Multidimensional aspects of burn wound treatment

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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.

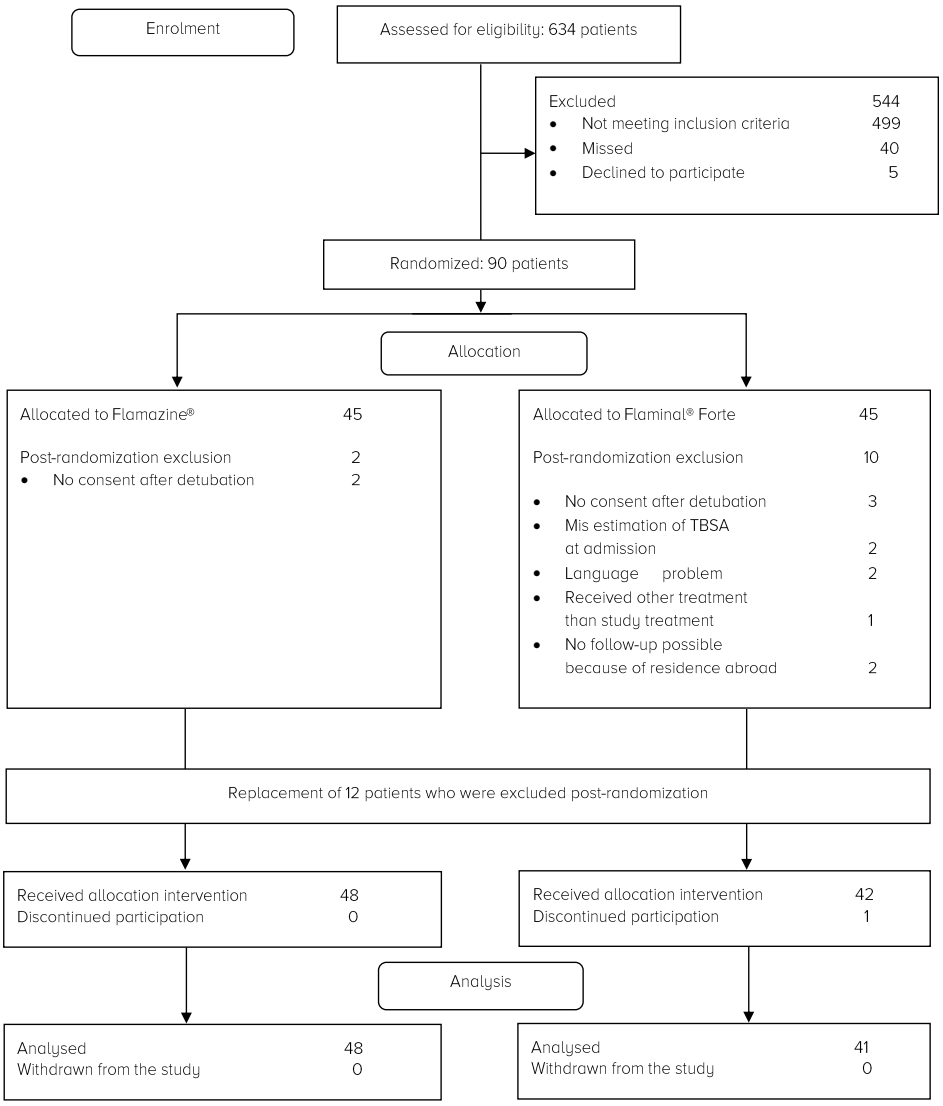

Figure 1. Flowchart of patients.

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.

