness burns	15 (8 - 32)	12 (7 - 27)	
Time to wound healing (days), median (range), n	n = 19	n = 22	0.08[2]
Need for operation, n (%)	5 / 19 (26%)	5 / 22 (23%)	0.89[3]
Deep partial thickness burns[1]	19 (11 - 49)	18 (11 - 48)	
Time to wound healing (days), median (range), n	n = 22	n = 26	0.92[2]
Need for operation, n (%)	16 / 22 (73%)	19 / 26 (73%)	0.79[3]

[1] Burn wounds with deep partial thickness burns as the deepest wound depth, [2] Mann-Whitney test, [3] Chi-square test.

Quality of life

For all nine domains of the BSHS-B, the amount of perceived problems decreased after hospital discharge. No statistically significant or clinically relevant differences between the treatment groups were found in any of the nine domains of BSHS-B at any follow-up moment (Table 3). The utility values for the patients' health states according to the Dutch EQ-5D-5L and EQ-VAS at 3, 6 and 12 months also showed no statically significant or clinically relevant differences between the treatment groups (Table 4). The mean QALYs based on the EQ-5D-5L results over the 12 months post-burn were 0.81 for enzyme alginogel group and 0.84 for SSD group. The difference in mean QALYs was not statistically significant (-0.03; 95% confidence interval [CI] -0.09 - 0.03; p = 0.30). The mean QALYs obtained using the VAS over the study period were 0.89 for enzyme alginogel group and 0.90 for SSD group. The difference in mean QALYs of EQ-VAS was not statistically significant (-0.01; 95% CI - 0.05 - 0.02; p = 0.42).

Healthcare costs (Table 5)

The mean costs of treatment per patient, including wound care, operation and scar therapy, were €4,352 for the enzyme alginogel group and €3,712 for the SSD group. The difference in mean costs was not statistically significant (€640; 95% CI €-769 - €2,049; p = 0.37). The mean of total healthcare costs per patient, including treatment, diagnostic procedures, clinical consultations, burn centre stay, outpatient burn care and other healthcare costs was €31,031 for the enzyme alginogel group and €27,821 for the SSD group, which were not statistically different (difference: €3,210; 95% CI €-1,247 - €7,667; p = 0.47). Burn centre stay costs represented the largest part of healthcare costs (63% in the enzyme alginogel group and 69% in the SSD group), followed by treatment costs (14% in the enzyme alginogel group 14% and 13% in the SSD group).

Table 3. Scores on the Burn Specific Health Scale (BSHS)-Brief during follow-up of 12 months.

	Enzyme alginogel			silver sulfadiazine			
	No.	**Median**	**Range**	**No.**	**Median**	**Range**	***p*[1]**
Simple abilities							
During admission	38	2.7	0.0 - 4.0	44	2.8	0.0 - 4.0	0.21
3 months post-burn	35	4.0	0.3 - 4.0	41	4.0	0.0 - 4.0	0.43
6 months post-burn	34	4.0	0.0 - 4.0	38	4.0	0.0 - 4.0	0.08
12 months post-burn	34	4.0	0.0 - 4.0	36	4.0	3.7 - 4.0	0.08
Heat sensitivity							
During admission	36	2.8	0.0 - 4.0	35	3.0	0.4 - 4.0	0.32
3 months post-burn	34	3.5	0.2 - 4.0	42	3.4	0.0 - 4.0	0.77
6 months post-burn	34	3.6	1.8 - 4.0	39	3.8	0.8 - 4.0	0.14
12 months post-burn	34	3.6	1.8 - 4.0	36	3.8	1.4 - 4.0	0.40
Hand function							
During admission	38	3.2	0.0 - 4.0	44	3.2	0.0 - 4.0	0.98
3 months post-burn	35	4.0	1.0 - 4.0	41	4.0	0.0 - 4.0	0.99
6 months post-burn	34	4.0	0.0 - 4.0	38	4.0	0.0 - 4.0	0.37
12 months post-burn	34	4.0	0.0 - 4.0	36	4.0	2.8 - 4.0	0.17
Treatment regimens							
During admission	37	3.2	0.2 - 4.0	33	3.2	0.0 - 4.0	0.42
3 months post-burn	34	3.8	0.2 - 4.0	42	4.0	0.8 - 4.0	0.86
6 months post-burn	34	4.0	2.0 - 4.0	39	4.0	2.2 - 4.0	0.80
12 months post-burn	34	4.0	2.0 - 4.0	36	4.0	0.8 - 4.0	0.38
Work							
During admission	36	2.0	0.0 - 4.0	40	1.1	0.0 - 4.0	0.28
3 months post-burn	35	3.3	0.0 - 4.0	42	3.1	0.0 - 4.0	0.71
6 months post-burn	34	3.6	0.5 - 4.0	39	3.8	0.0 - 4.0	0.47
12 months post-burn	34	4.0	2.3 - 4.0	34	4.0	0.0 - 4.0	0.18
Body image							
During admission	37	3.5	0.0 - 4.0	42	3.0	0.5 - 4.0	0.34
3 months post-burn	35	3.7	0.0 - 4.0	42	3.7	1.3 - 4.0	0.69
6 months post-burn	34	3.9	0.8 - 4.0	39	3.8	0.8 - 4.0	0.61
12 months post-burn	34	4.0	1.0 - 4.0	36	3.9	0.3 - 4.0	0.63
Affect							
During admission	37	3.4	1.0 - 4.0	43	3.6	1.1 - 4.0	0.99
3 months post-burn	35	3.7	1.0 - 4.0	42	4.0	1.4 - 4.0	0.28
6 months post-burn	34	4.0	0.7 - 4.0	39	4.0	2.7 - 4.0	0.34
12 months post-burn	34	4.0	2.8 - 4.0	36	4.0	2.4 - 4.0	0.08

Table 3. Continued.

	Enzyme alginogel			silver sulfadiazine			
	No.	**Median**	**Range**	**No.**	**Median**	**Range**	***p*[1]**
Interpersonal relationships							
During admission	37	3.5	0.0 - 4.0	40	4.0	1.0 - 4.0	0.09
3 months post-burn	34	4.0	1.8 - 4.0	41	4.0	1.0 - 4.0	0.66
6 months post-burn	34	4.0	0.5 - 4.0	39	4.0	2.8 - 4.0	0.56
12 months post-burn	34	4.0	1.5 - 4.0	35	4.0	3.5 - 4.0	0.42
Sexuality							
During admission	36	4.0	0.0 - 4.0	38	4.0	1.3 - 4.0	0.96
3 months post-burn	35	4.0	0.0 - 4.0	42	4.0	0.0 - 4.0	0.91
6 months post-burn	34	4.0	0.3 - 4.0	39	4.0	2.0 - 4.0	0.26
12 months post-burn	34	4.0	2.3 - 4.0	35	4.0	2.3 - 4.0	0.51

[1]Mann-Whitney test

Table 4. Utility values after treatment with enzyme alginogel and Silver sulfadiazine. Results are expressed as mean (standard error of the mean).

Measure	**Enzyme alginogel (n = 41)**	**Silver sulfadiazine (n = 48)**	**Difference**	***p*[1]**
EQ-5D-5L Dutch, utilities				
During admission	0.57	0.53	0.04 (-0.08 - 0.16)	0.52
3 months post-burn	0.80	0.84	-0.04 (-0.13 - 0.04)	0.30
6 months post-burn	0.84	0.89	-0.05 (-0.12 - 0.02)	0.19
12 months post-burn	0.89	0.92	-0.03 (-0.08 - 0.03)	0.30
EQ-VAS, utilities				
During admission	0.75	0.78	-0.03 (-0.11 - 0.05)	0.46
3 months post-burn	0.89	0.89	-0.001 (-0.05 - 0.05)	0.98
6 months post-burn	0.91	0.92	-0.01 (-0.05 - 0.03)	0.56
12 months post-burn	0.92	0.94	-0.02 (-0.05 - 0.01)	0.10

EQ-5D-5L Dutch, utilities: utilities obtained from EQ 5-D-5L (Dutch tariff), EQ-VAS, utilities: utilities obtained from EQ Visual Analogue Scale using the power transformation 1 - (1 - VAS / 100) [1.61]. [1]t test.

Non-healthcare costs and societal costs (Table 5)

The non-healthcare costs consisted mainly of loss of economic productivity due to absence of the patient from work, next to the absence of the partner of the patient from work and travel costs to the burn centre. The non-healthcare costs did not differ significantly between the treatment groups (€10,008 for enzyme alginogel and €9,841 for SSD group, p = 0.93). Combining the total healthcare and non-healthcare costs resulted in a total mean of societal

costs per patient of €41,039 for the enzyme alginogel group and €37,663 for the SSD group (difference: €3,377; 95% CI €-6,229 - €12,982; p = 0.49). Burn stay costs represented the largest part of the societal costs (48% in the enzyme alginogel group and 51% in the SSD group), followed by non-healthcare costs (24% in the enzyme alginogel group and 26% in the SSD group), and treatment costs (11% in the enzyme alginogel group and 10% in the SSD group).

Cost utility analysis

The combination of non-statistically higher societal costs and less favourable QALY outcomes after treatment with enzyme alginogel compared with SSD, resulted in a low probability that enzyme alginogel is cost effective compared to SSD. The probability that enzyme alginogel is cost effective compared with SSD was less than 25% for all values of the willingness to pay. (Figure 1) The same results were obtained when EQ-VAS utilities were used.

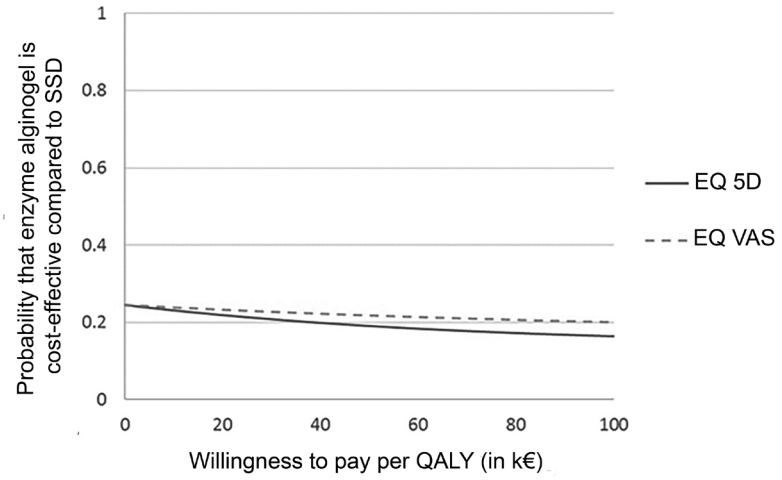

Figure 1. Cost-effectiveness acceptability curve for treatment with Flaminal® Forte compared to Flamazine®. QALY: Quality-adjusted life-year.

Table 5. Mean costs of health care and non-health care costs in € (2018) per patient.

	Enzyme alginogel (n = 41)		Silver sulfadiazine (n = 48)		Difference	
	Proportion of patients	Costs	Proportion of patients	Costs	Costs (95% confidence interval)	*p*
Treatment						
Wound care	1.00	2481	1.00	2156	325 (-458 - 1108)	0.42
Surgical treatment[1]	0.54	1638	0.52	1210	429 (-265 - 1123)	0.23
Blood products (erythrocytes)	0.07	0.94	0.08	0.61	0.34 (-1 - 2)	0.68
Pressure garments	0.41	211	0.52	329	-119 (-311 - 74)	0.23
Silicon therapy	0.20	10	0.25	10	0.04 (-10 - 10)	0.99
Splints	0.10	11	0.04	6	5 (-9 - 18)	0.51
Total treatment	1.00	4352	1.00	3712	640 (-769 - 2049)	0.37
Diagnostic procedures						
Swabs	0.98	585	1.00	565	20 (-152 - 192)	0.82
Lab tests	0.66	77	0.75	92	-16 (-95 - 64)	0.70
Bronchoscopy	0.07	61	0.04	17	44 (-33 - 120)	0.27
Radiology	0.32	75	0.40	92	-17 (-105 - 71)	0.71
Others	0.20	12	0.21	23	-10 (-30 - 10)	0.31
Total diagnostic procedures	0.98	810	1.00	789	21 (-314 - 356)	0.90
Clinical consultations						
Physiotherapist	0.78	40	0.90	45	-5 (-22 - 12)	0.54
Occupational therapist	0.56	22	0.56	30	-8 (-23 - 7)	0.31
Social worker	0.29	26	0.29	32	-7 (-34 – 22)	0.63
Dietitian	0.27	9	0.38	11	-2 (-10 - 6)	0.62
Psychologist	0.27	17	0.13	8	10 (-3 - 23)	0.15

Table 5. Continued

	Enzyme alginogel (n = 41)		Silver sulfadiazine (n = 48)		Difference	
	Proportion of patients	Costs	Proportion of patients	Costs	Costs (95% confidence interval)	*p*
Skin therapist	0.00	0.00	0.02	0.21	-0.21 (-0.61 - 0.20)	0.32
Psychiatrist	0.12	45	0.06	42	3 (-80 - 87)	0.94
Speech therapist	0.07	4	0.02	2	2 (-3 - 7)	0.44
Rehabilitation physician	0.02	5	0.04	3	0.55 (-8 - 9)	0.90
Total clinical consultations	0.90	167	0.98	174177	-10 (-119 - 99)	0.85
Burn centre stay						
Non-ICU burn centre days	1.00	15044	1.00	14737	307 (-3110 - 3724)	0.86
ICU burn centre days	0.12	4271	0.29	4112	159 (-4408 - 4725)	0.95
Re-admittance days	0.05	348	0.04	233	114 (-418 - 647)	0.67
Day care	0.05	10	0.04	63	-52 (-108 – 3)	0.35
Total burn centre stay	1.00	19672	1.00	19145	527 (527 - 527)	1.00
Outpatient burn care						
Outpatient wound care	0.88	240	0.92	226	15 (-88 - 117)	0.78
Outpatient scar care	0.95	328	0.92	296	32 (-26 - 91)	0.28
Occupational therapy	0.27	62	0.27	70	-9 (-70 - 52)	0.78
Plastic surgeon	0.15	70	0.13	28	21 (-28- 70)	0.40
Physiotherapist	0.27	55	0.27	62	-8 (-62 - 46)	0.78
Rehabilitation physician	0.05	6	0.06	19	-13 (-39 - 13)	0.33
Others	0.20	38	0.25	66	-28 (-103 - 47)	0.46
Total outpatient burn care	0.98	778	1.00	768	10 (-243 - 262)	0.94
Total costs specialised burn care	1,00	28154	1,00	26551	1604 (-2476 - 5684)	0.69

Table 5. Continued.

