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A comparative study of 1% silver sulphadiazine (Flammazine®) versus an enzyme alginogel (Flaminal®) in the treatment of partial thickness burns

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ABSTRACT

Introduction: In the conservative treatment of burns, rapid wound healing is desirable to obtain good a esthetic and functional results. The aim of this study was to compare the efficacy of 1% Silversulfadiazine (SSD/Flammazine®) and an enzyme alginogel (Flaminal® or Flaminal® Forte) on the healing of superficial and intermediate partial thickness burns.
Methods: In this retrospective cohort study comparable burn wounds treated with Flaminal® or with 1% SSD were included. Outcome parameters included: length of hospital stay, bacterial burden and time to wound closure. Significance was tested using SPSS package.
Results: 44 wounds in the Flaminal® group, and 39 wounds in the 1% SSD group were included. Wounds treated with Flaminal® showed a significantly higher bacterial load ($p = 0.024$) and contained significantly more bacterial species ($p = 0.010$) but showed a significantly shorter healing time of 17 vs. 24 days ($p < 0.0001$).
Conclusion: A significantly shorter healing time was demonstrated in partial thickness burn wounds treated with Flaminal® versus 1% SSD, which may lead to a shorter length of hospital stay and better scar quality. The possibility of accurate burn depth assessment and the results in this study corroborate the change in treatment protocol made in the year 2000 when we switched from 1% SSD to Flaminal®.

1. Introduction

It is generally accepted that in partial thickness burn wounds, which represent the large majority of burns, wound closure in less than 18–21 days is useful to avoid complications such as hypertrophic scarring and contractures [1,2]. In the conservative treatment of this category of burn wounds, rapid and undisturbed wound healing is beneficial to obtain good esthetic and functional results. The characteristics of an ideal burn wound dressing should include: ease of application and removal, unimpeded burn depth assessment clinically as well as by laser Doppler imaging, enhancement of wound healing by maintenance of an optimal moist but not too wet environment, bacterial burden control, comfort of the patient and cost-effectiveness [3,4].

One percent silver sulfadiazine (SSD) has long been the 'gold standard', the main topical product used in burns units for treatment of partial thickness burns worldwide [5–7]. It has remarkable antibacterial qualities against a broad spectrum of micro-organisms and led to an improved survival rate in severely burned patients [8–10]. As critical colonization or

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infection are recognized as an important factor to impair wound healing, SSD as wound dressing was the most easy and reliable solution to prevent these complications and for this specific reason SSD has a longstanding reputation [11,12]. However the antibacterial property of a product is not the only characteristic that determines the overall success of a dressing. Despite the many advantages of SSD, several studies have reported on its considerable negative side effects. Some of these issues include: the emergence of resistant strains of microbial species, low silver release levels, the lack of penetration, absorption, the rapid consumption of Ag+ ions, delayed separation of the burn eschar, leucopenia, renal toxicity and the impairment on wound healing due to the cytotoxic effects on keratinocytes and fibroblasts. Argyria, electrolyte imbalance and discomfort during dressing changes are other side effects [7,13–15].

Over the years, new silver dressings have been developed to overcome some of the disadvantages encountered with SSD cream. Silver containing cloths, e.g., are reported to achieve a more sustained release of silver allowing the dressing to be left in place for several days. This could reduce the numbers of nosocomial infections, reduce pain and increase patient's comfort [16–19].

However, other studies have demonstrated a degree of cytotoxicity, also that the patient's comfort is not always improved and clinical evaluation and LDI measurements are difficult or even impossible with these dressings in place [8,20–23]. Therefore the search for an ideal dressing continues.

At the burn center of the Ghent University Hospital, the precise decision whether or not a burn wound needs to be operated can usually be made between 48 and 72 h after burn and is based on the combination of clinical burn depth assessment and measurement of healing potential by laser Doppler imaging. This utilises of course an unimpaired evaluation of the burn wound which is very difficult when it is covered with a messy layer of SSD cream. To further improve the conservative treatment of partial thickness burns, our team was therefore looking for a new wound dressing which would ideally provide all of the following: a high degree of ease of use, a good clinical wound evaluation, no interference with laser Doppler imaging, sufficient antibacterial properties and last but not least enhancement of wound healing. In March 2000 a new amorphous wound care product called Flaminal® enzyme alginogel (Flen Pharma; Kontich, Belgium) was introduced to eventually replace SSD.

