Multidimensional aspects of burn wound treatment

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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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