Efficacy of a Gel Containing Polihexanide and Betaine in Deep Partial and Full Thickness Burns Requiring Split-thickness Skin Grafts: A Noncomparative Clinical Study

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Despite overall advances in burn therapy, wound infection remains one of the leading causes of morbidity and mortality in patients with severe burn injuries. This prospective, multicenter, noncomparative clinical trial was conducted to assess the efficacy and safety of Prontosan® Wound Gel X (PWX), a gel containing polihexanide and betaine, for moistening and cleansing in deep tissue burn wounds requiring split-thickness skin grafting. Patients with deep partial or full thickness burn wounds requiring split-thickness skin grafting were treated with the gel to evaluate its tolerability and safety as well as graft take and the healing of the skin graft. Target wounds were assessed clinically and by

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Competing Interests: None of the authors have any actual or potential conflicts of interest regarding the present research.

Ethical Approval and Consent to Participate: All documents that were subject to review were provided to the competent, ethical committees (ECs) throughout the study. Before initiating the study or implementing changes in the study conduct, the investigators obtained written and dated approvals from the ECs for the study protocol and amendments, written informed consent forms, consent form updates, patient recruitment procedures, and any other written information to be provided to patients. The clinical study was conducted in accordance with the Declaration of Helsinki (revised 59th General Assembly, Seoul, South Korea, 2008). It was carried out in compliance with Standard Operating Procedures, ISO 14155-2011 and with local laws and regulations relevant to the research of medical devices in the country of conduct.

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Competent Independent Ethics Committees reviewed the study protocol, any protocol amendments and the Patient Information Sheet and Consent Form.

Details of IECs consulted are listed below: Ethikkommission der medizinischen Fakultät der RUB: Christine Schnell, Bürkle-de-la-Camp-Platz 1, DE-44789 Bochum/Germany; Ethikkommission der Landesärztekammer Rheinland-Pfalz: Prof. Dr. Stephan Letzel, Deutschhausplatz 3, DE-55116 Mainz/Germany; Sächsische Landesärztekammer Ethikkommission: Ass. jur. Anke Schmieder, Leiterin Referat Ethikkommission, Schützenh.he 16, DE-01099 Dresden/Germany

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using a photo-planimetric analyzing software for re-epithelialization. From 04/2012 to 05/2015, burn patients from three burn centers in Germany were screened for the study, of which 51 patients met the inclusion criteria. Predominantly deep partial thickness burn wounds were found (88.2 %). Except for one graft failure, all patients reached complete re-epithelialization after one (n = 14), two (n = 31), or three (n = 5) administrations of the gel. The median time to complete graft take was 7 days and was below the average healing time reported in comparable studies. No wound infection or erythema occurred. This is the first study to document the outcomes of deep partial and full thickness burns treated with PWX for moistening and cleansing. The gel was shown to be efficacious, safe, and well tolerated for use in burn wounds requiring split-thickness skin grafts.

BACKGROUND

Burn injury is a severe pathology and a common type of traumatic injury causing substantial morbidity and mortality. Annually, approximately six million patients worldwide are affected by burn wounds with the majority of them treated in outpatient clinics.[1] In Europe, the average incidence of severe burn accidents is between 1.4% and 18%,[2] though exact numbers for burn wounds are still unavailable and most European countries do not provide a national registry system for hospitalized patients with severe burns.