Flaminal enzyme alginogel is a novel class of wound product. The products under this category have different ingredients to optimize wound debridement and healing. Flaminal enzyme alginogels comprise hydrated alginate polymers in a polyethylene glycol (PEG)/water matrix embedded with a patented antimicrobial enzymatic complex (GLG = glucose oxidase, lactoperoxidase, and guaiacol as stabilizer). As a consequence they combine the features of a hydrogel, an alginate and an antimicrobial product [24].

On the wound bed, PEG (humidifier/solvent) and water (solvent), quickly enhance the dissolution of compounds such as eschar, dry necrosis, fibrin, toxins and foreign particles that may be present or that may adhere to the wound bed (on-going autolysis). The alginate polymer then absorbs and physically bonds the dissolved material into its alginogel structure (on-going absorption). As the alginogel remains on the wound bed, this process creates and maintains a moist environment on the wound (moist wound healing). When an enzyme alginogel is put on a wound border, alginate will slowly deposit on that wound border and thus create a protective film (wound border protection) [24]. The antimicrobial enzyme system restores bacterial balance. Its mode of action is a 2 step mechanism: (1) glucose oxidase forms a peroxide (similar to honey) and (2) lactoperoxidase transforms the peroxide into oxygen radicals and hypoiodite radicals (ROS, reactive oxygen species). These radicals destroy the bacterial cell wall. Guaiacol stabilizes the radicals. The cytotoxic effect on epidermal cells appears to be low. Dermal and epidermal cells, responsible for wound healing, may therefore continue to rapidly multiply and so heal the wound. This enzyme system has a proven broad spectrum antibacterial effect against both Gram positive and Gram negative bacteria, as well as aerobic and anaerobic bacteria, including *Pseudomonas aeruginosa*, *Staphylococcus aureus* and even MRSA [25,26]. Consequently enzyme alginogels are different from typical antimicrobials. Enzyme alginogels restore and maintain the bacterial and cellular balance in the wound in 3 ways: removal of bacteria by continuous debridement, killing of bacteria by the enzyme system without damaging skin cells and enhancement of the patient's immune system by keeping the wound moist [24–26].

The purpose of this retrospective cohort study was to evaluate the effects of this enzyme alginogel (Flaminal®) on the time to healing and to compare this important outcome parameter with the results obtained with SSD. Secondly we wanted to evaluate the length of hospital stay for the admitted patients and the bacterial load of the treated burn wounds in both groups.

2. Materials and methods

2.1. Patient selection

This study was designed as a retrospective cohort study. Two research groups were composed, one group with SSD treated burns and the other group with Flaminal® treated burns. All ambulatory and hospitalized patients with burn wounds that were either treated with SSD or Flaminal®, between 1998 and 2003, were considered eligible for study inclusion. Superficial burns and burns treated with skin grafts were excluded from this study. Burn wounds were also excluded if insufficient data were available to register baseline or outcome parameters (e.g., incomplete file, change in topical treatment, insufficient photographs to confirm the initial burn depth assessment and to determine the exact moment of complete wound closure, etc.). If possible, multiple burn wounds were selected per patient.

2.2. Treatment regimen

As part of standard wound treatment in our burn center, loose skin and blisters, if present, were removed in all burns. After decontamination of the wounds by rinsing with a 10% solution of povidone-iodine in water, the burns were covered with a thick layer of 1% SSD in the control group and with Flaminal®

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in the experimental group. In both groups sterile dry gauze was used as a secondary dressing but in the Flaminal® group the sterile gauze was combined with a paraffin impregnated gauze (Jelonet®) to prevent sticking of the overlying sterile gauzes and bandages into the wound. The above mentioned procedure was performed on a daily basis until full epithelialization occurred.

2.3. Assessments

Classification of burn depth differs worldwide but plastic surgeons in our burn center consider as 'superficial partial thickness burns', those which are supposed to heal in less than 14 days and consider as 'intermediate burns' those which are supposed to heal between 14 and 21 days. Deep partial and full thickness burns do not heal within 21 days and are treated by means of surgery. Superficial burns are supposed to heal within 7 days. Initial clinical assessments on the day of burn and day 3 post burn, performed by surgeons experienced in burn care and noted in patients file, were retrospectively verified by using the wound photographs which are on a daily basis taken.

These standardized, high quality photographs were also evaluated by 2 burn wound experts to ensure a reliable assessment of the healing time. We are convinced that, in doing so, the determination of healing time based on photographs is at least as reliable as bedside evaluation of healing time, provided that this is a routine procedure and that the persons involved are experienced. The photographs allow the experts to compare the wounds day after day and are the ideal solution of mapping the wounds.

