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# Clinical Safety and Efficacy of a Novel Thermoreversible Polyhexanide-Preserved Wound Covering Gel

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**Key Words**
Wound therapy · Wound gel, clinical safety, efficacy · Flammazine

**Abstract**
***Background:*** An ideal topical formulation for wound therapy does not exist. The aim of this study was to develop a novel improved therapeutic option for the treatment of acute and chronic wounds. ***Methods:*** A transparent wound gel which is in a liquid state below and in a gel state at or above room temperature was developed. Forty-four patients were included in this open randomized controlled single-center study. Flammazine™ served as control in the treatment of skin graft donor sites. Wounds were assessed for time of dressing change and overall satisfaction of patients and health care providers. The data were analyzed using the nonparametric Mann-Whitney test. ***Results:*** The wound gel proved to be superior in comparison with Flammazine with respect to wound assessment ($p = 0.002$), staining ($p = 0.007$), leaking ($p = 0.032$) and smell ($p = 0.034$). Flammazine showed favorable results regarding the parameters dehydration of the dressings ($p = 0.012$) and wound adherence ($p = 0.005$). The evaluation of the overall dressing change process showed no significant differences. ***Conclusion:*** The thermoreversible wound gel containing polyhexanide allows for good handling and wound assessment. This study demonstrated a high satisfaction level of patient and health care providers, and the wound gel proved an effective alternative to commonly used treatments.



## Introduction

Dermal wound healing is a dynamic process involving complex cellular and extra-cellular mechanisms which can easily be jeopardized by chemical substances, diabetes mellitus, radiation or bacterial infections [1]. It is therefore of the utmost importance that any topical medical product used does not inhibit wound healing and protects the wound from infections. On the other hand, it should be easy to handle on a daily basis for health care providers and physicians. Furthermore, it should enable a direct assessment of the wound, keep it moist and make contact with the wound surface even in the case of deep wounds. In addition, it should be well tolerated by the patient.

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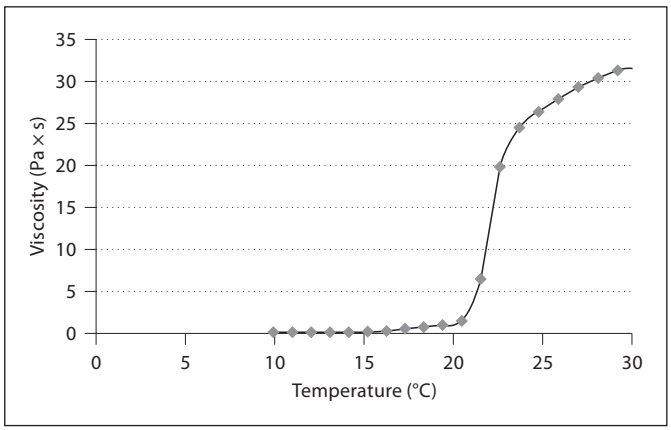


**Fig. 1.** Dependency of the viscosity on temperature. Up to 20°C the wound covering gel is in a liquid state, above 23° in a gel state. This phase change greatly facilitates the handling and covering of uneven wound surfaces or the filling of cavities.

At present, there are many ointments available, but none of them fulfills all the desired criteria. Frequent adverse drug reactions are allergies and toxic effects. Additional negative effects are staining of clothes and wounds, complicating wound assessment and reducing patient compliance as well as the difficult and painful filling of deep wounds.

To improve wound treatment a new thermoreversible wound covering gel whose ingredients are well tolerated was developed. Its transparency allows direct wound assessment without the need for painful cleaning of the stained wound. The antiseptic polyhexanide serves as preservation, while poloxamer 407 is responsible for the phase change from liquid below body temperature to gel state at or above body temperature (fig. 1) [2–4].

The aim of the study was to investigate the safety and efficacy of this novel wound covering gel compared to a standard wound management with a silver-sulfadiazine-containing formulation on the daily treatment of skin graft donor sites. The object was the time and painfulness of dressing change, skin sensation, skin-friendliness, pain, wound assessment, olfactics, infections and the overall satisfaction of patients and health care providers.