Despite remarkable advances in intensive care medicine and wound management, infection remains a major cause of morbidity and mortality in patients with severe burn injuries. Infection impairs wound healing and, therefore, impedes adequate skin grafting, increasing the risk of sepsis.[3] Thus, finding novel topical and systemic wound therapeutics is a focus of intense research and product development by the pharmaceutical industry. For decades, silver sulfadiazine-containing topicals have been commonly used for the treatment of burn wounds.[4] A systematic review conducted by the Cochrane group has revealed that there is insufficient evidence to show that silver-containing dressings or topical agents prevent wound infection or promote wound healing.[5] Some evidence for silver sulfadiazine has even suggested the opposite.[6,7] Silver sulfadiazine-containing topical agents are also opaque and, thus, impede clinical assessment of burn wounds. These silver-based topicals first need to be removed to allow for wound evaluation. In turn, this procedure leads to unnecessary discomfort with a subsequent need for pain-relieving medication for the patient. However, silver ion-releasing and silver nitrate dressing are not opaque and, thus, do not impede clinical assessments of burn wounds. Moreover, there are concerns about the use of silver sulfadiazine for superficial burns due to an increase of proinflammatory cytokines,[8] prolongation of inflammation leading to poor scarring,[9] and potentially severe side effects.[10,11] Wound penetration of silver-based antimicrobials is weak and limited to the surface epithelium due to binding of silver ions to surface proteins, particularly in the presence of eschar.[12,13] Furthermore, silver nitrates bear the potential of severe side effects, such as hyponatremia, hypochloremia, and in rare cases, (met-)hemoglobinemia.[13] Thus, an ideal topical agent for the treatment of burn wounds has not been found yet.

For deep partial and full thickness burns, split-thickness skin grafting (STSG) is the current gold standard of care. It includes epidermis, basement membrane, and a part of the upper dermis. To compensate for limited donor site availability of skin, STSGs can be meshed for expansion. Compared with nongrafted partial- or full-thickness burn wounds, the use of STSG provides regeneration of epidermis and reduces wound contraction and extracellular matrix deposition.[14] However, the application of STSG has disadvantages: the overall wound size is increased with both the recipient and donor site becoming susceptible to infections, pain, pigmentation changes, and to scarring.[15] There is also a paucity of available data concerning the use and dressing of STSG and, in particular, the prevention of wound infection. Most dressing protocols include several layers of paraffin gauze on top of the STSG with changes of dressing every other day.[16] Furthermore, the majority of clinical studies on burn wounds treated with STSG concentrate on wound care of the donor site rather than of the grafted site. To date, there have been few studies published assessing the use of polihexanide in burn wounds.

Prontosan® Wound Gel X (PWX) consists of polyaminopropyl biguanide (polihexanide) and betaine. The composition has been shown to have a broad spectrum of activity against Gram-positive and Gram-negative bacteria, biofilms, and fungi,[17,18] and it can be applied over an extended period due to its low-grade toxicity. PWX is intended for the physical cleansing, moistening, and decontamination of

acute, chronic, thermal, chemical, and radiation-induced wounds. Based on the clinical efficacy of a topical agent containing polihexanide and betaine in chronic wounds,[17,18] this is the first study to analyze the outcomes of burn wounds requiring STSG that were moistened and cleaned with PWX. The study objectives were to evaluate graft take and the healing of skin grafts. Furthermore, the PWX treatment was tested for its tolerability and safety when used for severe burns. The results from this study provide basic information regarding the outcomes of burn wounds when treated with PWX.

METHODS

This trial is a prospective, multicenter, noncomparative study with a single cohort planned for 50 evaluable patients with deep partial and full thickness burns requiring STSG.