	Enzyme alginogel (n = 41)		Silver sulfadiazine (n = 48)		Difference	
	Proportion of patients	Costs	Proportion of patients	Costs	Costs (95% confidence interval)	*p*
Other health care costs						
Rehabilitation centre	0.27	944	0.25	113	831 (-328 - 1989)	0.15
Nursing home	0.27	290	0.31	39	251 (0.68 - 503)	0.05
General practitioner	0.51	59	0.48	51	8 (-31 - 48)	0.68
Home (nursing) care	0.51	1102	0.44	505	597 (-180 - 1374)	0.14
Extramural physiotherapy	0.41	196	0.52	358	-162 (-411 - 87)	0.20
Others	0.54	286	0.44	205	81 (-118 - 280)	0.42
Total other healthcare costs	0.80	2877	0.69	1271	1606 (762 - 2451)	0.06
Total health care costs	1.00	31031	1.00	27821	3210 (-1247 - 7667)	0.47
Non-health care costs						
Work absence (hours) patient	0.59	7721	0.65	8158	-436 (-4074- 3202)	0.81
Work absence (hours) partner	0.46	2014	0.38	1400	613.44 (-1242.65 - 2469.53)	0.52
Travel costs (km)	1.00	273	1.00	283	-10 (-170 - 149)	0.90
Total non-health care costs	1.00	10008	1.00	9841	167 (-3658 - 3991)	0.93
Total societal costs per patient	1.00	41039	1.00	37663	3377 (-6229 - 12982)	0.49

[1]including reconstructive surgery.

DISCUSSION

The Flam study did not show any significant differences in QALYs and healthcare and societal costs between enzyme alginogel and SSD in the treatment of partial thickness burns over a period of one year. Based on the nonsignificant differences in QALYs and costs in favour of SSD, it was concluded that enzyme alginogel is not likely to be cost-effective compared to SSD (<25%). In both treatment groups, most of the societal costs were caused by burn centre stay, absence from work and the treatment. Time to wound healing and need for operation did not differ between the treatment groups, neither for patients with superficial and/ or intermediate partial thickness burns nor for patients with deep partial thickness burns as the deepest wound depth.

In the present study, no statistically significant or clinically relevant differences were found between the treatment groups in terms of quality of life when measured with BSHS-B. Quality of life improved with time for all measured domains. On average, the BSHS-B scores after burn injury were lowest for the domains 'simple abilities', 'heat sensitivity' and 'work' and improved during follow-up, which is in line with available literature.(28)

In the economic evaluation, we had expected enzyme alginogel to be cost-effective compared with SSD, because of less dressing changes in the enzyme alginogel group. Although the patients in the enzyme alginogel group did require significantly less dressing changes compared with the SSD group (Enzyme alginogel group median of 85% of the days admitted in hospital (range 52 - 100%) while in the SSD group almost daily, $p < 0.0001$)(9). This difference in dressing changes did not lead to significantly lower costs in the enzyme alginogel group for several reasons. First, wound colonization in the enzyme alginogel group was much more common compared with the SSD group (78% vs 33%, respectively; $p < 0.0001$), which required daily dressing changes according to our study protocol. For this reason, we think that the a priori assumed advantage of less dressing changes in the enzyme alginogel group was less prominent than expected, as reflected by similar utility scores in both treatment groups. Second, the unit price of enzyme alginogel was higher compared with SSD, which also resulted in comparable total costs of wound care in both treatment groups. Finally, wound care costs in the FLAM study contributed only to a small part of the societal costs (Enzyme alginogel 6%, SSD 5.7%; $p = 0.42$).

In the current study, burn centre stay was a major component of the health care and non-healthcare costs (societal costs) for both treatment groups, which is in line with other studies on burn care costs.(21, 24, 29-31) Productivity loss (non-healthcare costs) represented the second largest part of societal costs in both treatment groups (Enzyme alginogel group 24%, SSD 26%, respectively). Two Dutch studies found comparable results ranging between 25%

and 30% (21, 32). A Spanish study by Sanchez found that loss of productivity accounted for 80% of societal costs.(33) The higher estimation of costs of productivity loss by Sanchez compared with the FLAM study can partially be explained by a more comprehensive inclusion of non-health costs using the human capital approach. In the FLAM study, however, the friction cost method was used, including only actual absenteism from work in days during a friction period, i.e. the time span needed to restore the initial production level, and costs consisted of loss of productivity of the patient and patients' partner, while Sanchez also included loss of productivity of other caregivers. Given the composition of societal costs, future treatment and management of burn wounds should focus on reducing the length of burn centre stay and early return to work in order to be cost-effective, while optimal treatment should be warranted. Developing a wound dressing that does not require daily dressing changes is challenging, because burn wounds might produce considerable amount of wound exudate that require daily (secondary) dressing changes.

Cost studies are important to provide insights on the distribution of costs that, for example, can be used for cost-reduction measures. Cost-effectiveness studies on the other hand in which the difference in cost is divided by difference in outcomes between an intervention and its comparator to generate incremental cost-effectiveness ratio (ICER), provide information on the most favourable balance between cost and healthcare effects.(34) A systematic review on the economic burden of burn care demonstrated that the majority of the included studies were cost studies and only few studies were cost-effectiveness studies.(34) The authors demonstrated that mean total healthcare costs per burn patient in high-income countries were $88,218 (range $704 - $717,306; median $44,024). Noteworthy, the interpretation of these results should be seen in the light of the wide variety of methodological and cost prices that were used in the included studies. The mean total health-care costs in the current study was lower compared with the above described systematic review, which partially can be explained by the exclusion of %TBSA > 30 in the FLAM study. Higher TBSA is associated with higher health care costs.(34)

To date, few studies have included health care costs in the evaluation of the treatments of partial thickness burns in adult patients. Three RCTs that evaluated different treatments included only cost studies with included cost components that ranged from only material costs to costs including wound treatments, hospital fee and transportation and pain medications.(35-37) Another RCT on the surgical treatment of partial thickness and full-thickness burn wounds with dermal substitutes and split skin graft in combination with topical negative pressure performed a cost-minimisation analysis to compare difference in costs. No cost-effectiveness analyses was performed because there were no significant differences in the studied effect (elasticity).(21) This study comprehensively assessed the costs including treatments, hospital stay, clinical consultations, other health care costs (e.g. general practitioner) and absence from

work. The authors found no significant differences between total costs per patients for the studied interventions. Two studies performed a cost-effectiveness analysis in the treatment of partial thickness burns in adult patients. Sheckter et al. used a decision model to study the cost-effectiveness of enclosed silver dressings (Aquacel® Ag (ConvaTec, Skillman, NJ) and Mepilex® Ag ((Molnlycke Health Care, Gothenburg, Sweden)) compared to SSD.(38) Costs were based on the quantity of the used material, daily home assistance for dressing changes and outpatient visits. The incremental cost utility ratio, comparing the difference in costs between both treatments and QALYs, was calculated at USD 40,168/ QALY. Assuming a maximum willingness to pay of USD 50,000 / QALY, authors concluded that enclosed silver dressing were cost-effective. The results of this study, however, should be interpreted with caution because costs were not based on the individual patients but rather on the volume of used materials to treat 20% TBSA burn wound for a period of three weeks, including dressing changes at home if needed. Carayanni et al. compared moist exposed burn ointment (MEBO) to standard care consisting of povidone plus Bepanthenol cream (Bayer Consumer Care Ltd, Basel, Switzerland).(39) This study included direct medical costs related to wound treatments and medical visits by physicians and nurses and length of hospital stay. These costs were compared to reduction in hospital days and time of recovery. MEBO was found to result in non-significantly lower total costs than standard care and better effectiveness. Overall, it can be concluded that there is a wide variety between studies in regard to which costs and healthcare effects are used in the economic evaluation.

To the best of our knowledge, the FLAM study is the only study that comprehensively studied the clinical effectiveness, quality of life and cost-effectiveness of two standard treatments in the treatment of partial thickness burns for a follow-up period of one year. Our study had some limitations. First, the current study was not powered to detect relevant differences in quality of life or costs. Second, data on the daily dressing changes were missing in less than 10% and data on QALYs (EQ-5D-5L and EQ-VAS) were missing in 14%, 17% and 23% at respectively 3, 6 and 12 months post-burn. As advocated, however, multiple imputation was used to handle these missing data (40). Third, the follow-up period of this trial was one year, which does not cover the long term effects of both treatments on quality of life and costs. However, no significant differences were found in quality of life and costs between the treatment groups at twelve months post-burn. Since burn scar maturation and recovery is (nearly) completed at that point in patients with partial thickness burns, it is not expected that there are significant differences in quality of life and costs beyond one year post-burn.

CONCLUSION

No significant differences were found between enzyme alginogel and SSD in regard to burn-specific and general quality of life. From a societal perspective, treatment of partial thickness burns with enzyme alginogel is unlikely to be cost-effective compared with SSD. Finally, from an economic perspective, treatment and management of partial thickness burns should focus on reducing length of hospital stay and early return to work, to achieve optimal outcome.

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Part IV

Scar formation: patterns and predictors

Chapter 9

Patterns and predictors of burn scar outcome in the first 12 months post-burn: the patient's perspective

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ABSTRACT

Objective: This study aimed to provide insight into the patterns and factors that predict burn scar outcomes at 3, 6 and 12 months post-burn.

Methods: The Patient and Observer Scar Assessment Scale (POSAS) was used to assess the scar formation of each patient. Structural equation modelling was used. The predictor variables used in this study were sex, three age categories, TBSA, depth of the wound and cause of the burn.

Results: The POSAS patient total and individual item scores demonstrated a statistically significant decrease in the first 12 months post-burn, except for the relief item. Male patients had a lower total and items scores (better scar quality) for pain and pruritus compared with female patients. Full thickness burns had a higher scores for pruritus, pliability, thickness and relief compared to the partial-thickness burns. Ages younger than 5 years, higher TBSA values and flame burns were predictors of various POSAS items at 3 and 6 months post-burn.

Conclusion: The POSAS patient total and individual item scores demonstrated a statistically significant improvement in the scar quality in the first 12 months post-burn, except for the relief. Sex, age, depth of the wound, the percentage of TBSA and flame burns were predictors of various POSAS patient items at 3, 6 and 12 months post-burn.

INTRODUCTION

Burn scars have extensive impacts on burn patients in terms of quality of life, functional impairment and physiological problems.(1-3) Thus, the optimal management of burn scars requires more insight into the factors that influence the severity of burn scars.

To date, sex, age, skin type, location, bacterial colonisation, time to wound healing, type of graft, multiple surgical procedures, burn severity and the skin being subjected to stretching have been found to be risk factors for hypertrophic scarring.(4-8) The impacts of burn scars not only entail the appearance of the scar but also involve of its accompanying symptoms. Up to 47% of patients experience pain that is associated with their burn scars.(9) In addition, pruritus was found to still be present in 67% of the burn patients at two years post-burn.(10) It should be noted that different burn scar assessment strategies were used in these studies, and these studies were often limited by the lack of an appropriate tool for evaluating scar outcomes.

Currently, the Patient and Observer Scar Assessment Scale (POSAS) is widely used to assess scar quality.(11) The POSAS consists of observer and patient components and has been found to be a reliable and valid instrument for the assessment of burn scars. (12, 13) The POSAS patient scale by Draaijers et al. (version 1.0) incorporates scores for the following six items by using a 10-point rating scale: pain, itch, color, pliability, thickness and relief. (12, 14) A high score indicates a worse scar quality. There is a paucity of research investigating the changes in the POSAS scores after burns.(15) Van der Wal et al. described that full thickness wounds and a higher percentage of TBSA were significant predictors of a higher POSAS score, whereas the aetiology and age of the patient had no influence on the scar quality.(16) In addition, POSAS assessment a three months post-burn found to be predictive of final scar quality at twelve months post-burn.(17)

The purpose of the present study was to describe the influence of predictors on changes in POSAS patient scores at 3, 6 and 12 months post-burn.

MATERIALS AND METHODS

Recruitment and study population

This retrospective study was performed at the burn centre outpatient clinic at the Red Cross Hospital, Beverwijk in the Netherlands between June 2004 and December 2009. This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The POSAS questionnaire is a standard part of each routine

follow-up visit of each of the burn patients in the outpatient clinic at 3, 6 and 12 months at our specialized burn centre. The data of the patients who were admitted to the burn centre and who were subsequently seen at the outpatient clinic at 3, 6 and 12 months post-burn were included in the analysis. In this consecutive sample, the patients who participated in clinical trials for wound or scar treatments were excluded from the study. The parents or caregivers were asked to fill in the POSAS patient component for patients who were under the age of 5 years. Baseline characteristics such as sex, age at the time of burn, the percentage of total body surface area (TBSA), burn depth (partial or full thickness) and the cause of the burn wound (flame or scald) were collected. At our institution, patients with full-thickness burns were operated (skin grafting). Mixed burns (partial and full-thickness) were conservatively treated for approximately 10 to 14 days. Burn wounds of > 3 cm^2 that were not yet healed, were considered for skin grafting procedures. Partial-thickness burns were treated with topical antiseptics or hydrofibre dressings. This treatment algorithm was chosen because wound healing that takes more than three weeks to complete, is considered to be a risk factor for hypertrophic scar formation.(18) Patients were categorized into the following three age-groups: < 5 years, 5 - 18 years and > 18 years. The cut-off value of 5 years was chosen because of two reasons. First, the epidemiology of burn wounds tends to be different between children < 5 years and older children. In general, scald burns were more common in children who were younger than 5 years compared with older children.(19, 20) Second, the POSAS patient scores of this age category were completed by the caregivers, which may influence the outcomes compared with older children who completed the POSAS patient scores on their own. The study location at three months post-burn was defined as the most apparent part of the scar according to the patient. Standard treatment consisted of silicones or pressure garments depending on the location and scar activity. If there was a significant functional impairment during ADL, then there was an indication of reconstruction surgery during the first 12 months post-burn. After 12 months post-burn, an operation was indicated for both functional impairment and esthetical reasons.