Registration of baseline patient parameters included gender, age, number of burns per patient, burn cause, burn wound location, total burned surface area (TBSA, %), surface area of the study burn (%) and burn depth. The total percentage of TBSA and percentage of TBSA of the target burn was calculated by using the Lund and Browder chart. Length of hospital stay, healing time and infection parameters, including number of swabbed wounds and data on bacterial growth were also registered in the study database.

2.4. Outcome parameters

The primary outcome parameter was the healing time till complete wound closure. Each selected burn had been photographed at different stages and allowed a precise assessment of wound healing time. Wound healing was evaluated by two independent observers. If the determined healing time differed more than 10% between the two observers, a new evaluation was done by a third observer. Secondary outcome parameters included the length of hospital stay (LOS) for admitted patients and the bacterial load of the included burn wounds. Outpatients were excluded from the analysis of LOS.

Information of bacterial load was obtained by examining the patients file and includes bacterial growth, number of species and sort of species. Bacterial growth was defined as the number of microorganism present in the wound swabs. This was registered by using a semi-quantitative scale (0: no growth; 1: ± scanty; 2: + light; 3: ++ moderate; 4: +++ heavy; 5: no culture performed). The number of species and sort of species was registered using the categories: '0: zero; 1: one; 2: two; 3: three, 4: no culture performed' and 'No species; *S. aureus*; CONS; *P. aeruginosa*; other'.

2.5. Statistical analysis

Non-parametric tests were used to analyze data. All data were registered and analyzed using Predictive Analytics Software SPSS 15®, IBM Corporation 2010. Excel 2007 Microsoft Office was used to illustrate substantial results. Confidence interval of 95% was applied.

3. Results

The number of burn wounds analyzed was 44 in the Flaminal® group and 39 in the SSD group, representing 30 patients per research group. The maximum number of included burns was three per patient.

Neither baseline patient nor burn characteristics differed significantly between the groups studied except for gender ($p = 0.037$). We believe that this statistical difference is of no

Table 1 – Baseline parameters.

	Flaminal® group	1% SSD group	p-value
Number of patients	30	30	
Number of burns	44	39	0.274υ*
Gender (male/female)	26/4	19/11	0.037χ**
Burn depth			0.257υ*
SPTB	14/44 (31.8%)	6/39 (15.4%)	
INTPTB	30/44 (68.2%)	33/39 (84.6%)	
	Median (IQR)	Median (IQR)	
Age (years)	32 (23; 43)	30 (21; 48)	0.959υ*
% TBSA of all burns	8.8 (5.0; 13.1)	6.5 (2.4; 12.0)	0.133υ*
% TBSA of target burn	3.5 (1.5; 5.0)	3.7 (1.5; 5.0)	0.909υ*
Burn cause (numbers)			0.717χ*
Scald	15	16	
Contact	2	2	
Flame	4	2	
Chemical	6	3	
Electrical	0	1	
Flash	17	14	
Other	0	1	
Burn location (numbers)			0.330χ*
Head/neck	9	4	
Upper limb	16	18	
Trunk	3	4	
Lower limb	11	12	
Mixed location	5	1	

SPTB: superficial partial thickness burn; INTPTB: intermediate partial thickness burn; IQR: inter quartile range; TBSA: total body surface area; χ: Chi-squared test; υ: Mann–Whitney U test.
* $p > 0.05$, not significant.
** $p \leq 0.05$, statistically significant.

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Table 2 – Length of hospital stay (days).

		Flaminal® group		1% SSD group	*p*-value
Ratio hospitalized/ambulatory					0.053χ*
Hospitalized		27 (90%)		21 (70%)	
Ambulatory		3 (10%)		9 (30%)	
	n	Median (IQR)	*n*	Median (IQR)	
LOS	27	11 (6; 21)	21	15 (9; 27)	0.157υ*

IQR: inter quartile range; LOS: length of hospital stay; χ: Chi-squared test; υ: Mann–Whitney U test.
* $p > 0.05$, not significant.

consequence to the other results obtained from this study. Detailed information is given in Table 1.

In the Flaminal® group 27 patients were hospitalized and 3 patients received ambulatory care. In the SSD group 21 patients were hospitalized and 9 patients received ambulatory care. Outpatients were not included to analyze the length of stay (LOS). Median length of hospital stay was 11 days (IQR: 6; 21) in the Flaminal® group and 15 days (IQR: 9; 27) in the SSD group. No statistically significant differences were found between the research groups neither for LOS nor for group consistency in regard to number of hospitalized and ambulatory patients per research group (Table 2).