## Materials and Methods

The open randomized controlled single-center study was carried out on 44 patients in 2 parallel groups (Traumasept® wound covering gel vs. Flammazine®) in the Department of Plastic Surgery, Burn Center, of the BG University Hospital Bergmannsheil, Bochum, Germany, during a 9-month period. The study was approved by the ethics committee of the Ruhr University Bochum (AZ 3108-07). It was performed in accordance with the principles of the Declaration of Helsinki (1964) and Edinburgh (2000), the Federal Institute for Drugs and Medical Devices and the note for guidance on good clinical practice from 1997.

Inclusion criteria were undergoing skin graft harvest from thigh, age 18–70 years, sterile donor site, responsive patient and obtained informed consent.

Patient were excluded from the study if there was evidence or suspected infection of the skin graft donor site, pregnancy or lactation period, parameters leading to delayed wound healing such as malignancies, vascular abnormalities, immunodeficiencies, diabetes, severe kidney disease or dialysis and artificial respiration as well as medications within 30 days before the outset of the study which impair wound healing such as chemotherapy and immunosuppressives, known incompatibility to the ingredients of the test solutions, alcohol or drug abuse, unresponsive patient and no signed consent form.

The ingredients of Traumasept wound covering gel (Dr. August Wolff GmbH & Co. KG Arzneimittel, Bielefeld, Germany), apart from water, are only the antiseptic polyhexanide (1.5%), the sugar alcohol glycerol and the hydrophilic nonionic surfactant poloxamer 407, a copolymer containing ethylene oxide and propylene oxide blocks, which are responsible for the thermoreversible gel formulation (fig. 1) [3].

In contrast, the main active agent of Flammazine (Solvay Arzneimittel, Hannover, Germany) is silver sulfadiazine (concentration: 10 mg/g), a combination of a sulfonamide-based antibiotic and silver, with a known potential for intolerance reactions. In addition, it contains polysorbates as emulsifiers, glycerol, the alkane hydrocarbons hexadecane and paraffin and water.

The wound was created by taking skin grafts from the thigh using a compressed air dermatome, which was adjusted to 200 μm (8/100 inch). After creation of the wound either the polyhexanide preserved wound covering gel (thickness = 3–8 mm) or Flammazine (thickness = 2–3 mm) was applied to the wound and covered by fatty gauze and sterile cotton gauze.

The primary parameter was the time of dressing change (minutes). Secondary parameters were the evaluations of the dressing change by the patient and by the staff. The evaluation of the dressing change by the patient included skin sensation after application (very good, good, neutral, unpleasant), type of skin sensation (pleasantly cool, none, mild itching, intense itching), skin friendliness (very good, good, moderate, poor), skin redness (none, minor, moderate, intense) and wound staining (none, minor, moderate, intense). A pain assessment was performed using visual analogue scale 0–10 during dressing removal (0 = no pain; 1–2 = slight pain; 3–4 = mild pain; 5 = moderate pain; 6–9 = moderately severe pain; 10 = severe pain).

The evaluation of the dressing change and the wound by the caregiver focused on removal of the dressing (very good, good, neutral, unpleasant), dressing dehydration (none, minor, moderate, intense), assessment of the wound (very good, good, moderate, poor), patient friendliness of the dressing change (very good, good, moderate, poor), pain during dressing change (none, minor, moderate, intense), staining of the dressing (none, minor, moderate, intense), leakage of the ointment (none, minor, moderate, intense) and olfactics (none, minor, moderate, intense).

The evaluation of inflammatory response was performed through clinical assessment and wound swabs.