The POSAS

To the best of our knowledge, there is conflicting data in the literature concerning the analysis of the POSAS patient scores. Van der Wal et al. found that the POSAS patient questionnaire was unidimensional. Therefore, the individual and sum of the items of the POSAS patient scores could be used for statistical analysis.(21) Conversely, de Jong et al. found that the POSAS patient questionnaire was multidimensional. Therefore, the only individual POSAS patients scores could be used for statistical analysis.(13) In this study, we used both the individual and sum of the POSAS patient scores for statistical analysis. If the patient was unable to answer the questionnaire, e.g. in the case of children < 5 years or in the case of mentally impaired patients, then the caretaker was asked to score the items.

Study model and statistical analyses

Structural equation modelling (SEM) was performed using the IBM SPSS statistical package AMOS[TL] 24.(22) We applied a latent growth curve model (LGM), which was a special application of the SEM with several advantages. Latent growth curve modelling in AMOS was able to accommodate irregularly spaced measurements at the three time points (3, 6 and 12 months post-burn) in our data. (23) In addition, the use of LGM made it possible to assess the fit of the model to the data and to effectively compute the maximum likelihood estimates in our dataset, which was not completed at all three of the time points (Appendix B). The Inter-individual differences in the changes over time were assessed, and group-level statistics such as the mean change rates and mean intercepts were provided. The LGM accounts for the of change (slope curve analysis) at the individual level (patient) and at the group level (for instance, the depth of the burn wound, sex, etc.). The fit of the LGM was tested. The absolute and comparative fit indices were calculated.

The following predictor variables were entered into the models: sex, age < 5 years, age 5 - 18 years and age > 18 years, the percentage of TBSA, depth of the wound and cause of the burn. Our model was based on our earlier study that used the POSAS patient scale to study the influence of time-invariant predictors (such as sex, the percentage of TBSA, wound depth and age categories) on the POSAS scale in the same group of patients.(16) The three different intercept estimates represented the patients' total scores at 3, 6 or 12 months. The time moment of the intercept was dependent on how the time values were coded (0, 1, 3; –1, 0, 2 or –3, –2, 0). The slope estimates represented the patients' rates of change between 3, 6 and 12 months post-burn. Positive intercepts indicated higher POSAS scores at 3, 6 and 12 months post-burn, which thus indicated a worse scar quality compared to that of the reference group. Significant negative slopes in the POSAS scores indicated a slower rate of change in the presented predictor category compared to that in the reference category (for example, flame burns compared to the reference category scald burns).

The correlations between the intercepts and slopes were calculated. A positive value indicated a high initial score at 3 months post-burn with a greater rate of change, whereas a negative correlation indicated a high initial score at 3 months post-burn with a lower rate of change.

The LGM was investigated in a model for the total score and was individually investigated in a model for the six items that were incorporated in the POSAS patient scale, both with and without predictors. The intercept estimate can be interpreted as the influence of the predictors on the POSAS patient scores at 3, 6 and 12 months post-burn. The positive intercepts implied higher POSAS scores compared to the reference category. The slope estimate can be interpreted as the influence of the predictors on the changes in the POSAS scores over time. Positive slopes indicate higher degree of change over time compared to the reference category. An detailed description of the study model and statistical analyses can be found in Appendix D.

RESULTS

Baseline characteristics

A total of 284 children and 190 adult patients were included in this study. The patients' characteristics are shown in Table 1. There were no statistically significant differences in the total TBSA (p = 0.99, independent *t*-test), full-thickness burns (p = 0.30, independent *t*-test), or surgeries on the evaluated scars (p = 0.53, chi-square test) that were observed between the groups of patients who completed all three evaluations (n = 157) and the patients who completed one or two of the evaluations moments (n = 317).

Table 1. Patient characteristics.

Characteristic	< 18 years	≥ 18 years
Number of patients (%)	284 (60)	190 (40)
Sex, n (%)		
- Male	186 (64.5)	103 (54.2)
- Female	98 (34.5)	87 (45.8)
Age at burn, median in years (range)	2.5 (0.7 - 17.8)	43.2 (18.6 - 85.6)
TBSA, median (range)		
- Total	7 (0.5 - 76)	7.3 (0.5 - 85)
- Full thickness	1 (0.5 - 75)	3 (0.5 - 60)
Cause of the burn (%)		
- Scald	172 (60.6)	26 (13.7)
- (Flash)flame	70 (24.6)	115 (60.5)
- Contact	19 (6.7)	15 (7.9)
- Oil/ fat	20 (7.0)	27 (14.2)
- Chemical	0 (0)	6 (3.2)
- Electricity	3 (1.1)	0 (0)
- Other	0 (0)	1 (0.5)
Treatment of evaluated scar		
- Conservative treatment, n (%)	86 (30.3)	31 (16.3)
- Surgery (skin grafting), n (%)	198 (69.7)	159 (83.7)
Evaluated, n (%)		
- At 3 months post burn	224 (78.9)	135 (71.1)
- At 6 months post burn	205 (72.2)	122 (64.2)
- At 12 months post burn	156 (55.3)	76 (40.0)
Total evaluations, n (%)		
- One evaluation completed	76 (26.8)	81 (42.6)
- Two evaluations completed	101 (35.6)	71 (37.4)
- Three evaluations completed	97 (34.2)	38 (20.0)

TBSA: Total body surface area.

The fit indices for the different models

The fit indices for the different models are presented in Appendix B. The fit indices for the model with the total score and the six predictors (Appendix A) revealed the following results: The minimum discrepancy (CMIN) was 6.751 with 7 degrees of freedom (df) and a *p*-value of 0.455. The comparative fit index (CFI) was 1.00. The root mean square error of approximation (RMSEA) was 0.0001 with a confidence interval of 0.0001 - 0.055. These values of the fit indices agree with a good-to-perfect fit with the total score and the six predictors. All of the models that evaluated the six individual items had a perfect fit. The model with the total score without the six predictors had a moderate fit, and the models with the items of thickness or relief and without the six predictors had a poor fit.

Patterns of change in the POSAS patient scores

The parameter estimates for the intercept and slopes of the model that evaluated the separate total POSAS patient scale scores and the separate 6 items without the 6 predictors are shown in Table 2. The parameter estimates for the total POSAS scores obtained from the predictor models are presented in Table 2 and Appendix A. Pain had the lowest separate intercept score, which implied that pain had the lowest item score out of the six items in the POSAS at 3 months post-burn. The total score and all of the items (except relief) had significant negative slopes, which implied that the rates of change in the scores showed a decreasing trend. The covariances between the predictor variables of the total POSAS patient scale scores are shown in Appendix C.

Sex

Male patients had lower total POSAS patient scores at 3, 6 and 12 months post-burn, with no significant difference in the rate of change when compared to female patients.(Table 3) The male patients had lower pain scores at 3 and 6 months post-burn, with an equal rate of change compared to females. Men tended to have lower itch scores at 3 and 6 months post-burn. Nevertheless, the changes in the scores over time were comparable.(Table 4A) Male patients had higher POSAS scores for relief at 3 and 6 months post-burn, with lower pliability scores at 6 and 12 months post-burn. However, the changes in the scores were comparable to those observed in female patients.(Table 4B)

Table 2. Estimates of the intercepts, slopes and covariances between intercepts and slopes of the total scores and items pain, pruritus, color, pliability, thickness and relief without predictors.

POSAS patient scale	**Intercept**				**Slope**				**Covariances**			
	Estimate	**SE**	**CR**	***p***	**Estimate**	**SE**	**CR**	***p***	**Estimate**	**SE**	**CR**	***p***
Total score												
3 months	29.18	0.55	53.25	**< 0.001**	-2.02	0.25	-8.25	**< 0.001**	-2.86	4.56	-0.63	0.531
6 months	27.16	0.47	57.75	**< 0.001**					-1.13	2.94	-0.38	0.701
12 months	23.12	0.65	35.60	**< 0.001**					2.34	8.83	0.26	0.791
Items:												
Pain												
3 months	2.38	0.10	22.45	**< 0.001**	-0. 17		-4.26	**< 0.001**	-0.07	0.14	-0.47	0.637
6 months	2.21	0.09	25.01	**< 0.001**					0.01	0.09	0.07	0.942
12 months	1.87	0.11	16.75	**< 0.001**					0.15	0.27	0.55	0.581
Pruritus												
3 months	4.54	0.13	33.81	**< 0.001**	-0.49	0.06	-8.09	**< 0.001**	-0.67	0.26	-2.55	**0.011**
6 months	4.05	0.11	36.05	**< 0.001**					-0.10	0.18	-0.54	0.592
12 months	3.07	0.15	19.92	**< 0.001**					1.05	0.51	2.06	**0.039**
Color												
3 months	6.94	0.11	64.43	**< 0.001**	-0.54	0.06	-9.56	**< 0.001**	-0.52	0.21	-2.52	**0.012**
6 months	6.40	0.09	74.02	**< 0.001**					-0.17	0.14	-1.27	0.204
12 months	5.32	0.14	39.26	**< 0.001**					0.52	0.39	1.32	0.187

Table 2. Continued.

POSAS patient scale	Intercept				Slope				Covariances			
	Estimate	**SE**	**CR**	***p***	**Estimate**	**SE**	**CR**	***p***	**Estimate**	**SE**	**CR**	***p***
Pliability												
3 months	5.79	0.13	44.66	**< 0.001**	-0.47	0.07	-7.07	**< 0.001**	-0.40	0.30	-1.37	0.172
6 months	5.33	0.11	50.73	**< 0.001**					-0.10	0.19	-0.52	0.600
12 months	4.40	0.16	27.59	**< 0.001**					0.50	0.58	0.87	0.383
Thickness												
3 months	5.26	0.13	39.84	**< 0.001**	-0.31	0.06	-5.06	**< 0.001**	0.08	0.28	0.29	0.770
6 months	4.96	0.11	43.61	**< 0.001**					0.10	0.18	0.52	0.601
12 months	4.34	0.16	26.80	**< 0.001**					0.12	0.57	0.21	0.832
Relief												
3 months	5.08	0.13	39.10	**< 0.001**	-0.09	0.06	-1.34	0.179	-0.35	0.29	-1.19	0.236
6 months	5.00	0.11	47.33	**< 0.001**					-0.07	0.19	-0.37	0.715
12 months	4.82	0.16	30.83	**< 0.001**					0.48	0.57	0.85	0.397

SE: standard error, CR: critical ratio.

Wound depth

Patients with full thickness burns had higher POSAS patient total scores at 3 months post-burn and a lower rate of change during the first 12 months post-burn compared to patients with partial thickness burns. The total POSAS scores for full thickness and partial thickness burns showed no difference at 12 months post-burn.(Table 3) Pruritus scores at 3 months were significantly higher in patients with full thickness burns than those in patients with partial thickness burns. The rate of change in the pruritus scores was significantly lower in patients with full thickness burns.(Table 4A) Finally, patients with full thickness burns had significantly higher POSAS scores for pliability, thickness and relief at 3 and 6 months post-burn compared with patients with partial thickness burns.(Table 4B)

Age

There was no significant difference in the total POSAS scores between younger patients or patients who were older than 5 years. However, patients who were younger than 5 years had significantly lower pruritus scores at 12 months post-burn and lower rates of change compared to older patients.(Table 4A) Patients aged below 5 years had higher scar color, pliability and thickness scores at 3 and 6 months post-burn, while patients older than 18 years had a higher scar color scores at 12 months post-burn and a greater change in scores than the younger patients.(Table 4B) Patients older than 18 years had higher pain scores at 3, 6 and 12 months post-burn than younger patients, but groups of patients had equal rates of change.(Table 4A)

Aetiology and percentage of TBSA

The covariances between the predictor variables of the total POSAS patient score are shown in Appendix A and Appendix C. No effects of the percentage of TBSA or cause of burn were found on the total POSAS patient scale.(Table 3) Patients with flame burns generally had significantly higher color scores at 3 and 6 months post-burn.(Table 4A) Patients with a higher percentage of TBSA had higher POSAS score for relief at 3 and 6 months post-burn. (Table 4B) Pruritus scores at 6 and 12 months post-burn were higher in patients with a higher percentage of TBSA values.

Table 3. Regression weights and *p*-values of the POSAS patient scores and the predictors TBSA, burn depth, age category, sex and cause of burn.

POSAS patient scale total score					
Predictors		**Estimate**	**SE**	**CR**	***p***
Sex: male	Intercept at 3 months	-3.327	1.138	-2.922	**0.003**
	Intercept at 6 months	-3.204	0.973	-3.292	**< 0.001**
	Intercept at 12 months	-2.959	1.332	-2.222	**0.026**
	Slope	0.122	0.504	0.243	0.808
Depth: full thickness	Intercept at 3 months	3.543	1.283	2.762	**0.006**
	Intercept at 6 months	1.997	1.097	1.820	0.069
	Intercept at 12 months	-1.095	1.501	-0.730	0.466
	Slope	-1.546	0.568	-2.722	**0.006**
Age < 5 years	Intercept at 3 months	3.130	1.664	1.881	0.060
	Intercept at 6 months	1.673	1.423	1.176	0.240
	Intercept at 12 months	-1.242	1.942	-0.640	0.522
	Slope	-1.458	0.735	-1.984	**0.047**
Age > 18 years	Intercept at 3 months	0.649	1.443	0.450	0.653
	Intercept at 6 months	1.229	1.234	0.996	0.319
	Intercept at 12 months	2.388	1.689	1.414	0.157
	Slope	0.580	0.639	0.907	0.364
Cause: flame burns	Intercept at 3 months	1.006	1.490	0.675	0.499
	Intercept at 6 months	0.840	1.272	0.661	0.509
	Intercept at 12 months	0.509	1.719	0.296	0.767
	Slope	-0.166	0.651	-0.255	0.799
TBSA	Intercept at 3 months	0.024	0.044	0.552	0.581
	Intercept at 6 months	0.041	0.037	1.107	0.268
	Intercept at 12 months	0.076	0.051	1.486	0.137
	Slope	0.017	0.019	0.893	0.372

SE: standard error, CR: critical ratio. Reference categories were female sex, partial thickness burns, age 5 - 18 years, scald burns. TBSA was a continuous variable in the model.

Table 4A. Regression weights and *p*-values of the items pain, pruritus and color of the POSAS patient scale from the predictors TBSA, burn depth, age category, sex and cause of burn.