Study Design

A sample size of 50 evaluable patients was planned. Patients (aged ≥ 18 years) from three different study centers (Berufsgenossenschaftliche Unfallklinik Ludwigshafen, Germany, trial center number: 200; Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil, Bochum, Germany, trial center number: 300; St. Georg Klinikum, Leipzig, Germany, trial center number: 400), with clinically assessed deep partial or full thickness burns requiring STSGs, were followed in the trial. The depth of burn wounds was determined in accordance with the European Guidelines for Burn Care.[19,20] In detail, burn wounds were classified as deep partial thickness or deep dermal, and full thickness burns. Only patients with burn wounds, which required surgical debridement followed by split-thickness skin grafting, were included. The target burn wound size had to be between 10 cm^2 and 1000 cm^2. Prior to the surgical debridement and skin grafting, burn wounds were disinfected using a wound-cleansing solution (Octenisept®) and dressed with impregnated vaseline gauzes every other day. Octenidine dihydrochloride, a bispyridine derivative, has broad-spectrum antimicrobial efficacy and does not impair wound healing.[13] The target wounds were assigned for surgical excision within 3 to 5 days after the initial burn accident once complete demarcation of the deep dermal or full thickness burns was visible. Furthermore, the locations and etiology of the target wounds were collected. For the patients under investigation, the standard mesh expansion of the skin grafts was 1:1 for burn wounds involving the hand, feet, face, neck, décolleté or genitals, and 1:1.5 for any other body part. These mesh expansion ratios were consistent within all three study centers.

Women of childbearing potential had to test negative on a standard urine pregnancy test and had to agree to practice appropriate contraceptive methods for the duration of the study. Patients with exposed hyaline cartilage, previous skin graft failure, a total burn surface area of ≥ 70% or infection at the target wound site were excluded. Except for immunosuppression, steroid therapy or chronic hemodialysis, there were no other restrictions regarding concomitant therapy. Patients with insulin-dependent type I diabetes or an allergy or sensitivity to any of the ingredients of PWX or chlorhexidine were excluded from the trial. In addition, patient factors including age, gender, body mass index (BMI) and comorbidities (eg, hypertension, tobacco use, anemia, a history of surgical procedures performed, and clinically relevant diseases) were collected.

The study was reviewed and approved by the ethical committees of each study center. Written informed consent was obtained from every patient. The clinical study (ClinicalTrials.gov Identifier: NCT01534858, registered February 17, 2012) was conducted in accordance with the Declaration of Helsinki (revised 59th General Assembly, Seoul, South Korea, 2008).

Investigational Product and Wound Treatment

PWX is a ready-to-use, clear, colorless, and odorless hydrogel, which is well tolerated. The product is sterile and has an 8-week shelf-life after opening. It is free from animal origin components or substances derived from animal origin components, as well as from human blood derivatives. The ingredients of PWX are 0.1% polyaminopropyl biguanide (polihexanide), 0.14% betaine, glycerin, hydroxyethylcellulose, and purified water. Betaine is a surfactant which enables penetration of difficult coatings to stimulate wound healing. Polyaminopropyl biguanide is a polymer or oligomer with biguanide functional groups connected by hexyl hydrocarbon chains. It is bactericidal at very low concentrations, and it is also fungicidal. The polymer strands are incorporated into the bacterial cell membrane thus disrupting the membrane and reducing its permeability. Furthermore, polyhexanide is bactericidal by binding to bacterial DNA and altering bacterial transcription. As it is not toxic or irritating, it can be directly applied to wounds. Thus, polihexanide is used as an antimicrobial agent in products for

intraoperative wound irrigation, surgical and non-surgical wound dressings, wound bed preparation in chronic wounds such as diabetic foot ulcers, leg ulcers, and pressure ulcers, and in burn wound management. Biguanides themselves are cationic emulsifiers with biocidal properties of which chlorhexidine is the most commonly used one.[13] However, in contrast to polymeric biguanides, more traditional disinfectants, such as alcohol or chlorhexidine, can cause skin irritation. Furthermore, chlorhexidine is only bactericidal at high concentration.