*Statistical Analysis*

The hypothesis was that the time for dressing change summarized over study days 3, 6 and 9 would be shorter in the group receiving the wound gel compared to that treated with silver-sulfadiazine-containing formulation. The sample size calculation was based on the following assumptions: it was expected that the time for dressing change would be substantially shorter in the wound gel group (effect size $>0.8$). Based on a power of 0.9 ($1 - \beta$) and $p < 0.05$ ($\alpha$) a sample size of 40 patients (20 per group) was calculated. The 2-sided Mann-Whitney test was used to test this hypothesis because the data deviated from normal distribution. The primary evaluation was done by intention-to-treat analysis.

Superiority of the wound covering gel was also expected for the secondary parameters. For the evaluation of the secondary parameter (sum score of all 3 dressing changes) nonparametric, the 2-sided Mann-Whitney- est was used as well. Because multiple tests were performed without adjustment of $\alpha$ (and reported p values were not adjusted), the results regarding secondary parameters should be interpreted as explorative (and not as confirmative tests).

A blinded study setting was not feasible due to different color and consistency of the agents applied.

## Results

All patients included in the study matched the inclusion criteria and informed consent was obtained. There were 4 dropouts, 2 in each group. The reasons were self-discharge, application of the wrong dressing by a nurse, recall of the consent form and diseases not mentioned before starting the trial.

The study population had a mean age of 49.5 years (SD = 15.1), ranging from 19.7 to 70.6 years. Thirteen female and 28 male patients took part in the study.

The mean wound size was 0.92 ± 0.73% of the body surface area (range = 0.04–2.7) or 173.9 ± 136.7 $cm^2$ (range = 9.0–522).

The donor area was the ventral thigh in 4 out of 5 cases. There were no significant differences between the 2 groups concerning demographic data and wound characteristics.

The mean sum of time assessed for dressing change on days 3, 6 and 9 in the group treated with wound covering gel was 31:43 ± 18:11 min (median = 24:34, 25th percentile = 19:23, 75th percentile = 37:25) and in the case of silver-sulfadiazine-containing formulation 22:19 ± 6:27 min (median = 22:54, 25th percentile = 18:44, 75th percentile = 26:08). There was no significant difference between the wound covering gel and the silver-sulfadiazine-containing formulation ($p = 0.19$; fig. 2).

It should be noted that figure 2 shows 8 outliers in the wound gel group, which are mainly responsible for the difference in means (the median showed a lesser difference).

The analysis of secondary parameters indicated some dissimilarities between wound gel and Flammazine: the pain decreased during the study course. By day 3 no differences could be observed between the 2 groups ($p > 0.1$), by days 6 and 9 the pain was evaluated higher by patients in the wound-covering gel group ($p = 0.007$ and $p = 0.035$, wound gel vs. Flammazine, respectively). The staining was considered lower in the wound gel group ($p < 0.003$).

The secondary parameters showed variation in the evaluation of the nurses on the different days: on day 3 the medical assessment of the wound yielded significantly better values in the wound gel group ($p = 0.042$) and the smell of the wound was significantly less ($p = 0.034$).

On day 6 the wound assessment in the wound gel group was better ($p = 0.006$), but the removal of the dressing was more complicated ($p = 0.014$), and the wound adherence ($p = 0.029$) as well as the pain were more marked ($p = 0.005$) than in the Flammazine group.

On day 9 the wound gel showed better values concerning wound assessment ($p = 0.020$), staining of the dressing ($p < 0.005$) and leaking of the ointments ($p = 0.023$).

All in all, the sum-score of the evaluation by the nurses showed less dehydration and wound adherence of the dressings in the Flammazine group and a significantly better wound assessment, less staining and leaking in the wound gel group.

The sum score of the assessment by the patients showed less wound staining in the wound gel group and less pain during dressing removal in the Flammazine group. The other parameters showed no significant differences.

The overall assessment of the dressing change by the caregiver or patient revealed no significant differences between Flammazine and the wound covering gel.

No adverse events could be observed in either group.

## Discussion

An ideal wound dressing should not inhibit wound healing, protect the wound from infections, be easy to handle even in the case of deep wounds, allow direct assessment of the wound, keep the wound moist and be well tolerated by the patient.