Items POSAS patient scale		**Pain**		**Pruritus**		**Color**	
Predictors		**Estimate**	***p***	**Estimate**	***p***	**Estimate**	***p***
Sex: male	Intercept 3 months	-0.730	**< 0.001**	-0.676	**0.015**	-0.181	0.419
	Intercept 6 months	-0.598	**< 0.001**	-0.614	**0.009**	-0.039	0.830
	Intercept 12 months	-0.335	0.124	-0.489	0.118	0.246	0.375
	Slope	0.132	0.117	0.062	0.611	0.143	0.217
Depth: full thickness	Intercept 3 months	0.125	0.572	0.756	**0.016**	0.249	0.324
	Intercept 6 months	0.090	0.631	0.374	0.156	0.100	0.624
	Intercept 12 months	0.019	0.939	-0.392	0.266	-0.200	0.524
	Slope	-0.035	0.708	-0.383	**0.005**	-0.150	0.250
Age < 5 years	Intercept 3 months	-0.070	0.807	0.069	0.866	1.031	**0.002**
	Intercept 6 months	-0.071	0.771	-0.316	0.355	0.660	**0.012**
	Intercept 12 months	-0.072	0.822	-1.084	**0.017**	-0.082	0.839
	Slope	0.000	0.997	-0.384	**0.031**	-0.371	**0.027**
Age > 18 years	Intercept 3 months	1.282	**< 0.001**	-0.480	0.175	0.008	0.978
	Intercept 6 months	1.330	**< 0.001**	-0.311	0.294	0.360	0.115
	Intercept 12 months	1.427	**< 0.001**	-0.009	0.983	1.065	**0.003**
	Slope	0.049	0.648	0.169	0.275	0.352	**0.016**
Cause: flame burns	Intercept 3 months	0.303	0.240	-0.065	0.858	0.951	**0.001**
	Intercept 6 months	0.313	0.150	-0.027	0.929	0.527	**0.025**
	Intercept 12 months	0.333	0.236	0.049	0.903	-0.320	0.371
	Slope	-0.010	0.926	0.038	0.810	-0.424	**0.004**
TBSA	Intercept 3 months	0.001	0.854	0.020	0.067	0.001	0.900
	Intercept 6 months	0.002	0.801	0.023	**0.011**	0.005	0.491
	Intercept 12 months	0.002	0.808	0.029	**0.016**	0.012	0.254
	Slope	0.000	0.948	0.003	0.506	0.004	0.405

Reference categories were female sex, partial thickness burns, age 5 - 18 years, scald burns. TBSA was a continuous variable in the model.

Table 4B. Regression weights and *p*-values of the items pliability, thickness and relief of the POSAS patient scale from the predictors TBSA, burn depth, age category, sex and cause of burn.

Items POSAS patient scale		**Pliability**		**Thickness**		**Relief**	
Predictors		**Estimate**	***p***	**Estimate**	***p***	**Estimate**	***p***
Sex: male	Intercept 3 months	-0.393	0.138	-0.136	0.617	-0.520	**0.051**
	Intercept 6 months	-0.545	**0.012**	-0.269	0.252	-0.435	**0.045**
	Intercept 12 months	-0.847	**0.011**	-0.537	0.114	-0.264	0.421
	Slope	-0.151	0.262	-0.134	0.294	0.085	0.528
Depth: full thickness	Intercept 3 months	1.151	**< 0.001**	0.797	**0.009**	1.076	**< 0.001**
	Intercept 6 months	0.682	**0.005**	0.463	**0.080**	0.863	**< 0.001**
	Intercept 12 months	-0.254	0.497	-0.204	0.595	0.438	0.238
	Slope	-0.468	**0.002**	-0.334	**0.020**	-0.213	0.162
Age < 5 years	Intercept 3 months	1.333	**< 0.001**	0.953	**0.016**	0.574	0.141
	Intercept 6 months	0.799	**0.012**	0.787	**0.022**	0.453	0.153
	Intercept 12 months	-0.267	0.580	0.453	0.360	0.209	0.662
	Slope	-0.533	**0.007**	-0.167	0.369	-0.122	0.536
Age > 18 years	Intercept 3 months	0.492	0.143	0.026	0.940	-0.031	0.928
	Intercept 6 months	0.307	0.264	0.018	0.951	0.147	0.592
	Intercept 12 months	-0.062	0.882	0.004	0.993	0.503	0.228
	Slope	-0.185	0.280	-0.007	0.964	0.178	0.299
Cause: flame burns	Intercept 3 months	0.277	0.425	-0.514	0.147	-0.025	0.942
	Intercept 6 months	0.318	0.262	-0.302	0.325	-0.153	0.589
	Intercept 12 months	0.400	0.349	0.123	0.780	-0.408	0.336
	Slope	0.041	0.813	0.212	0.196	-0.127	0.465
TBSA	Intercept 3 months	0.004	0.667	0.021	**0.042**	0.026	**0.010**
	Intercept 6 months	0.006	0.508	0.015	0.094	0.023	**0.006**
	Intercept 12 months	0.008	0.541	0.003	0.821	0.016	0.200
	Slope	0.001	0.827	-0.006	0.212	-0.003	0.517

Reference categories were female sex, partial thickness burns, age 5 - 18 years, scald burns. TBSA was a continuous variable in the model.

DISCUSSION

The change in the POSAS patient scale scores was studied between 3 and 6 months post-burn and between 6 and 12 months post-burn. The POSAS patient total score and all of the item scores showed a statistically significant decline in these two time periods, except for the relief item. The greatest decline was observed during the longer time period between 6 and 12 months post-burn. The pain item scale presented the lowest decline score, and the color item exhibited the highest decline score. Therefore, the pain and color items had the lowest and highest influences on the total POSAS score, respectively. The low pain scores could be the result of effective medication for pain and/or the result of real low pain values in patients after 3 months post-burn. The high color values represent the importance of color for the patient assessment of his or her scars. Patients with the highest total and item scores presented the lowest changes during the 3 and 6 months post-burn, thus leading to the lowest decline in the total score.

In our study, a strong effect of sex was observed on the total POSAS patient score. Male patients had a better scar quality, which was caused by lower score of pruritus and pain, as well as a better score for pliability and relief compared to the scar quality in female patients. Various studies have demonstrated higher pain-related symptoms in women compared with men.(24-26) Sex role beliefs, pain coping strategies, pain-related expectations and even hormonal factors may possibly explain the difference in pain experience between males and females.(27) In line with our study, two studies observed higher itch intensity scores in women compared to men, although this phenomenon is not well understood.(10, 28) Higher pliability and relief scores in the female group in our study could possibly be explained by the differences in body images between males and females. In general, women have a more negative body image compared to men.(29-31) Dyer et al. observed that women with scars that resulted from accidents or surgeries reported a more negative body image.(31)

Patients with full thickness burns had higher total POSAS scores, which were caused by higher scores for the pruritus, pliability, thickness and relief items. Other studies have also described higher itching scores for full thickness burns and grafted wounds.(10, 28, 32) An increase in both mediators and neuronal damage are thought to contribute to pruritus symptoms in full thickness burns.(33) In our study, pruritus diminished after 3 months post-burn; a finding that has been previously described in other studies.(10, 16) Higher POSAS scores for pliability, thickness and relief are explained by the loss of epidermal and dermal structures.

Previous studies have found that the age of the patient does not influence scar behavior. (6, 16, 34) Our results are consistent with these reports when considering the total POSAS score. However, this is not the case when looking at the separate items. Patients who were aged below 5 years had significantly higher scores for color, pliability and thickness at 3 and

6 months post-burn, and these patients also had significantly less pruritus at 12 months post-burn. The fact that caretakers completed the questionnaires for the patients under 5 years old may have contributed to the differences in the outcomes between the age groups. We did not find any studies that reported the influence of age on color change in burn scars.

Furthermore, it should be noted that different studies have described a negative association between age and hypertrophic scar formation.(35) This finding is supported by the decreased proliferation, reepithelization and inflammatory responses that are observed during wound healing, as well as the slower epidermal turnover and the different remodeling phase that are observed in aged individuals.(7, 35, 36) However, the present study did not investigate hypertrophic scar formation. Finally, patients who were above 18 years had higher pain scores at 3, 6 and 12 months post-burn compared to patients who were below 18 years.

The percentage of TBSA was a predictor for the pruritus, thickness and relief item scores. The effect of the percentage of TBSA on pruritus has been well described in various studies. However, there are conflicting data on the effect of the percentage of TBSA on the duration of pruritus. Van Loey et al. described a higher TBSA to be a risk factor for pruritus at 3 months post-burn.(10) The scar tissue modulation and nerve density which are thought to be highest in the first 6 months post-burn could explain this effect. However, in line with other studies, we found the effect of the percentage of TBSA to be significant even at 12 months post-burn.(28, 37) Furthermore, the effect of full thickness burns and the percentage of TBSA on itching is different than the effect of full thickness burns on pain. Pain scores were observed to be the lowest of all the scored items on the POSAS patient scale. This could be caused by a different mechanism or by a better treatment for pain.

Scald injuries are more often observed in patients who are under 5 years, whereas fire/flame burns are observed more often in older patients. Additionally, more males than females are admitted to burn centres. Full thickness burns and burns with a higher percentage of TBSA tend to occur more often in patients who are older than 18 years. Flame burns are more often deep dermal or full-thickness burns. Overall, our data are corroborated by the findings of various epidemiological studies.(19, 38)

Our study had several limitations. First, the age-related findings of the patients who were under 5 years should be interpreted with caution, given that the care givers completed the questionnaires. Second, no sample size calculation was performed, given the large number of included patients and given that the data were retrospectively collected. However, a sample size calculation could still be relevant, based on the amount of missing data. Third, the extent of the influence of the excluded patients on the results of the current study is unknown, because no data of the excluded patients were recorded. Fourth, there are conflicting data

on whether the POSAS score is a unidimensional instrument. Therefore, the scores of the individual items could be summed into a total score.(13, 21) In theory, the POSAS patient questionnaire is based on a formative model in which the individual items of the POSAS patient score are causal indicators of the scar quality. A formative questionnaire could consist of more than one dimension. Thus the individual items could be summed to a final score, for example as is done for the Apgar score. Finally, the included study predictors were obtained from the available literature, whereas no systematic search was performed. As a result, there may be predictors that are not included in the current study, which may be relevant in the context of changes in the POSAS scores at 3, 6 and 12 months post-burn.

CONCLUSION

This retrospective study, the POSAS patient total and individual item scores demonstrated a statistically significant improvement in the first 12 months post-burn, except for the relief item. Furthermore, sex, age, depth of the wound, percentage of TBSA and flame burns were predictors of various POSAS patient items at 3, 6 and 12 months post-burn. However, the effect of these predictors was not the same for the individual POSAS patient items.

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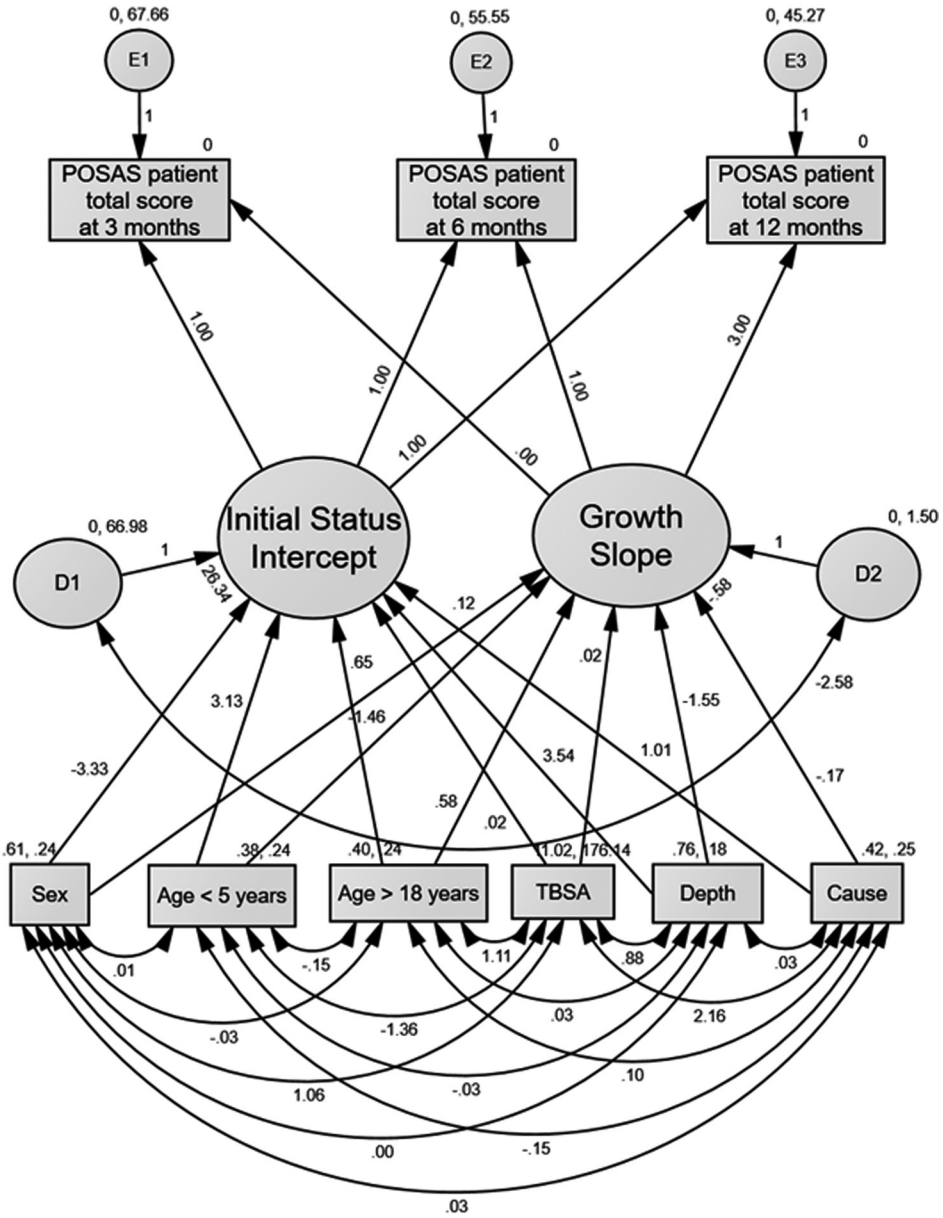

Appendix A. Hypothesized latent growth curve model of total POSAS patient scores measured at 3, 6 and 12 months post-burn with the estimates of several parameters. The time of the slope is coded 0, 1 and 3.