Preoperatively, every study patient received a single shot of a second-generation cephalosporin antibiotic systemically. In case of allergy, clindamycin was used as a preoperative antibiotic. If possible, full thickness burn wounds were excised to the subcutaneous level for skin grafting. After surgical debridement of the burn wounds, STSGs of 0.2 to 0.3 mm thickness depending on the quality of the donor site skin were harvested using a dermatome, then mesh-expanded as described above, and transferred to the wound area. Skin grafts applied to burn wounds involving the hand, feet, face, neck, décolleté or genitals were secured with resorbable sutures, while engraftments applied to the trunk or extremities were secured with staples. Immediately after split-thickness skin grafting, PWX was applied topically as a thin layer (3–4 mm) to the entire grafted area (Figure 1). The cover dressing of the treated burn wounds consisted of vaseline gauzes followed by sterile compresses and elastic bandages. PWX treatment was repeated on postoperative day 5 and continued every other day until postoperative day 29 or earlier if complete graft take occurred. No systemic antimicrobials were administered postoperatively unless the clinical condition of the treated wounds required the use of antibiotics which would have consequently been rated as a serious adverse event. Wounds were assessed clinically on every treatment day before applying PWX to the grafted area. The postoperative assessment included the clinical evaluation of the primary and secondary study variables as well as proper photo documentation of the grafted site.

Primary Study Variables

The primary study objective was to evaluate the healing of STSGs treated with PWX in patients with deep partial and full thickness burns. Therefore, the time to complete re-epithelialization of the graft interstices and graft take itself were estimated by clinical assessment starting on postoperative day 5 and continuing every other day until complete graft take occurred. The re-epithelialization of STSGs was also assessed on photographs by using a photo-planimetric analyzing software (Optimas 6, Media Cybernetics, Silver Spring, MD). The percentage of epithelialization (%) was determined in comparison to the size of the grafted area (cm^2) immediately following skin grafting (=baseline) by digitally assessing a representative 10 cm^2 rectangular section (5 × 5 cm) of the grafted

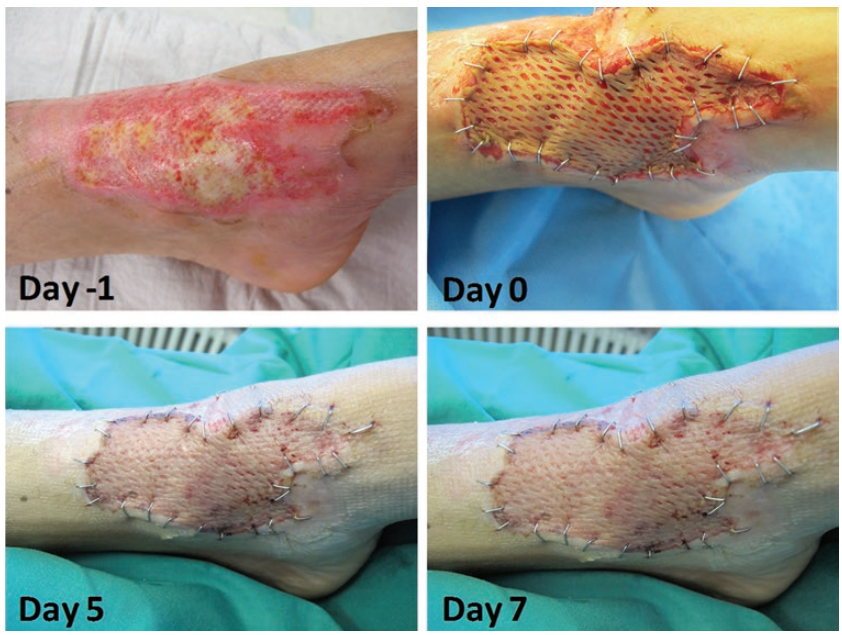

Figure 1. Deep partial thickness skin burn (grade IIb) on the dorsum of a foot treated with split-thickness skin grafting and Prontosan® Wound Gel X (PWX). On postoperative day 5, there is a good take of the skin graft while on postoperative day 7 complete epithelialization can already be observed.

wound. This image analysis toolset allowed differentiation between epithelialized and nonepithelialized surface areas by measuring open interstices and had been validated for use in the evaluation of the re-epithelialization rate of meshed skin grafts.[21] In the present study, a re-epithelialization of 95 % represented complete wound healing and graft take.