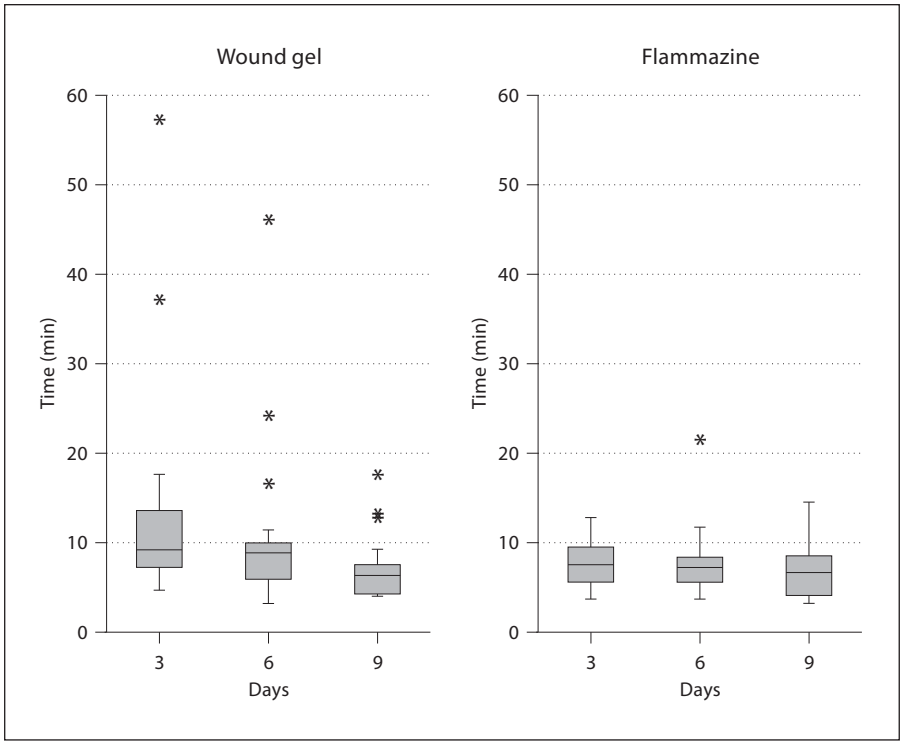


**Fig. 2.** Time of dressing change on days 3, 6 and 9. It is conspicuous that 8 outliers (asterisks) occurred in the wound gel group, whereas the Flammazine group merely showed 1. The time of dressing change in the wound gel group decreased from day 3 to day 9, whereas the time in the Flammazine group remained relatively constant.

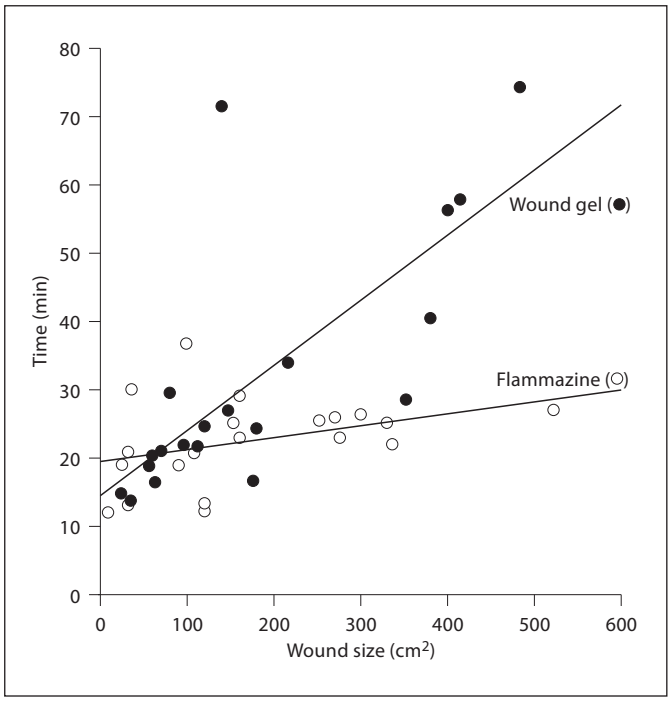


**Fig. 3.** Time of dressing change depending on wound size. The results of the regression analyses revealed that the time of dressing change was dependent on the wound size.