Appendix B. Fit indices for the different latent growth curve models.

Model	CMIN	df	*p*-value	CFI	RMSEA
Total score	3.58	1	0.059	0.98	0.07
Pain	0.11	1	0.744	1.00	0.00
Pruritus	2.19	1	0.139	0.99	0.05
Color	0.002	1	0.961	1.00	0.00
Pliability	0.000	1	1.00	1.00	0.00
Thickness	12.30	1	0.000	0.89	0.16
Relief	6.80	1	0.009	0.90	0.11
Total score + 6 predictors	6.75	7	0.455	1.00	0.00
Pain + 6 predictors	2.83	7	0.900	1.00	0.00
Pruritus + 6 predictors	5.29	7	0.624	1.00	0.00
Color + 6 predictors	8.38	7	0.301	0.99	0.02
Pliability + 6 predictors	8.74	7	0.272	0.99	0.02
Thickness + 6 predictors	12.90	7	0.075	0.99	0.04
Relief + 6 predictors	13.33	7	0.064	0.99	0.04

CMIN: minimum discrepancy, df: degrees of freedom, CFI: comparative fit index, RMSEA: root mean square error of approximation.

Appendix C. Covariances between predictor variables.

Predictor variables			Estimate	S.E.	C.R.	*p*
TBSA	-	Sex: male	1.060	0.302	3.512	**< 0.001**
TBSA	-	Depth: full thickness	0.876	0.265	3.307	**< 0.001**
TBSA	-	Age < 5 years	-1.361	0.303	4.494	**< 0.001**
TBSA	-	Age 5-18 years	0.249	0.253	0.983	0.326
TBSA	-	Age >18 years	0.249	0.253	0.983	0.326
TBSA	-	Cause: flame burns	2.161	0.327	6.613	**< 0.001**
Depth: full thickness	-	Sex: male	-0.004	0.010	-0.413	0.679
Depth: full thickness	-	Age < 5 years	-0.034	0.010	-3.553	**< 0.001**
Depth: full thickness	-	Age 5-18 years	< 0.001	0.008	0.060	0.952
Depth: full thickness	-	Age > 18 years	0.034	0.010	3.471	**< 0.001**
Depth: full thickness	-	Cause: flame burns	0.031	0.010	3.029	0.002
Cause: flame burns	-	Age < 5 years	-0.145	0.013	-11.019	**< 0.001**
Cause: flame burns	-	Age 5-18 years	0.044	0.010	4.449	**< 0.001**
Cause: flame burns	-	Age > 18 years	0.101	0.012	8.173	**< 0.001**
Sex: male	-	Age < 5 years	0.009	0.011	0.824	0.410
Sex: male	-	Age 5-18 years	0.018	0.009	1.945	0.052
Sex: male	-	Age > 18 years	-0.027	0.011	-2.449	**0.014**
Sex: male	-	Cause: flame burns	0.026	0.011	2.274	**0.023**
Age 5-18 years	-	Age < 5 years	-0.083	0.010	-8.334	**< 0.001**
Age 5-18 years	-	Age < 18 years	-0.088	0.010	-8.653	**< 0.001**
D1	-	D2	-2.585	4.372	-0.591	0.554

SE: standard error, CR: critical ratio, D1 - D2 is residual covariance.

Appendix D

Study model and statistical analyses

Absolute and comparative indices were calculated to test whether a latent growth curve model (LGM) fit in our model. As absolute fit indices, the minimum discrepancy (CMIN) and the comparative fit index (CFI) were presented. For the comparative fit index, the root mean square error of approximation (RMSEA) was calculated. The higher the probability associated with CMIN, the closer the fit was between the hypothesized model and the perfect fit. For CFI values, scores greater than 0.95 represented a well-fitting model. RMSEA values less than 0.05 were considered to be a good fit; those between 0.05 and 0.08 were considered a reasonable fit.(23, 39)

In AMOS, the estimates of the parameters, their standard errors and critical ratios (CR) were calculated. The CR refers to the estimates divided by their standard errors. Using a significance level of 0.05, any CR that exceeds 1.96 in magnitude is considered significant.

The path diagram is presented in Appendix A. Circles or ellipses represent unobserved latent variables and measurement errors or residual errors. Aspects of change (intercepts and slopes) are considered latent variables and are represented by arrows. The path from the intercept is constrained to the value 1, which reflects the fact that the intercept value remains constant across the three study time-points for each patient. The three fixed-slope variables 0, 1 and 3 represent the three time intervals of 3, 6 and 12 months elapsed since the burn. This fixed path was not estimated. Squares are measured variables: these include repeated measures of the dependent variable, POSAS patient scores and independent variables as predictors. Single-headed arrows indicate path coefficients (regression weights) and double-headed arrows indicate covariance between a pair of variables. E1, E2 and E3 are random measurement errors (residuals or disturbances). D1 and D2 are residuals that represent individual differences with respect to the intercept and slope parameters. The means of all five error terms were constrained to zero (marked by 0 in Appendix A); however, the error variances of these error terms were not constrained. The means and variances of the intercept and slope were not constrained equally across time in the model shown.

Chapter 10

General discussion

GENERAL DISCUSSION

Part I: Clinimetric studies on three-dimensional imaging

Part I of this thesis seeks to investigate three-dimensional imaging using the Artec MHT™ Scanner and software (The Artec group, San Diego, CA, USA) as a novel technique to measure wound surface area and %TBSA. Three-dimensional imaging may overcome limitations of methods that are used to estimate %TBSA in the current clinical practice. In **Chapter 2**, the feasibility, validity and reliability of three-dimensional imaging using the Artec MHT™ Scanner was studied to measure wound surface on 58 burn wounds. In **Chapter 3**, the feasibility and reliability of this novel method was compared with methods that are used in clinical practice (the rule of nine and the palm method) to estimate %TBSA in 48 burn patients.

In **Chapter 2**, the validity of the Artec MHT™ Scanner and software for measuring wound surface area was established. Since %TBSA is calculated based on two components, as (wound surface area in mm^2 / BSA in mm^2) x100, the validity of %TBSA measurements also depends on a valid assessment of BSA. Direct measurement of BSA of patients by using a whole body CT-scan is not feasible in clinical practice, because this method is time consuming, costly, patient-unfriendly and, especially in case of children, unethical because of the radiation burden. In **Chapter 3**, the duBois & duBois (adults) and Haycock (children) formulae were therefore used to calculate BSA to overcome the practical difficulties of measuring BSA. Both formulae are widely used in the field of medicine, especially to calculate dosing of anticancer agents. Validation studies of tools for calculating BSA compared with direct measurements of BSA are rare. To date, only one study in adult patients compared BSA calculated with duBois & duBois formula with direct measurement of BSA obtained by CT-scan, that showed a close correlation ($r>0.90$) between both measurements.(8) In a recent study of patients younger than 18 years, the Haycock formula was compared with mean values of seven other formulae to calculate BSA as a norm value for comparison.(9) In this study, the Haycock formula was found to have the lowest error (0.004 m^2) compared with the mean BSA value of the seven formulae.

In **Chapter 2** and **3** the reliability of the Artec MHT™ Scanner and software for measuring wound surface area and %TBSA was extensively studied. Although the ICC is a popular correlation parameter to test reliability and validity in clinical research,(5-7) it does not give information on the absolute measurement error of an individual measurement, which is important in the clinical setting.(6) In addition, the ICC can be artificially high if the range of the measurements is wide. (6) Therefore, the reliability in both studies was studied more in detail using a modified Bland and Altman plot with its limits of agreement (LoA) in such a way that 95% of the differences between pairs of measurements lies within these limits. In **Chapter 2**, three-dimensional imaging using the Artec MHT™ Scanner and software was found to be reliable for measuring wound surface area. The study described in **Chapter 3**

study confirmed the common belief in clinical practice and results from previous studies (1-4), that have shown a poor inter-observer agreement between %TBSA estimations by residents or referring physicians and %TBSA estimations by burn specialists when the rule of nine or the palm method are used: The wide limits of agreement (LoA) between a resident and burn specialist using the rule of nine and palm method in the modified Bland and Altman plot shown in **Chapter 3** suggest that these methods could lead to a serious error in %TBSA estimation. The inter-observer reliability of %TBSA estimation using three-dimensional imaging was substantially better compared with the rule of nine and the palm method.

In the studies described in **Chapter 2** and **3**, some challenges were solved but others remain to be improved. In the acute care setting, it is important to have an easy and quick method to estimate %TBSA of burn patients, e.g. to decide whether a burn patient has to be transferred to a specialized burn unit, to assess the need for intravenous fluid resuscitation and for clinical purposes as described in the *Introduction*. The Artec MHT™ Scanner is a portable, light-weight device and therefore easy to handle. The scan can be performed in less than two minutes, while post-processing the data and measuring the wound surface area could take between 15 minutes and one hour, depending on the wound surface area. The Artec 3D software is still in development and currently significant improvements have been achieved to reduce post-processing time. Noteworthy, the Artec MHT™ Scanner and software are not developed specifically for burn care but rather for industrial manufacturing, art & design and, to a lesser extent, for healthcare use, e.g. use in customized orthopaedic products. Therefore, the full potential of this technique for measuring %TBSA is yet to be realized.

Implications and future perspectives

Based on the studies described in this part of the thesis, three-dimensional imaging using the Artec MHT™ Scanner and software is a promising technique for measuring wound surface area and %TBSA. However, the feasibility should be improved in terms of post-processing the data and measuring the wound surface area before this technique can be routinely used in clinical practice. Moreover, more studies are needed to study the validation of formulae that are used to calculate BSA since %TBSA not only depends on a valid and reliable measurement of the wound surface area but also on a valid estimation of the BSA. Future studies could use the Artec MHT™ scanner and software to scan the whole body and therefore provide a direct measurement of BSA.

While advances in the field of three-dimensional imaging occur rapidly nowadays, the application of this technique is still new and costly in the field of medicine, because this technology is primarily developed for non-medical use. Thus, little or no input has been sought from clinicians or patients during the development even though these kinds of

technologies are advocated as useful in healthcare by their manufacturers. Even so, physicians should still think 'outside the box' and be aware of developments outside the field of medicine in order to solve challenges like the lack of a gold standard to estimate %TBSA. In this light, a potential example to measure %TBSA and even BSA might be the GO!SCAN 50tm 3d-scanner, which is a portable, hand-held and full-colour three-dimensional scanner, that is mainly used in engineering. In the industrial sector, similar to the field of medicine, feasible and detailed three-dimensional reconstruction of objects is mandatory. These three-dimensional reconstructions can vary for example from small components of aircrafts to a full-scale three-dimensional reconstruction of a vehicle. Systematic evaluation of the feasibility of these new tools is essential to adjust these techniques for the purpose of measuring %TBSA in clinical practice. Furthermore, future studies of implementing three-dimensional imaging for measuring %TBSA should include a critical appraisal of the clinimetric properties of the study method. Not only information on the relative measurement error, often expressed as ICC, is essential but also parameters for the absolute measurement error such as standard error of measurement (SEM) and the coefficient of variation (CV) and visualization of the absolute agreement between observers in a modified Bland and Altman plot with its LoA are needed. Finally, clinical studies on %TBSA estimation, regardless which tool is used, should also involve the consequences of inaccurate estimation of %TBSA, for example in terms of resuscitation and transfer to a burn unit. Only then, the consequences of misestimation of the %TBSA can be revealed.

Part II: Partial thickness burn in paediatric patients

In part II, the central focus is the treatment of partial thickness burn wounds in paediatric patients. Application of SSD cream is a popular partial thickness burn wound treatment in paediatric patients with serious disadvantages, e.g. forming of a pseudoeschar, daily dressing changes and cytotoxicity to the wound bed. Therefore, **Chapter 4** described a meta-analysis of controlled randomized trials that assessed the clinical effectiveness of SSD compared to nonsilver treatments of partial thickness burns in paediatric patients**.** The seven randomized controlled trials in this meta-analysis included a total of 473 patients. Six of these studies compared temporary wound dressings (Amniotic membrane, Biobrane®, TransCyte® and Mepitel®) to SDD. These temporary wound dressings can be challenging to use in clinical practice. Amniotic membrane is not a common treatment in the high-income countries. Biobrane® and TransCyte® are derived from pigs and therefore not acceptable for all patients because of cultural or religious objections. Mepitel® is a non-adherent wound dressing that has to be removed after fourteen days post-burn. The non-adherent property of Mepitel® on the wound bed can induce pain and damage to the wound bed during out-layer dressing changes. The conclusion of the meta-analysis in **Chapter 4** was that nonsilver treatment may be preferred over SSD in terms of wound healing time, dressing changes, pain, and LOS, whereas no treatment differences were found regarding infection and grafting rates. All the

included studies had a high risk of bias. Overall, the results of this meta-analysis showed that there is a need for high quality RCT's and new treatment modalities with advantages of temporary wound dressing (e.g. less dressing changes) but without the limitations of the included temporary wound dressings that are described in **Chapter 4**.

The majority of new treatments in burn care are designed for adult patients and only studied in adult patients. Studies on the usability and clinical effectiveness of these new treatments are mandatory in paediatric patients before implementing them for the paediatric burn population. In particular, the adherence of wound dressings should be evaluated in paediatric patients, because children have more body curvatures compared with adults and are more mobile. In **Chapter 5**, Suprathel® (PolyMedics Innovations GmbH, Filderstadt, Germany) was studied to investigate whether this novel treatment is useful and clinically effective in the treatment of partial thickness in paediatric patients. Suprathel® was interesting to study in paediatric patients for several reasons. First, Suprathel® is a non-animal derived wound dressing and therefore acceptable for all patient groups. Second, according to the manufacturer, Suprathel® is adherent to the wound bed and requires only outer-layer dressing changes. It is therefore less traumatic to the wound and reduces procedural pain. Third, Suprathel® is water-soluble and dissolves within four weeks so that removal of the dressing is not required. The available literature reported excellent material adherence of Suprathel® on wound beds in adult patients with partial thickness burns, while no further details were reported on the debridement technique.(5-7) The prospective, observational, non-comparative study described in **Chapter 5** in 21 paediatric patients with partial thickness burns with a follow-up of 6 months showed promising results with respect to pain, number of dressing changes and scar formation. The study did not confirm the excellent adherence of this wound dressing on the wound bed, however. On the contrary, adherence of Suprathel® on the wound bed was only achieved when Versajet® hydrosurgery was used, while no adherence was seen in most of the cases when burn wounds were cleaned by rinsing and superficial debridement of loose skin remnants and blisters. Extensive removal of wound eschar might be a requirement of optimal adherence of Suprathel® in paediatric patients.