Further primary study criteria were the incidence of wound infection and reoperation of the grafted site defined as any surgical procedure performed at the grafted site during the 30-day study period.

Secondary Study Variables

The secondary study objective was to evaluate the tolerability and safety of PWX. To assess the tolerability and safety of PWX pruritus was assessed by asking the patient to rate its presence at the grafted site using a scale (0 = no pruritus, 1 = mild, 2 = moderate, 3 = severe pruritus). Erythema of the skin at the grafted site was also clinically assessed by the investigator using a scale (0 = no redness, 1 = mild, 2 = moderate, 3 = severe erythema). Additionally, pain at the grafted site was evaluated using an unmarked and unscaled 100 mm visual analog scale (VAS) where 0 mm corresponds to no pain and 100 mm corresponds to the worst pain imaginable. After patients had marked the VAS according to their current pain level at the treated site, the investigator measured the VAS.

The standard pain management slightly differed between the trial centers. At trial centers 200 and 300, low doses of nonsteroidal anti-inflammatory drugs and weak opioids were administered orally at regular intervals following surgery. The administration of the weak opioid was stopped as soon as possible. At trial center 400, stronger opioids were administered within the first 24 hours postoperatively. Afterward, opioid was given intravenously if necessary. The subjective perception of pain was assessed using the VAS at baseline (day 0, directly after the surgery), on day 5, and continued every other day until day 29 or until complete graft take occurred. Adverse events occurring until the end of the study were documented in detail and reported.

Statistical Analysis

A sample size calculation was not conducted based on the study type. A sample size of 50 patients was chosen as this number of patients is usually regarded as sufficient to gain experience in a first postmarketing surveillance study. Thus, this study may serve as the basis for a sample size calculation for a future randomized, controlled trial. All drop-outs were replaced.

The final statistical analysis was performed after the last patient completed the study and after checking and cleaning the database. Data from the case report forms were analyzed. Wilcoxon and Kruskal-Wallis tests were used for statistical analysis of clinical and photo-planimetric assessment of re-epithelialization of grafted burn wounds. The time to complete re-epithelialization was determined using survival analysis (product-limit survival estimate; Kaplan-Meier plot; log-rank test) based on the clinical assessment. To compare "pain over time," a rank-test for monotonic trend was performed. Data are presented as a percentage, mean values ± standard deviation, medians, and ranges. A P value of less than .05 was regarded as statistically significant.

RESULTS

In total, 56 patients were included in the investigational study (Figure 2). Preoperatively, two patients were unwilling to further participate in the trial and withdrew their consent. In two other cases, patients did not receive STSGs after an intraoperative reassessment of the burn wounds. In addition, one patient was not treated with PWX due to an existing allergy to polihexanide.

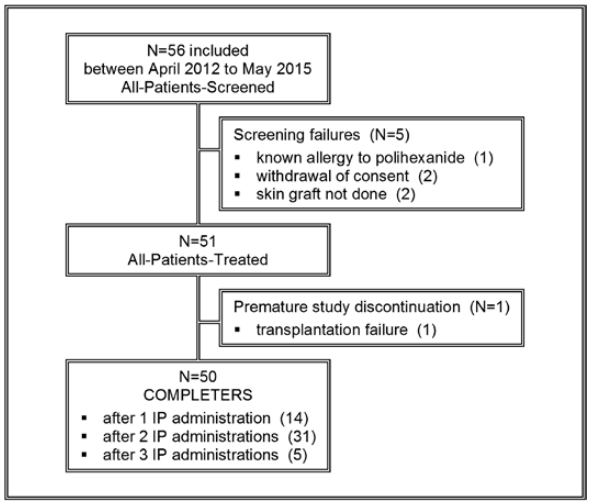

Figure 2. Disposal of patients and IP (IP = investigational product, Prontosan® Wound Gel X [PWX]). In total, 56 patients were screened with five patients being excluded based on exclusion criteria. Patients were included from April 2012 to May 2015.