Until now, no ointment fulfills all preferable criteria. The main problems are allergic reactions and toxic effects, staining of wounds, as well as difficulties and pain in the treatment of deep wounds.

To evaluate the quality of the wound covering gel in day-to-day use, we compared it to the standard wound management with the silver sulfadiazine solution Flammazine on skin graft donor sites on standardized wounds [5]. The wound dressings were changed on days 3, 6 and 9 and the wounds were assessed for the duration of dressing change, pain, colors, skin sensation, olfactics, infections and the overall satisfaction of the patients and health care providers.

The mean time of dressing change of the polyhexanide-preserved wound covering gel tended to be longer than with Flammazine, but no significant differences were observed (mean = 31:43 vs. 22:19 min; p = 0.19). There are some reasons that could explain this: in a few outliers with large wounds the gel had dried (high water ratio compared to Flammazine) and had to be softened before removing (fig. 2 and 3). A replacement on every or every second day, which would be usual in the treatment of wounds, would be no problem. A second reason was the use of cooled wound gel (refrigerated, up to patient 29), which delayed the phase change from fluid to gel and

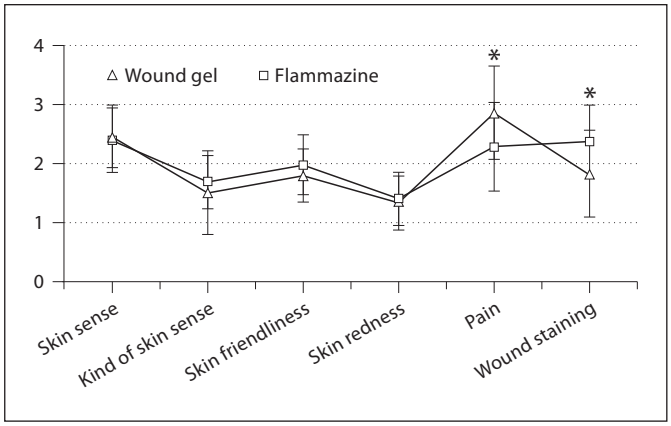


**Fig. 4.** Differences in dressing change, assessment by patients. The sum score (sum of the mean values of days 3, 6 and 9; Gaussian distribution) of the single parameters showed that wound staining was evaluated higher in the wound gel group ($p = 0.025$), whereas pain during dressing removal was considered higher in the Flammazine group ($p = 0.030$). * $p < 0.05$.

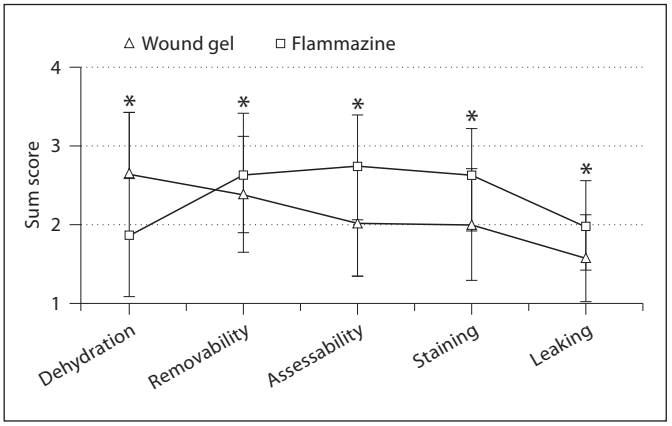


**Fig. 5.** Differences in dressing change of the wound, overall assessment by the nurses. The sum score (sum of the mean values of days 3, 6 and 9; Gaussian distribution) of the single parameters showed less dehydration of the dressings ($p = 0.012$) and better removability ($p = 0.005$) in the Flammazine group and better wound assessment ($p = 0.002$), less staining ($p = 0.007$) and leaking ($p = 0.032$) in the wound gel group. The other parameters showed no significant differences. * $p < 0.05$.