Minimizing the procedural pain during dressing changes should be an important aspect of modern treatment of burn wounds, because procedural pain showed to be an important source of anxiety and distress in burn patients.(8) Particularly in children, procedural pain is difficult to manage and often requires deep sedation, introducing new challenges with regard to the presence of sedation staffing (anaesthesiologist) and costs.(9) When lighter sedation is still possible, whereby airway reflexes and ventilatory functions are unaffected, it is important to realize that paediatric burn patients reported that dressing changes were one of the most traumatizing aspects of their burn injury.(10) Minimizing procedural pain can be achieved in different ways. Membranous wound dressings (e.g. Suprathel®) that only require out-layer

dressing changes are ideal because these require minimal manipulation of the wound which is also less traumatic to the wound bed and thus stimulates the wound healing process. In **Chapter 5**, Suprathel® was found to have potential advantages regarding pain compared with the available literature on (semi)synthetic dressings in the treatment of partial thickness burns in paediatric patients. Minimal differences were found between background and procedural pain, which can be explained by the fact that there is minimal wound bed manipulation during dressing changes. Only the outer layer dressing is changed during dressing changes, while Suprathel® is left in situ.

Implications and future perspectives

Results of the meta-analysis described in **Chapter 4** revealed some interesting insights that provide important lessons for future studies on the treatment of partial thickness in paediatric burn patients. First, 5 of the 7 included RCTs used a membranous dressing as a comparator. This implies that progression has been made in the development of membranous dressings with the main advantage of shorter wound healing time, less pain and less dressing changes compared with SDD in the treatment of burn wounds in paediatric patients. Second, none of the included RCTs evaluated scar formation, which is one of the most important outcomes in burn patients.

Based on results discussed in **Chapter 5**, it seems that Suprathel® should only be used in the treatment of partial thickness burns in paediatric patients if an extensive wound debridement, preferably by Versajet® hydrosurgery, is possible. Minimal manipulation of the wound bed during dressing changes may have some beneficial effects in the daily clinical practice. Not only the procedural pain is limited to a minimum, but also less pain medication or even less sedation during dressing changes are required, which ultimately lowers the burden of wound care in these patients. Comparative studies are warranted to study the clinical effectiveness of Suprathel® in the treatment of partial thickness burns in paediatric patients when extensive wound debridement is needed. Suprathel® can best be compared with wound dressings that require no daily dressing changes or only the outer-layer dressing changes, e.g. biological wound dressings (such as amnion membrane, allograft skin), synthetic wound dressings (such as Mepitel®, Aquacel® or Opsite®) or even silver containing wound dressings (Aquacel® Ag) as silver containing wound dressings are believed to be less toxic for the wound bed than SSD.

A recommendation which treatment to choose in the treatment of partial thickness burns in paediatric patients cannot be given since there are many treatment options and there is no consensus on the optimal treatment. The Dutch guideline for the management of burn patients in the first 24 hours after injury (11) does not include recommendations on the wound treatment, while the *Dutch College* of *General Practitioners*' (*NHG*) practice *guideline* "Burn wounds" discourages burn wound treatment with SSD without giving a clear advice on which

local wound treatment to use.(12) The Dutch burn centres have their own local protocol for treatment of partial thickness burns. No consensus between the Dutch burn centres on this subject has been realized yet. Therefore, there is a need for a nationwide consensus on with treatment to choose in the treatment of partial thickness burns in paediatric patients.

Future studies should focus on optimal wound healing with minimal scar formation and less dressing changes to reduce pain, anxiety and wound bed manipulation. In this context, membranous dressings are interesting to study. However, membranous dressings must completely be removed when LDI is performed between 2 – 5 days post-burn. The removal and application of such a membranous dressing for the purpose of performing LDI, might damage the wound bed, can be painful and often requires deep sedation. To solve this problem, ointment based treatments can be applied on the burn wound until LDI is performed. It is worth bearing in mind that some topical antiseptics, e.g. SDD, form a pseudoeschar that negatively affects the evaluation of LDI. Also, in clinical practice not all burn wounds are suitable for membranous dressing treatment in paediatric burn patients. On some anatomical parts of the body, e.g. face and joints, membranous dressings are difficult to apply. In these cases ointment based treatments, mostly SSD, are used despite the disadvantages of SSD. Therefore, there is a need for more studies on the ointment based treatments, e.g. topical antibiotics and hydrogels. In this context, treatment with SDD should be re-evaluated with strategies that minimize the cytotoxicity of SDD on the wound bed. One strategy is to alternate SDD with a different ointment that is less cytotoxic to the wound. In adults with partial thickness burns, the alternated treatment SDD/ Furacine Soluble Dressing is a common treatment strategy. This might be an effective and safe strategy also for children. Overall, SSD should be reserved for burn wounds on difficult anatomical locations, e.g. joints, and should not be applied for a long period of time in the treatment of partial thickness burns in paediatric patients. Studies of alternated treatment strategies with SDD can help to establish whether there is still a place for SDD in the modern treatment of paediatric burn wounds.

Part III: Partial thickness burn wounds in adult patients

Part III of this thesis addresses the evaluation of two partial thickness burn wound treatment strategies in adult burn wound patients. Flaminal® Forte is popular in Belgium while SSD (Flamazine®) is commonly used in the Netherlands.

A randomized controlled trial was performed measuring the clinical effectiveness, scar formation, quality of life and cost-effectiveness of Flaminal® Forte versus Flamazine® in the treatment of partial thickness burns in adult patients (FLAM study). Retrospective clinical studies demonstrated faster wound healing when Flaminal® Forte was compared with Flamazine® in the treatment of partial thickness burns in adult patients.(13, 14) In these retrospective studies Flamazine® was used as mono therapy during the whole treatment period. As described earlier prolonged treatment with

SSD is cytotoxic for the wound. Therefore, in the FLAM study an alternated treatment strategy of Flamazine®/ Furacine Soluble Dressing was chosen to reduce the cytotoxicity of Flamazine® on the wound bed. This alternated treatment strategy of Flamazine®/ Furacine Soluble Dressing was already a commonly used treatment of partial thickness burns at one of the burn units participating in the FLAM study. However, the effectiveness of this alternated treatment strategy was not studied yet in a comparative trial. Treatment with Flamazine® consisted of daily dressing changes until 6th day post-burn. Thereafter, Furacine Soluble Dressing was alternately used from the 6th post-burn day on the odd post-burn days and Flamazine® on the even post-burn days according to the study protocol (**Chapter 6**). Flaminal® Forte was changed daily during the first three days post-burn and thereafter every other day until complete wound healing or surgery according to the manufacturer's recommendations.

The clinical results of the FLAM study showed no statistically significant difference between the treatment groups regarding time to wound healing, while more wound colonisations in the Flaminal® Forte group were found compared with the Flamazine® group (78% vs 33%, respectively; $p < 0.0001$) (**Chapter 7**). Available evidence on the clinical effectiveness of Flamazine® that was used to design the FLAM study, was based on studies in which Flamazine® was applied during the whole treatment period. In this study, however, the alternating treatment in the Flamazine® group of the FLAM study may have minimized the known cytotoxicity of Flamazine® on the wound bed, that otherwise would have presented with Flamazine® as a monotherapy.(15, 16) However, the role of wound colonisation on time to wound healing in both treatment groups is yet to be established. Treatment of wound colonisation and/ or infection in both treatment groups according to the wound culture, may have prevented delayed wound healing and may therefore have minimized differences in time to wound healing despite the high colonisation incidence in the Flaminal® Forte group. However, studies have shown that not the presence of wound colonisation in itself but a critical wound colonisation that ended in wound infection, is likely to result in delayed wound healing.(17) In addition, Flaminal® Forte is supposed to have a continuous debridement effect. Flaminal® Forte is based on hydrated alginates polymers in a polyethyleneglycol (PEG) matrix embedded with a biologic antimicrobial system. Dry scab and necrosis are dissolved by short chain PEG which results in lysed material. Wound exudate, including bacteria, and lysed material are absorbed by alginates in hydrated form which is thought to result in the continuous debridement effect. This effect of Flaminal® Forte could also reduce the bacterial load on the wound bed in case of wound colonisation which might result in shorter time to wound healing despite the presence of wound colonisation.

As expected, patients in the Flaminal® group required less dressing changes compared with the patients in the Flamazine® group. This observation is relevant from the patients' perspective. Patients in the Flaminal® group experienced less moments of procedural pain compared with the Flamazine® group. During dressing changes, manipulation of the wound bed is inevitable and

leads to procedural pain, which has been described to induce significant anxiety and distress in burn patients.(8) In the FLAM study, less dressing changes in the Flaminal® group did not lead to less pain-related and anticipatory anxiety, measured by BSPAS, compared with the Flaminal® group. An explanation for this finding may be the fact that the BSPAS scores are assumed to be directly related to the %TBSA(18); which was the same for both treatment groups. Also, the FLAM study was not powered to detect changes in BSPAS scores.

Scar formation is perhaps one of the most important outcomes of modern management of burn wounds. The FLAM study showed no statistically significant or clinically relevant differences between the treatment groups in this respect. Not only did the POSAS score improve in both treatment groups during the follow-up of 12 months, but also the melanin and erythema indices (DSM II colorimeter) and elasticity and maximal extension of the scar (Cutometer®). This finding underline that both treatments result in comparable effects on the scar formation.

With regard to health-related quality of life (HRQoL), no significant or clinically relevant differences were found between the treatment groups (**Chapter 8**). This finding was expected because both treatment groups were comparable with regard to outcomes that influence the quality of life in burn patients, e.g. pain, length of hospital stay, number of operations, %TBSA and scar quality.(19, 20) Nevertheless, important patterns could be observed in the quality of life which were similar in both treatment groups during a follow-up of twelve months. The quality of life at three months post-burn was good, with utilities derived from EQ-5D-5L and EQ-VAS >0.80, for both treatment groups and improved during twelve months post-burn. Furthermore, the self-reported outcomes of the BSHS-B domains ‘simple abilities’, ‘heat sensitivity’ and ‘work’ were found to be most problematic in both treatment groups on short term. However, all the BSHS-B domains also improved during twelve months of follow-up. Overall, the results of HRQoL suggest that both treatments have a favourable effect on patients’ well-being.

Before performing the trial, treatment with Flaminal® Forte was expected to be cost-effective compared with Flamazine® because it was assumed that significantly less dressing changes in the Flaminal® Forte group would be needed. This hypothesis was not confirmed in the FLAM study for several reasons. First, there were significantly more wound colonisations in the Flaminal® Forte group compared with Flamazine® group that required daily dressing changes according to our study protocol. The favourable effect of lower treatment costs because of less dressing changes in the Flaminal® Forte group was therefore less prominent than expected. Second, the unit price of Flaminal® Forte is much higher than that of Flamazine®. The lower number of dressing changes in Flaminal® Forte group could not compensate the high cost of Flaminal® Forte in the FLAM study. Finally, wound care costs in both treatment groups contributed only to a small part (6% in both the Flaminal® Forte and the Flamazine® group) of total healthcare costs and non-health costs (societal costs) together.

Implications and future perspectives

In clinical practice, Flaminal® Forte and alternated treatment with Flamazine® and Furacine Soluble Dressing both can be used in the treatment of partial thickness burns. Both treatments are comparable in terms of wound healing, scar quality, quality of life and costs, while the incidence of wound colonisation probably is higher when using Flaminal® Forte. Flaminal® Forte requires less dressing changes and may therefore be preferred because of the lower burden of wound care. Based on the results of the FLAM study and recent economic studies in burn care, future studies should focus on reducing length of hospital stay, early return to work and in treatment costs in order to be cost-effective, while optimal quality of care is warranted.

Some recommendations can be given for future studies based on the results of the FLAM study. While according to the manufacturer of Flaminal® Forte daily dressing changes were not supposed to be required after the 3rd day post-burn, there is a possibility that dressing changes every 48 hours were in fact one of the reasons for the higher wound colonisation incidence in the Flaminal® group compared to the Flamazine® group. Therefore, future studies should also study the effect of daily dressing changes of Flaminal® Forte on wound colonisation and infection, and its effect on time to wound healing. Future studies with Flaminal® should be powered on wound infection instead of time to wound healing based on the results of the FLAM study. Moreover, the effectiveness of Flaminal® Forte could be optimized and studied in the treatment of partial thickness burns by an alternated treatment strategy with, e.g. Furacine Soluble Dressing. This treatment combination may warrant the antiseptic property of the combination of both treatments while the cytotoxic effect of SDD is avoided.

In the last decades treatment of burn wounds have been further optimized so that the clinical differences between different treatments have become smaller and less clinically relevant. Therefore, modern management of burn wound should focus on other important outcomes of burn care, i.e. scar formation, quality of life and costs. The concept of quality of life in burn patients is multidimensional and includes physical, social and psychological rehabilitation after the burn injury. Both generic and burn specific self-reported outcome measures should be used to demonstrate the impact of the burn injury on the well-being of burn patients. Burn specific measures are relevant because they measure specific domains of quality of life that are affected in burn patients, e.g. hand function. The use of generic tools is vital for comparing the health-related quality of life of burn patients with patients with other clinical conditions. Future studies should focus on which generic and burn specific tools are best to use in burn patients. Cost-effectiveness analysis in comparative studies on the treatment of burn wounds should measure quality-adjusted life years to assess the effectiveness of treatment (e.g. using the EQ-5D-5L). Also, an economic evaluation from the societal perspective, including both health-care costs and non-health care costs (such as absence from work), is warranted to reveal the economic burden of a treatment.

Part IV: Scar formation: patterns and predictors

The final part of this thesis focuses on patterns and predictors of burn scar outcomes from the patients' perspective during the first twelve months post-burn. Knowledge of the natural course of scar formation is crucial to help clinicians to manage patients' expectations on this subject and to help them to cope with the consequences of their scars. Informing the patient about the natural course of scar formation is challenging for clinicians, because scar formation is not a single entity but involves different aspects including visuality (color), tactility (stiffness, thickness, irregularity) as well as pain and pruritus. Little is known about how and when these different properties of scar formation will change over time and which factors influence these properties of scar formation and in what way. In this part of the thesis, attempts have been made to clarify these aspects of scar formation.