In the Flaminal® group 28/44 (63.6%) wounds were cultured. This was lower in the SSD group ($p = 0.039$), where only 16/39 (41.0%) wounds were cultured. This was mostly due to a higher number of wounds that were swabbed prior to the first dressing application (Flaminal® group: 27/44 [61.4%]; SSD group: 12/39 [30.8%]). Only burns on which cultures were performed were included for the analyses of bacterial load. Statistical analysis focused on worst bacterial growth observed in each wound during treatment. The maximum number of harvested species from one wound swab was limited to one at that moment.

There was no statistically significant difference between the research groups for bacterial burden before start of topical treatment (Table 3).

During treatment, there was significantly more bacterial growth ($p = 0.024$) and there was a higher number of bacterial species ($p = 0.010$) in the Flaminal® group compared to the SSD group. Considering the sort of species, we found significantly more Pseudomonas strains in the Flaminal® group ($p = 0.025$) during treatment (Table 3).

Table 3 – Bacterial load.

		Prior to treatment	During treatment
Bacterial growth		$p = 0.463\chi^{*}$	$p = 0.024\chi^{**}$
Number of species		$p = 0.469\chi^{*}$	$p = 0.010\chi^{**}$
Sort of species	S.a.	$p = 0.947\upsilon^{*}$	$p = 0.101\upsilon^{*}$
	P.a.	$p = 1.000\upsilon^{*}$	$p = 0.025\upsilon^{**}$
	CONS	$p = 0.538\upsilon^{*}$	$p = 0.716\upsilon^{*}$
	Other	$p = 1.000\upsilon^{*}$	$p = 0.094\upsilon^{*}$

S.a.: *Staphylococcus aureus*; P.a.: *Pseudomonas aeruginosa*; CONS: coagulase negative *Staphylococcus*; χ: Chi-squared test; υ: Mann–Whitney U test.
* $p > 0.05$, not significant.
** $p \leq 0.05$, statistically significant.

Haemocultures were performed on 7 patients and all results were negative. Only 2 patients received i.v. antibiotics and this was for prophylactic reasons or for other reasons (not local wound infection). No statistical analyses were performed on these data.

If we take all burn wounds into account, the median healing time in the Flaminal® group was 17 days compared to 24 days in the 1% SSD group. This difference is statistically significant ($p < 0.0001$). Details are listed in Table 4 and Fig. 1.

4. Discussion

Silver has a long history in wound management but renewed interest came after the introduction by Moyer in 1965 of silver nitrate solution (0.5% $AgNO_3$) in the therapy of burns [15,27,28].

Table 4 – Healing time (days).

	Flaminal group (*n* = 44)		1% SSD group (*n* = 39)		*p*-value
	n	Median (IQR)	*n*	Median (IQR)	
All burns	44	17 (11; 22)	39	24 (19; 33)	<0.0001υ*

IQR: inter quartile range; υ: Mann–Whitney U test.
* $p \leq 0.05$, statistically significant.

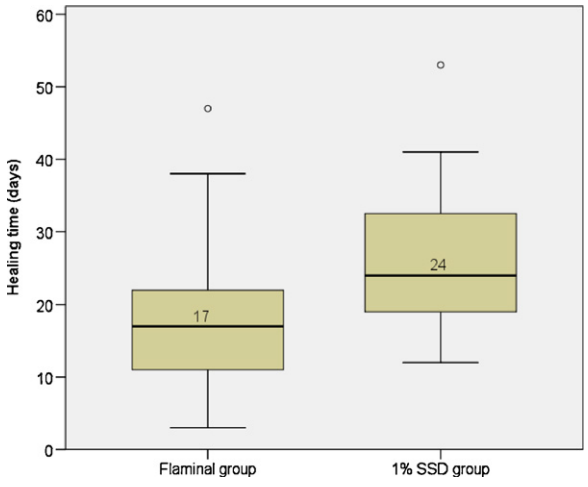

Fig. 1 – Wound healing time was shorter in the Flaminal® group compared to the 1% SSD group ($p < 0.0001$).