Patient Demographics and Other Baseline Characteristics

Fifty-one patients aged between 19 and 87 years (median age 38 years) and in need of STSG due to burn injuries were treated with PWX. Male patients represented more than two-thirds of the included patients (70.6%). The BMI in the study population was 26.3 ± 4.3 kg/m^2, and the percentage of smokers was 47.1%. The mean total burn surface area amounted to 10.7 ± 11.9% of the body surface. The size of the target wound was 177.2 ± 191.2 cm^2 (range 10–950 cm^2). Injury mechanisms were direct flame, contact burns, and scalds. Burn wounds mostly involved the upper or lower extremities (86.9%) and were predominantly deep partial thickness burns (88.2%; full thickness burns: 11.8%). The median size of the meshed skin graft was 110 cm^2 (range 10–950 cm^2) resulting in a markedly higher mean ± standard deviation value of 175.6 ± 191.5 cm^2. The thickness of the graft was 0.2 mm in most cases (96.1%) (Table 1).

Clinically relevant diseases within the last 5 years were reported in eight patients (15.7%). Current clinically relevant conditions were present in 26 patients (51.0%), predominantly vascular, metabolic, and nutritional disorders. Concomitant medication was reported in nearly all included patients (96.1%), that is, pain and antithrombotic medication. Concurrent procedures and therapies were applied in five cases (9.8%), that is, physiotherapy, respiratory therapy, and ophthalmologic treatment in one case with additional deep dermal burns of the periorbital region.

Primary Outcome Results

The clinical assessment of re-epithelialization and the time to complete re-epithelialization is visualized for all study centers in Figure 3. On postoperative day 5, complete graft take was seen in 14 patients (27.5%). The median time to complete re-epithelialization was 7 days (product-limit survival estimate; Kaplan–Meier plot, mean 7.1 ± 0.2, 95% confidence interval 5–9 days). Overall, high rates of re-epithelialization were recorded during the first clinical assessment after surgery. Only five patients did not show complete graft take on postoperative day 7, and none on day 9. Except for one case of graft failure, the clinical assessment of re-epithelialization yielded a complete graft take after one, two, or three administrations of PWX. The changes from baseline were significant at all centers, but there were no differences between centers (log-rank test, $P = .54$). Notably, the time to complete re-epithelialization did not depend on the size of the target wound at baseline (tested as a covariate in the log-rank test, $P = .92$).

Table 1. Demographic data and wound history of all evaluable events ($N = 51$)

Mean Age (years)	43 ± 16.6	
Gender	Male	15 (29.4%)
	Female	36 (70.6%)
BMI (kg/m^2)	26.3 ± 4.3	
Smokers	yes: 47.1%	No: 52.9%
Mean total burn surface area (%)	10.7 ± 11.9	
Mean size of target wound (cm^2)	177.2 ± 191.2	
Depth of target burn wound	Deep partial thickness	45 (88.2%)
	Full thickness	6 (11.8%)

BMI, body mass index.

Photo-planimetric Assessment

The course of photo-planimetric assessment of re-epithelialization was assessed for the three trial centers by analyzing a representative 10 cm^2 rectangular section (5 × 5 cm) of the grafted wound. The image analysis toolset (Optimas 6) allowed differentiation between epithelialized and nonepithelialized surface areas by digitally measuring the open interstices. Notably, the photo-planimetric evaluation is dependent on the manual placement of the meshed skin grafts which can lead to high baseline values on day 0. Thus, the photo-planimetric assessment of the epithelialization differed from the clinical assessment in two centers. Due to this issue, the changes within each center from baseline (day 0) were statistically significant in center 200 (Wilcoxon test, $P_{200} < .01$), but not in the other two centers ($P_{300} = .06$, $P_{400} = .09$). Therefore, this method was only of supportive value.