In **Chapter 9**, different scar characteristics, measured with the POSAS patient scale, and the influence of different predictors on the scar quality at three, six and twelve months post-burn were studied. In this study 284 paediatric and 190 adult patients were included. This study revealed that all the items of the POSAS patient scale (pain, pruritus, color, pliability, thickness and relief) improved during the first twelve months post-burn. However, the degree of improvement was not the same for all scar properties. For example, pain showed the least, and color the most improvement from the patients' perspective. Also, the time of improvement was found to be different during the first twelve months post-burn: the greatest improvements of scar properties were seen between six and twelve months post-burn.

After more insight was gained into changes of different scar characteristics over time, the next step was to study the influence of various predictors on these scar characteristics. This knowledge is crucial to inform patients about the different aspects of scar formation and to manage their expectations. Previous studies on this subject found female sex, young age, wound colonisation, prolonged wound healing to be risk factors of pathological scar formation, e.g. keloids.(21, 22) However, the influence of these factors on different scar characteristics were not studied from the patients' perspective. Our study found predictors for scores on different subscales of the POSAS: male patients scored a better scar quality compared with female patients mainly because of better scores for pruritus, pain, pliability and relief. These results may be attributed to differences between men and women with regard to body image, pain-related expectations and even hormonal factors. (23, 24) The results of this study emphasize the difference in clinical consequences of partial thickness burns compared with full thickness burns in which more dermal structures are damaged. Patients with full thickness burns had worse total POSAS scores due to higher scores on the subscales for pruritus at three months post-burn and higher scores for the pliability, thickness and relief at three and six months post-burn. However, these differences were diminished at twelve months post-burn. Furthermore, %TBSA was found to be a predictor of pruritus even at twelve months

post-burn. In this study all items of POSAS patient scores improved during the first twelve months post-burn, except relief. Sex, age, depth of the wound, the percentage of TBSA and flame burns were found to be a predictor of various POSAS patient items at three, six and twelve months post-burn.

Implications and future perspectives

From both the patients' and clinicians' perspective, there is a great need to be informed with regard to the course and factors that influence different properties of scar formation. Based on results presented in **Chapter 9**, it can be said that pain, pruritus, colour, pliability and thickness of the scar will improve from the patients' perspective in the first 12 months post-burn. Extra attention should be paid to pruritus and pain in female patients in the first six months post-burn because they report worse scores on these aspects compared to male patients. Likewise, patients with full-thickness burns require extra attention in the first three months post-burn with regard to pruritus because of the worse scores compared with patients with partial thickness burns.

The results of the study described in **Chapter 9** may be used to create a prediction tool for providing personalized patient information on the natural course of their burn scars based on their patient specific characteristics. Ideally, such a prediction tool is based on a multivariate model that combines individual patient characteristics and burn wound characteristics to predict how and at what time different properties of scar formation are likely to change. Such a tool can also be used for a personalized scar treatment and follow-up of scar formation. For example, patients with risk factors for extensive scar formation, may undergo extensive prophylactic scar treatment and more frequent out-patient visits. Likewise, a personalized patient approach could lead to less prophylactic scar treatment and follow-up for patients without these risk factors, resulting in less overtreatment and decreasing medical costs. While the study described in **Chapter 9** provided valuable insights into patterns and predictors of scar formation in the first twelve months post-burn, these data are not sufficient for creating a tool for personalizing treatment of individual burn patients. In **Chapter 9**, predictors for scar formation were included based on the available literature and our clinical experience. However, more insights are needed to identify other factors influencing scar formation like patient characteristics that influence wound healing and therefore scar formation (e.g. age, co-morbidities, BMI, type of skin), wound treatment (e.g. type of local treatment), complications (e.g. wound colonisation or infection, re-operation).

In general, interpretation of the POSAS patient scores for patients younger than fifteen years should be interpreted with caution. The original validation study of the POSAS included patients between 15 and 73 years old.(25) Van der Wal et al. showed that the POSAS is a reliable and valid measure for scar quality assessment in a population between 0.4 to 86 years.(26) However, no stratification for different age categories was performed

in this study. Also, parents or caregivers completed the observer part of POSAS for patients younger than 6 years old. Therefore, there is a need for validation of the POSAS for patients < 15 years and for scores on the POSAS patient scale provided by parents of caregivers.

Summarizing, this thesis describes a multidimensional approach to improve burn wound treatment. The possibilities of three-dimensional imaging to overcome the limitations of the rule nine and the palm method to estimate %TBSA were explored. It was revealed that three-dimensional imaging using the Artec MHT™ Scanner and software is a promising novel technique to overcome the limitations of the rule nine and the palm method, while feasibility is still subject to improvement. Furthermore, the current treatment modalities in the treatment of partial thickness burns in paediatric and adult patients were evaluated. The review of the available literature found that nonsilver may be preferred over SSD in the treatment of partial thickness burns in paediatric patients. In this light, Suprathel® was shown to have potential advantages with regard to scar formation and procedural pain, while extensive debridement was necessary for the optimal adherence of Suprathel® on the wound bed. Furthermore, a RCT was performed to evaluate two commonly used treatments for the partial thickness burns in adult patients (FLAM study). To be implemented in modern burn care, it is not sufficient to establish the clinical effectiveness of a specific burn wound treatment. Therefore, comparative studies of burn wound treatment should also study scar formation, qualify of life and cost-effectiveness as outcomes. The FLAM study showed that Flaminal® Forte and alternated treatment with SSD/ Furacine Soluble Dressing were comparable in the treatment of partial thickness burns in terms of wound healing, scar quality, HRQoL and costs, while Flaminal® Forte was to be preferred because of less dressing changes and therefore to lower burden of wound care in burn patients. However, the higher incidence of wound colonisation in the Flaminal® Forte group and its effect on the wound healing should be further studied in future studies. Lastly, valuable insights were provided into the course of various properties of scar formation, measured from the patients' perspective with the POSAS patient scale, during the first twelve months post-burn and the influence of various predictors on these properties of scar formation was demonstrated. This information can be used for a better understanding of the natural course of various properties of scar formation and factors that influence these properties of scar formation for a better management of the patients' expectations, effective prophylactic and therapeutic treatment of adverse scar formation and personalized follow-up strategies.

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Appendices

SUMMARY

This thesis focuses on the optimization of burn wound treatment by a multidimensional approach of burn wound management. The thesis comprises four parts. The first part examines the clinimetric properties (feasibility, validity and reliability) of three-dimensional imaging for measuring of wound surface area and percentage of the total body surface area (%TBSA). The second part evaluates treatments of partial thickness burns in paediatric patients. The third part is devoted to the FLAM study where two commonly used treatments (Flaminal® Forte versus Flammazine® for partial thickness burns in adult patients were compared with regard to clinical effectiveness, scar formation, qualify of life and cost-effectiveness. Finally, the course of different properties of scar formation was explored and factors that influence these properties of scar formation from the patients' perspective were studied.

Part I: Clinimetric studies on three-dimensional imaging

Burn wound size estimation, defined as %TBSA, is an essential part of burn wound management. %TBSA is used as a criterion for whether a burn patient must be transferred to a specialized burn unit, for the need for and the volume of intravenous fluid resuscitation and management of nutritional support, for which initial local wound treatment to start and for the evaluation of the treatment effectiveness. However, the reliability of methods that are used in clinical practice to estimate %TBSA are highly dependent on the experience of the physician, size and irregularity of the wound and the body mass index of the patient.

In **Chapter 2** and **3**, thorough clinimetric evaluations of three-dimensional imaging to measure wound surface area and estimate %TBSA with the Artec MHT™ Scanner and software were performed. Three-dimensional imaging found to be a valid technique to measure wound surface area. However, the validation of this technique also depends on a valid measurement of the body surface area (BSA) since %TBSA is calculated by dividing the wound surface area by the body surface area (BSA) x 100. BSA was obtained from two commonly used formulae in the field of medicine, the duBois & duBois formula (for adults) and the Haycock formula (for children), while validation studies of these formulae are rare in the literature. Therefore, more studies are needed to validate formulas to calculate BSA since the validity of %TBSA mainly depends on these formulas.

Furthermore in **Chapter 2** and **3**, it was illustrated that three-dimensional imaging is a reliable method to estimate wound surface area and %TBSA. Additionally, in **Chapter 3**, the reliability of three-dimensional imaging using the Artec MHT™ Scanner and software was found to be superior compared to the reliability of the rule of nine or the palm method that are used by physicians in clinical practice. In terms of feasibility, the Artec MHT™ Scanner and software

were found to be easy to use although post-processing the data and measurement of the wound surface area may take a long time: between 15 to 60 minutes depending on the size of the burn wound. In short, three-dimensional imaging using the Artec MHT™ Scanner and software is a novel and promising technique to overcome the limitations of methods used in current clinical practice, while the feasibility of this method requires improvements before this method can be implemented in daily clinical practice.

Part II: Partial thickness burn in paediatric patients

A wide range of treatment modalities are available in the treatment of partial thickness burns in paediatric patients, while currently there is no consensus on which treatment is the gold standard. Silver sulfadiazine (SSD), such as (Flammazine®), is widely used in the treatment of partial thickness burns in paediatric patients due to its easy application on the burn wounds and excellent anti-microbial properties, although dressing changes with SSD are often painful and prolonged use of SSD leads to delayed wound healing.

In **Chapter 4**, a systematic review and meta-analysis of the literature are reported that compared the clinical effectiveness of SSD to nonsilver treatment for partial thickness burns in paediatric patients. It was demonstrated that nonsilver treatment may be preferred over SSD with regard to wound healing time, number of dressing changes, pain, and length of hospital stay (LOS), whereas no treatment differences were found in terms of infection and number of graft procedures.

Chapter 5 represents an observational, prospective study on the usability and clinical effectiveness of Suprathel® in the treatment of partial thickness burns in paediatric patients. Suprathel® is a water-soluble, non-animal derived synthetic burn wound dressing that only requires outer layer dressing changes. This study demonstrated that Suprathel® has potential advantages with regard to scar formation and pain, due to minimal wound bed manipulation during dressing changes, when compared with the available literature on (semi)synthetic dressings in the treatment of partial thickness burns in paediatric patients. However, this study showed also that an extensive wound debridement (for example by using Versajet® hydrosurgery) was necessary for the optimal adherence of Suprathel® on the wound bed. This study found no better outcomes for wound healing, need for grafting, wound colonisation and infection compared to the available literature. We recommend to use Suprathel® in the treatment of partial thickness burns in paediatric patients only if an extensive wound debridement is warranted. Additionally, comparative studies are needed to study the clinical effectiveness of Suprathel® in the treatment of partial thickness burns in paediatric patients.

Part III: Partial thickness burn wounds in adult patients

The advances in burn wound treatment in the last decades did not lead to a gold standard in the treatment of partial thickness burn wounds in adult patients. In the Netherlands, SSD is a popular modality in burn wound treatment while in Belgium Flaminal® Forte is frequently used in the treatment of partial thickness burns. Before this thesis, no prospective comparative study had been performed to help the physicians to choose between these two treatment strategies for the treatment of partial thickness burns.

Therefore, a randomized controlled trial (RCT) was performed to study the differences between Flaminal® Forte and treatment with SSD alternated with Furacine Soluble Dressing, based on the multidimensional aspects of modern management of burn wounds that includes clinical-effectiveness, scar quality, quality of life and cost-effectiveness (FLAM study). **Chapter 6** presents the study protocol of this RCT. In **Chapter 7**, the results of the clinical effectiveness and scar formation of the FLAM study are presented. In this study no statistically significant difference in wound healing was found between both treatment groups, while the incidence of wound colonization was much higher in the Flaminal® Forte group compared with the SSD group. With regard to scar formation, no differences were found between both treatment groups, while scar formation improved during follow-up of twelve months post-burn for both treatment groups.

Chapter 8 provides the results of health-related quality of life and cost-effectiveness of the FLAM study. There were no statistically significant or clinically relevant differences in health-related quality of life between the treatment groups. Most importantly, the health-related quality of life was similarly high in both treatment groups and improved during a follow-up of twelve months post-burn. This indicates that both treatment strategies are excellent to achieve good health-related quality of life. Treatment with Flaminal® Forte was not found to be cost-effective compared with SSD despite less dressing changes in the Flaminal® Forte group for several reasons. There was more wound colonisation in the Flaminal® Forte group that required daily dressing changes and the unit price of Flaminal® Forte was higher compared with SSD. Additionally, it was brought to light that the total healthcare costs and non-health costs (societal costs) in both treatment groups were largely determined by the costs of burn center stay and absence from work and in third place by the treatment costs, which were less than 6% in both treatment groups.

Overall, Flaminal® Forte and alternated treatment with SSD/ Furacine Soluble Dressing were comparable in terms of wound healing, scar quality, HRQoL and costs. However, treatment with Flaminal® Forte is to be preferred because it requires less dressing changes and therefore lowers the burden of wound care in burn patients. However, the role of wound colonisation in both treatment groups should be further studied in future research.

Part IV: Scar formation: patterns and predictors

The last part of this thesis describes the course of different properties of scar formation, measured with the POSAS patient scale, and the influence of various predictors on these scar properties at three, six and twelve months post-burn from the perspective of 284 paediatric and 190 adult burn patients. In **Chapter 9** with the exception of relief, all other aspects measured with the POSAS patient scale (pain, pruritus, color, pliability and thickness) improved during the first twelve months post-burn, while the degree of improvement was not the same for all these aspects. Female patients, age younger than 5 years, large burn wounds, full-thickness burns and flame burns were found to be predictors of worse scores on various POSAS patient items.

The results of the study described in **Chapter 9** can be used to inform burn patients and clinicians about the natural course of different properties of scar formation and factors that influence these scar properties. This information can ultimately be used for therapeutic and personalized follow-up strategies. However, larger studies are warranted to strengthen our results.