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Hartford stated that what the authors were introducing was not just the application of a particular substance but a 'system of burn care' [29]. From the moment SSD became available in 1967 it quickly became the standard topical agent for burn wound treatment worldwide [8,9]. The main advantage of SSD is the antibacterial activity but the mode of action is not clearly elucidated. It is generally accepted that it is a combination of the bacteriostatic effect of sulfadiazine and the bactericidal effect of silver. The bactericidal effect of silver is the result of the binding of silver with DNA, amino-acids, bacterial cell walls and by interfering with the respiratory chain. It is the combination of these different target sites which determines the excellent antibacterial properties and the low resistance rate [30–32]. The lower bioburden, led to a reduction of morbidity and mortality from burn wound sepsis [33].

As stated above, the major advantage of SSD is the excellent antimicrobial activity. Only few randomized clinical trials were able to show a significant advantage of the studied dressings over SSD regarding infection parameters [34–50]. The bioburden results of this study are in accordance with the literature as wounds treated with SSD showed a lower bacterial load. In contrast to SSD with its multiple target sites of silver on bacteria, the antibacterial effect of Flaminal® is mainly due to the release of reactive oxygen species, generated by an enzyme complex of glucose oxidase and lactoperoxidase comparable to this of honey [24–26].

The less pronounced antibacterial properties of Flaminal® did not lead to a higher incidence of wound infection, positive haemocultures or to an elevated use of antibiotics. Flaminal® will interact with bacteria, in addition to the enzyme complex, by neutralizing damaging particles as toxins and enzymes due to an ongoing removal of these particles and a continuous autolytic debridement of the wound bed. We could question the value of positive cultures on wounds when there are no signs of critical colonization and even worse, infection. The positive cultures will reach normal levels in time and will not result in any retarding effects on wound healing. Some authors even demonstrated beneficial effects of subinfective levels of bacteria. It appears to accelerate wound healing and formation of granulation tissue with increased infiltrate of neutrophils, monocytes and macrophages and increased levels of prostaglandin E2, and an increase in collagen formation [51]. Still it is important to avoid evolution to critical colonization and local and/or invasive infection.

Despite all aforementioned advantages, silver sulphadiazine also has several disadvantages, as the reported cytotoxic effect on fibroblasts and keratinocytes delaying the wound healing rate [20–22]. Moreover, the formation of an adherent sloughy layer on the wound bed, resulting in less accurate clinical evaluations or LDI scanning, also is an important drawback. Other disadvantages include: allergic contact reactions, skin irritation, discoloration (argyria), neutropenia, leucopenia and methemoglobinemia [7,13–15,52–54].

Over the last 20 years, there has been a substantial overall improvement in burn care due to early resuscitation, improved ventilation of patients with inhalation injuries, objective and accurate burn depth assessment, better control of bioburden, early excision and skin grafting and the use of dermal substitutes and cultured keratinocytes. As a consequence, much more severely burned patients do survive. The therapeutic emphasis has nowadays shifted from purely 'survival' to 'quality of survival' which requires optimal esthetic and functional outcomes. To obtain this, unimpaired healing and fast wound closure are the most important parameters [1,2,55].

Full thickness burns and deep partial thickness burns diagnosed to heal in more than 21 days usually require surgical treatment. On the other hand, burn wounds that have a predicted healing time of less than 18–21 days should be treated conservatively. The difference in healing of a burn wound in 7 or 14 days is probably not very important because the final result will be the same. On the other hand healing in 17 days instead of 24 days can make a tremendous difference in final outcome due to the substantially increased risk of hypertrophic scarring and contractures when healing take more than 3 weeks [1,2]. For this reason we continuously try to improve the conservative treatment to achieve a faster wound closure in this category of burn wounds.

The precise assessment of burn depth is of course essential to determine the optimal therapeutic approach. Laser Doppler imaging of the wound between 48 and 72 h after injury is the most accurate way to assess the depth of the burn wound and to exactly predict the time to wound healing [56–61]. However, to allow an optimal assessment by LDI in combination with clinical assessment, the wound bed should be as clean as possible and free of debris, loose skin or covering cream. The formation of a sloughy layer by SSD not only interferes with the clinical assessment of depth and with the correlation between this clinical assessment and the LDI flux values, but interferes also with later wound assessments (Fig. 2). This is one of the reasons the treatment protocol in our burn unit was changed, in the year 2000, when Flaminal® was introduced as an alternative for SSD. The new ointment provides a clean wound bed, which enables a good visual evaluation during the whole treatment (Figs. 2–6).

The results of our study showed, with the highest level of evidence ($p < 0.0001$), that burns treated with Flaminal® heal faster (17 days) than similar burns treated with 1% SSD (24 days). The publications of Deitch et al. and of Cubison et al. [1,2], who also demonstrated that burn wounds which heal in less than 21days have less risk of developing hypertrophic scars and contractures, is in accordance with our clinical impression of improved esthetic and functional

Fig. 2 – Clinical assessment of wound healing is difficult due to the sloughy layer of 1% SSD.