made it complicated to keep the gel on the curved wound. The following dressing changes were made with the gel stored at room temperature, leading to shorter dressing changes and improved usage. In addition, there was a lack of experience of the nurses with the wound covering gel, whereas they had been used to Flammazine for many years.

The better results of Flammazine as regards pain during dressing removal, dehydration of the dressing and wound adherence (fig. 4 and 5) could be explained by the fact that the wound covering gel – because of its high amount of water – ran dry on the third day. Thus it stuck to the wound, which meant the dressing had to be soaked, leading to significantly extended dressing times. Not surprisingly, the resulting adherence of the dressings caused more pain as compared to the fatty ointment Flammazine.

The better results of the wound gel – better wound assessment and less staining – could easily be explained by the transparent gel and was one of our main targets in the development. The better outcome in leaking/spread of the wound gel was probably attributable to the fluid state, which made it easy to apply to the wound, followed by the gel state allowing to keep it in place. The olfacts of the wound gel were evaluated as 100% neutral, whereas Flammazine was described as sour and rotten; significant differences could be observed.

The other parameter – skin sensation, skin friendliness and skin reddening – showed good results in both groups, no significant differences could be detected. We considered these results favorable for the newly developed wound gel in view of the usage of Flammazine over decades.

In the literature the preservation of the wound gel, polyhexanide, is described as well tolerated: a clinical study on mesh grafts in burn wounds proved polyhexanide to be superior to povidone-iodine and silver nitrate regarding re-epithelialization [6]. Experimental data of the impact of wound gel on microcirculation and wound healing in mice in our research team showed no toxic effects [7]. Another study of our team found an integrity loss of the endothelium and a decrease in the functional vessel density after 1 hour of topical exposures in ears of mice [8]. These results contrast with others, who recommend polyhexanide as the local antiseptic of choice [9]. A study on wound healing in pigs showed significantly faster healing of polihexanide versus octenidine and no difference to Ringer solution [4]. A comparative in vitro study of cell toxicity reported best results of polyhexanide compared to octenidine and povidone-iodine [10]. Thus far no toxic effects of polyhexanide on wound healing have been reported in the literature [4, 6, 11, 12], whereas polyhexanide shows a good microbicidal activity and therefore qualifies for reduction in bacterial populations on the wounds [2, 13, 14]. Accordingly, in our study no infection was seen.

The second component of the wound gel, poloxamer 407, is responsible for the phase change from liquid below body temperature to gel state at or above body temperature and allows a more constant and sustained drug release resulting in improved drug efficacy and fewer adverse side effects [3, 15]. Poloxamer 407 is described as nontoxic and even used for topical, parenteral and intramuscular administrations in drugs [15–18]. In high doses it could elevate the cholesterol and triglyceride levels by stimulation of the HMG-CoA reductase activity and alterations in the renal filtration [3, 18].

In contrast to the excellent tolerability of polihexanide many adverse reactions (cholestase, hemogram shifts, prohibited during pregnancy, inhibition of carboanhydrase) and allergies to the sulfonamides, one of the main active agents of Flammazine, are known to date [19]. In addition the second active antimicrobial agent is silver with its known tissue toxics [20, 21].

## Conclusion

The newly developed wound covering gel shows good results for wound treatment and represents an alternative to Flammazine or iodine-based ointments [22] which are toxic and associated with many allergic reactions.

The transparency and absence of staining allow for good wound assessment, without the need for painful cleaning, and the change from the fluid to the gel state enables easy handling and filling of wound cavities. Therefore, the wound covering gel comes a little bit closer to the ideal ointment.


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