NEDERLANDSE SAMENVATTING

Dit proefschrift richt zich op de optimalisatie van de behandeling van brandwonden vanuit een multidimensionale benadering. Het proefschrift omvat vier delen. Het eerste deel richt zich op de klinimetrische eigenschappen (gebruiksvriendelijkheid, validiteit en betrouwbaarheid) van de driedimensionale beeldvorming voor het meten van het percentage verbrand lichaamsoppervlak dat aangeduid wordt als het Totaal Verbrand LichaamsOppervlak (TVLO). Het tweede deel evalueert de optimale behandeling van tweedegraads brandwonden bij kinderen. Het derde deel is gewijd aan de FLAM studie waarin twee veelgebruikte lokale behandelingen (Flaminal® Forte en Flammazine®) met elkaar worden vergeleken met betrekking tot klinische effectiviteit, littekenvorming, kwaliteit van leven en kosteneffectiviteit. Tot slot zijn het beloop van verschillende littekeneigenschappen na een brandwond en factoren die deze littekeneigenschappen mogelijk beïnvloeden, geanalyseerd vanuit het perspectief van de brandwondenpatiënt.

Deel I: Klinimetrische studies naar driedimensionale beeldvorming

Het inschatten van TVLO is een essentieel onderdeel voor de behandeling van brandwonden. Tijdens de eerste opvang van een brandwondenpatiënt wordt het TVLO gebruikt voor het berekenen van het volume voor vloeistofresuscitatie en dient het TVLO tevens als een verwijzingscriterium naar een brandwondencentrum. Eveneens wordt het TVLO gebruikt om te bepalen welke lokale behandeling gestart moet worden, voor het berekenen van voedingsbehoefte en het evalueren van de effectiviteit van de ingestelde behandeling. Echter, de huidige meetmethodes die in de klinische praktijk gebruikt worden voor het inschatten van het TVLO, zijn onderwerp van discussie, omdat de betrouwbaarheid van deze methodes sterk afhankelijk is van de ervaring van de arts die het TVLO inschat, de grootte en de onregelmatigheid van de brandwond en de body mass index (BMI) van de patiënt, en omdat een verkeerde inschatting veel consequenties kan hebben voor de behandeling.

In de **Hoofdstukken 2** en **3** zijn de klinimetrische eigenschappen van de driedimensionale beeldvorming met behulp van de Artec MHT™ scanner en software voor het meten van het brandwondoppervlak en het TVLO uitgebreid onderzocht. De driedimensionale beeldvorming bleek een valide techniek te zijn voor het meten van het wondoppervlak. Echter, voor het meten van het TVLO hangt de validiteit van deze methode ook af van een valide bepaling van het totale *lichaamsoppervlak* (body surface area, *BSA*). Het TVLO wordt namelijk berekend door de grootte van een brandwondoppervlak te delen door het BSA x 100. Het BSA werd berekend aan de hand van twee veel gebruikte formules in de verschillende takken van de geneeskunde: de formule van duBois & duBois voor volwassenen en de formule van Haycock voor kinderen. Beide formules zijn nauwelijks gevalideerd in de wetenschappelijke literatuur. Meer onderzoek is noodzakelijk op dit gebied aangezien een valide berekening van het TVLO ook van deze formules afhangt.

In de **Hoofdstukken 2** en **3** werd verder aangetoond dat de driedimensionale beeldvorming met behulp van de Artec MHT™ scanner en software een betrouwbare methode is voor het meten van het brandwondoppervlak en het TVLO. De driedimensionale beeldvorming bleek tevens superieur te zijn in vergelijking met de huidige methodes die in de kliniek worden gebruikt voor het meten van het TVLO, namelijk de “Regel van 9” en de “hand-methode”. Het gebruik van de Artec MHT™ scanner en software is eenvoudig, terwijl het verwerken van de data en het meten van de wondoppervlak, afhankelijk van de grootte van de wond, 15 tot 60 minuten kan duren. Samenvattend, driedimensionale beeldvorming met behulp van de Artec MHT™ scanner en software is een veelbelovende techniek die potentieel een oplossing kan zijn voor de beperkingen van de huidige methodes voor het inschatten van het TVLO. Echter, op het gebied van gebruiksvriendelijkheid zijn er verbeteringen noodzakelijk voordat deze methode geïmplementeerd kan worden in de dagelijks klinische praktijk.

Deel II: Tweedegraads brandwonden bij kinderen

De behandeling van tweedegraads brandwonden bij kinderen omvat een breed scala aan behandelingsmogelijkheden, terwijl er tot op heden geen consensus bestaat over de gouden standaard. Zilversulfadiazine (ZSD), bijvoorbeeld Flammazine®, wordt veel gebruikt bij de behandeling van tweedegraads brandwonden omdat dit gemakkelijk kan worden aangebracht door de zorgverlener en vanwege de uitstekende antimicrobiële eigenschappen van dit middel. Echter, de verbandwissels met ZSD zijn vaak pijnlijk voor de patiënt en het langdurig gebruik van ZSD kan leiden tot vertraagde wondgenezing.

In een systematische review en meta-analyse van de literatuur in **Hoofdstuk 4** werd de klinische effectiviteit van ZSD vergeleken met niet-zilver houdende middelen in de behandeling van tweedegraads brandwonden in kinderen. Deze literatuurstudie liet zien dat niet-zilver houdende middelen te prefereren zijn over ZSD wat betreft de wondgenezing, het aantal verbandwissels, pijn en het aantal ligdagen in het ziekenhuis, terwijl er geen verschil werd aangetoond tussen ZSD en niet-zilver houdende middelen met betrekking tot de incidentie van infectie en het aantal operaties (huidtransplantaties).

In **Hoofdstuk 5** wordt een observationeel, prospectief onderzoek naar de bruikbaarheid en de klinische effectiviteit van Suprathel® in de behandeling van tweedegraads brandwonden bij kinderen beschreven. Suprathel® valt onder de synthetische wondbedekkers. Dit middel heeft als voordeel dat het wateroplosbaar is, niet gemaakt is van dierlijk materiaal en dat tijdens de verbandwissels enkel de buitenlaag verwisseld hoeft te worden terwijl het middel zelf in situ wordt gelaten.

De resultaten van deze studie toonden aan dat Suprathel® mogelijk voordelen biedt wat betreft de littekenvorming en wat betreft pijn tijdens de verbandwissels vanwege minimale manipulatie aan het wondbed, in vergelijking met de literatuur over andere (semi)synthetische middelen in de behandeling van tweedegraads brandwonden bij kinderen. Deze studie toonde echter ook aan dat er een uitgebreide debridering (bijvoorbeeld door middel van Versajet® hydrochirurgie) noodzakelijk is voor een optimale applicatie van Suprathel® op het wondbed. Suprathel® liet geen duidelijke voordelen zien ten aanzien van de uitkomsten wondgenezing, het aantal huidtransplantaties, wondkolonisatie en infectie in vergelijking met de literatuur. De conclusie is dat Suprathel® het beste gebruikt kan worden indien een uitgebreide debridering van de wond is verricht. Daarnaast is prospectief, vergelijkend vervolgonderzoek nodig om de klinische effectiviteit van Suprathel® aan te tonen in de behandeling van tweedegraads brandwonden bij kinderen.

Deel III: Tweedegraads brandwonden bij volwassenen

Ook voor de volwassen brandwondpatiënten geldt dat er geen gouden standaard bestaat wat betreft de behandeling van tweedegraads brandwonden. In Nederland is ZSD een veelgebruikte behandeling, terwijl in België Flaminal® Forte vaak wordt gebruikt bij de behandeling van tweedegraads brandwonden bij volwassenen. Vóór dit proefschrift was er geen prospectief vergelijkend onderzoek voorhanden dat clinici op weg kon helpen bij het maken van een keuze tussen deze behandelingen.

Derhalve werd een gerandomiseerde gecontroleerde trial (RCT) uitgevoerd, waarin Flaminal® Forte vergeleken werd met een wisseltherapie van ZSD en Furacine in de behandeling van de tweedegraads brandwonden bij volwassenen (FLAM studie). In deze studie werden de klinische effectiviteit, littekenkwaliteit, kwaliteit van leven en kosteneffectiviteit geëvalueerd. In **Hoofdstuk 6** wordt het studieprotocol van de FLAM studie beschreven. In **Hoofdstuk 7** zijn de resultaten van de klinische effectiviteit en de littekenvorming gepresenteerd, waarbij voor de wondgenezing (primaire uitkomstmaat) geen statistisch significant verschil werd gevonden tussen beide groepen. Echter, de incidentie van wondkolonisatie in de Flaminal® Forte groep was hoger dan in de ZSD groep. Voorts waren er geen verschillen tussen beide behandelgroepen wat betreft littekenvorming, terwijl deze in beide behandelgroepen verbeterde gedurende een follow-up periode van twaalf maanden.

Vervolgens zijn in **Hoofdstuk 8** de resultaten van de kwaliteit van leven en de kosteneffectiviteit van de FLAM studie beschreven. Er werden geen statistisch significante of klinisch relevante verschillen gevonden tussen beide behandelgroepen met betrekking tot de kwaliteit van leven. Een belangrijke constatering is dat de kwaliteit van leven hoog was in beide groepen en verbeterde gedurende een follow-up periode van twaalf maanden. Behandeling met Flaminal® Forte was niet kosteneffectief vergeleken met de behandeling met ZSD, ondanks

significant minder verbandwissels in de Flaminal® Forte groep, om verschillende redenen. In de Flaminal® Forte groep ontstonden, zoals eerder beschreven, meer wondkolonisaties waarvoor dagelijks verbandwissels nodig waren. Bovendien was de kostprijs per eenheid van Flaminal® Forte hoger vergeleken met ZSD. Tot slot werden de totale kosten vanuit een maatschappelijk perspectief (kosten binnen en buiten de gezondheidzorg) juist grotendeels bepaald door de kosten van het aantal ligdagen in het brandwondencentrum en de kosten van het werkverzuim ten gevolge van het ongeval en werden zij niet zozeer bepaald door de behandelkosten. In de derde plaats werden de kosten vanuit een maatschappelijk perspectief gezien bepaald door de behandelkosten, die in beide behandelgroepen minder dan 6% bedroegen. Samengevat kan worden gesteld dat de behandeling met Flaminal® Forte en ZSD / Furacine vergelijkbare resultaten oplevert voor wat betreft wondgenezing, littekenkwaliteit, kwaliteit van leven en kosten in de behandeling van tweedegraads brandwonden bij volwassenen. Behandeling met Flaminal® Forte verdient echter de voorkeur, omdat dit middel minder verbandwissels vereist waardoor een patiënt minder ongemak ondervindt van een verbandwissel. De rol van wondkolonisatie in beide behandelingsgroepen moet verder worden bestudeerd in toekomstige studies.

Deel IV: littekenvorming: beloop en voorspellers

Het laatste deel van dit proefschrift geeft een gedetailleerde analyse van de veranderingen van brandwondenlittekens drie, zes en twaalf maanden na de verbranding. In **Hoofdstuk 9** werd bij een cohort van 284 kinderen en 190 volwassenen met brandwonden de littekenkwaliteit door de patiënt zelf beoordeeld met behulp van de POSAS littekenschaal. In deze studie werd gekeken naar het beloop van verschillende littekeneigenschappen in de tijd vanuit het perspectief van de brandwondenpatiënt en naar de invloed van verschillende factoren op deze littekeneigenschappen. Deze studie liet zien dat, met uitzondering van het reliëf, alle andere met de POSAS beoordeelde littekeneigenschappen (pijn, jeuk, kleur, stugheid en dikte) verbeterden gedurende de eerste twaalf maanden na de verbranding. Echter, de mate van deze verbetering was niet hetzelfde voor alle littekeneigenschappen. Voorspellers voor slechtere littekenvorming waren vrouwelijk geslacht, leeftijd jonger dan 5 jaar, grote brandwonden, derdegraads brandwonden en vlamverbranding.

De resultaten beschreven in **Hoofdstuk 9** kunnen gebruikt worden om de brandwondpatiënten en zorgverleners optimaal te informeren over het natuurlijke beloop van verschillende eigenschappen van de littekenvorming en factoren die deze littekeneigenschappen beïnvloeden. Deze informatie zou ook gebruikt kunnen worden voor therapeutische doeleinden en gepersonaliseerde vervolgstrategieën van een brandwondenpatiënt. Grootschaliger studies zijn echter nodig om deze resultaten te bevestigen.

LIST OF PUBLICATIONS

Long-term quality of life and cost-effectiveness of treatment of partial thickness burns: a randomized controlled trial comparing enzyme alginogel versus silver sulfadiazine (FLAM study)
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ABOUT THE AUTHOR

Zjir Mezjda Rashaan was born on May 17th 1984 in Slemani in Iraqi-Kurdistan, a city between ancient mountains and stunning nature, as the son of a surgeon and an English teacher. Together with his parents and three sisters, Zjir moved to the Netherlands at the age of 16 years. He went on to finish high school at Christelijk Lyceum Delft (CLD), Delft. He graduated in 2003 and was successfully accepted into Medicine at Leiden University.

Zjir always had a profound interest in the art of language and during his study Medicine this translated to his dedication for writing as editor-in-chief for Leiden Bio-Medical Journal (LBMJ) and also for Predoctor (magazine of the Medical Faculty for Students from Leiden (MFLS)).

Aside his writing ambitions, he was keen on expanding his horizon and thus went to Japan and Surinam for several semesters as a medical student. In his final year of his study medicine he completed a research project on the topic of breast cancer at the department of Surgery at Leiden University Medical Center (LUMC) under supervision of dr. G.J. Liefers which led to an academic publication. At this point, his love for surgery was awakened and confirmed.

Upon graduating in 2010 he started as a non-training resident (ANIOS) at Bronovo Hospital, The Hague under supervision of dr. H.J. Smeets. It was in July 2012 when he got the opportunity to commence his PhD programme under the guidance of prof. dr. R.S. Breederveld at the department of Surgery at LUMC in conjunction with Rode Kruis Ziekenhuis (RKZ), Beverwijk.

During this project he initiated and conducted various studies on multidimensional aspects of burn wound treatment which resulted in the current dissertation. Alongside his clinical research, he was also an active board member of the LUMC Association of PhD candidates (LAP).

His surgical residency commenced in January 2015 at RKZ, Beverwijk under supervision of dr. H.A. Cense and Amsterdam University Medical Centre, VU location, Amsterdam under supervision of prof. dr. D.L. van der Peet.

Currently, he is finalising his surgical residency, specialising in gastro-intestinal surgery at RKZ, Beverwijk.

When not busy working academically, Zjir is found practising avidly on various oriental string instruments such as the lute (Ud) and T'ar.