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Fig. 3 – Flame burn on day of admission. Clinical assessment: full thickness burn.

Fig. 6 – Day 20 post burn, almost completely re-epithelialized.

Fig. 4 – Day 4 post burn. Good clinical assessment in combination with LDI measurement possible, due to a clean wound bed.

results at long term follow-up, since the change in topical treatment in our center. Although we have been able to demonstrate that healing with Flaminal took almost seven full days less than healing with silver sulfadiazine, still we have not been able to objectively evaluate the scarring due to the limitations of this retrospective study.

The possible reason for the huge difference in healing time is the non aggressive way Flaminal® restores the bacterial balance in the wound [24–26]. Killing the bacteria by the enzyme system, removal of the bacteria by debridement and enhancement of patient's immune system by keeping the wound moist, is far less aggressive for keratinocytes and fibroblasts than the way silver works. Very important to keep in mind is the statement of Poon and Burd that silver-based products cannot discriminate between healthy cells involved in wound healing and pathogenic bacteria [20]. For rapidly proliferating cells, as keratinocytes in partial thickness burns, this could be a tremendous load leading to an unintended delay in wound healing.

A faster wound healing time would inevitably result in a shorter length of hospital stay. In this study, patients in the Flaminal® group stayed 11 days (median) in the hospital whereas patients in the 1% SSD group stayed 15 days. This difference however was not statistically significant ($p = 0.157$) and this might be related to other confounding variables such as the need for skin grafts on other burns, associated injuries, comorbidities, etc. which are very difficult to evaluate. Secondly, a significant result might have been calculated if the population size would have been larger. We believe that this shorter length of stay in the Flaminal® group is related to the treatment but this needs further investigation in a prospective study.

Due to the nature of retrospective cohort studies, this comparative study shows some weaknesses. Outcome parameters and quality of data are determined by the precision of registration in the past. We only selected burns of which sufficient data were available (complete patients file and sufficient photographs allowing a precise determination of wound healing time). This study was limited in population size, especially for the analysis of LOS and bacterial load, and statistical test on subgroups sometimes lacked power to draw definite conclusions. A prospective study on a larger population, using LDI for burn depth assessment would probably provide stronger evidence for secondary outcome parameters in this study.

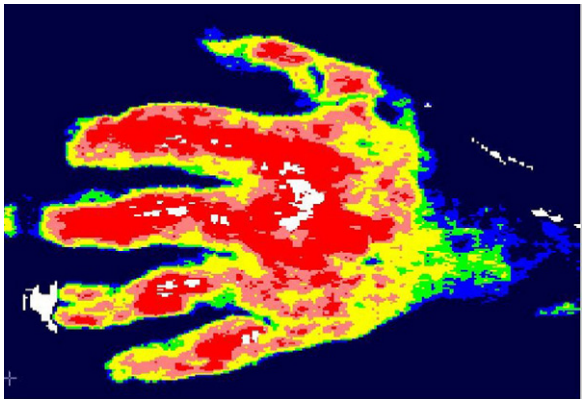

Fig. 5 – Laser Doppler imaging shows flux values corresponding with healing potential (HP) 14–21 days. The expected healing time based on LDI measurement and clinical assessment is 18–21 days.

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5. Conclusion

This study clearly demonstrates that burn wounds treated with Flaminal® show a significantly faster wound healing compared to burns treated with silver sulfadiazine ($p < 0.0001$). We are convinced, based on the extensive literature on this subject as well as on the clinical experience in our own department, that this results in better scar quality. The clinical significance of the higher bioburden can be questioned, as there were no signs of infection, positive haemocultures or increased use of antibiotics in the Flaminal® group. We also believe that the favorable healing time is related to a shorter length of hospital stay and could result in a better cost-efficiency profile. We had started to use Flaminal because it allowed a better assessment of the burn wound, both by clinical evaluation and even more important-by unimpaired LDI examination: the results of this comparative study and the significantly reduced healing time have additionally convinced us to continue to use this enzyme alginogel Flaminal® in our hospital and burn unit as the standard treatment for all partial thickness burns.

Conflict of interest

All authors disclose any financial or personal relationship with other people or organization that could inappropriately influence this work.

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This study was performed in an independent way and there was no involvement of any sponsorship.

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