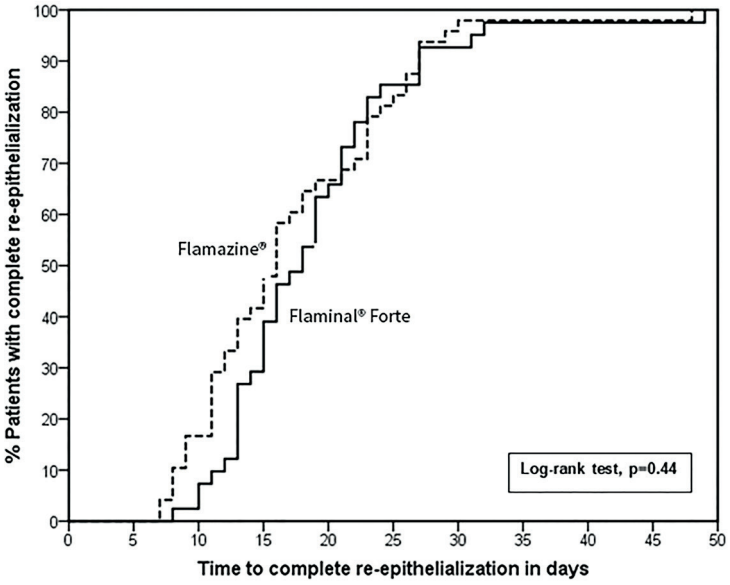

Figure 2. Kaplan-Meier curves for time to wound healing of partial thickness burn in the Flaminal® Forte and Flamazine® group.

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.

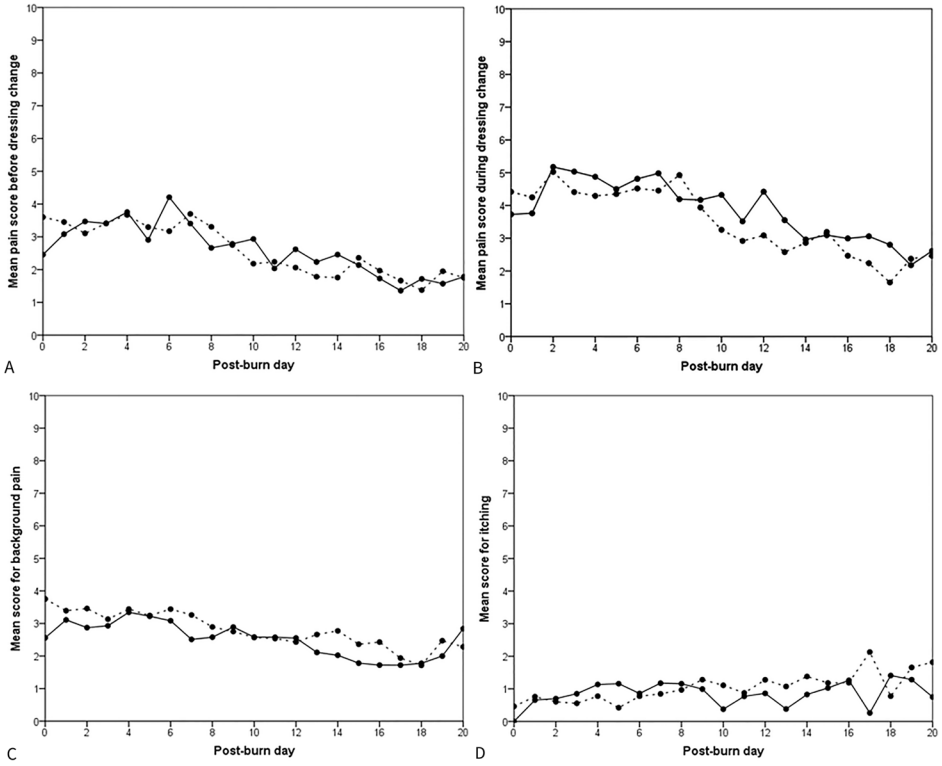

Figure 3. Mean scores for (A) pain before dressing change, (B) pain during dressing change, (C) background pain and (D) pruritus of the study area in the Flaminal group (solid line) and Flamazine® group (dotted line). Scores are presented up to 20 days post-burn; scores thereafter are not shown as these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