Secondary Outcome Results

In total, no wound infections were reported for any of the 51 evaluable patients at any of the three trial centers. There was one case of graft failure which was classified as a serious adverse event. The causal relationship of the graft failure with PWX was regarded to be unlikely in this patient due to the patient's massive consumption of nicotine, severe comorbidities, and overall insufficient compliance. For this patient, the study had to be terminated prematurely due to the need for reoperation 4 days after the first meshed skin grafting.

Additionally, 12 patients (23.5 %) experienced one to four adverse events resulting in 28

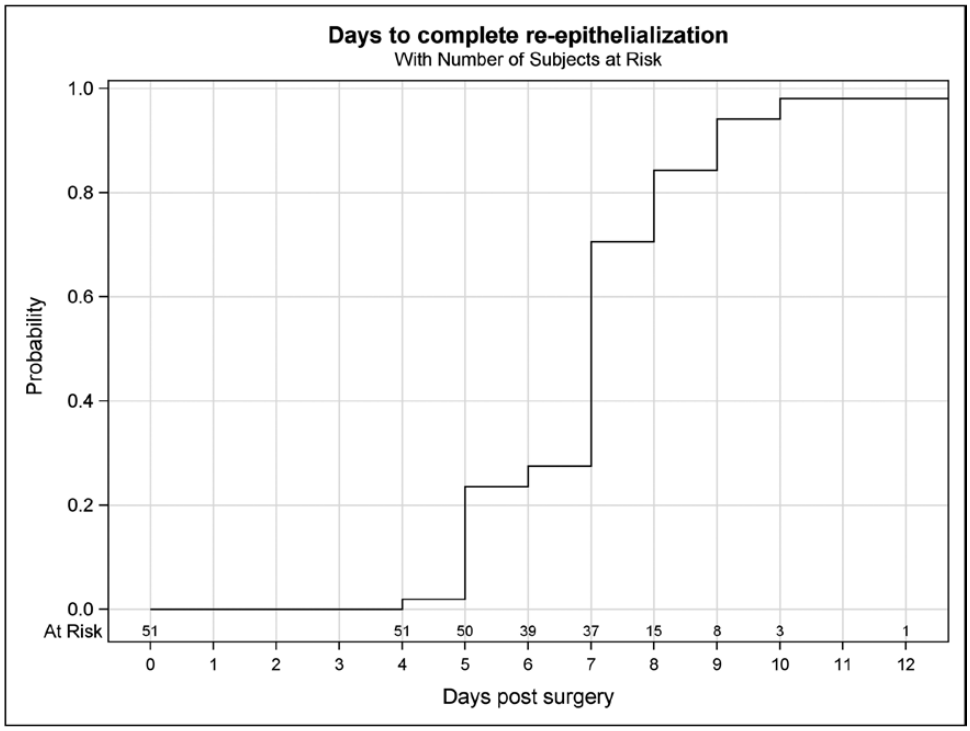

Figure 3. The course of clinical assessment of re-epithelialization in the study population visualized by Kaplan–Meier plot. On postoperative day 5 (after one administration of the investigational product [IP]), complete graft take and re-epithelialization were seen in 14 patients (27.5%). Only five patients showed a re-epithelialization of less than 100% on postoperative day 7 (after two IP treatments) and none on day 9 (after three IP treatments). The median time to complete re-epithelialization was 7 days (product-limit survival estimate; Kaplan–Meier plot, mean 7.1 ± 0.2, 95% confidence interval 5–9 days).

individually different events. Mild to moderate pruritus at skin graft sites, with a possible relationship to PWX, occurred in only two patients. In one further patient, a severe adverse event was reported due to itching in the donor area. The causal relationship to PWX was classified as unlikely as PWX was never applied to donor sites. The itching was resolved by the end of the study without sequelae. An overview of the characteristics of all adverse events is provided in Tables 2 and 3.

Pain Assessment

The course of pain evaluated by the VAS is shown in Figure 4. The changes of pain over time showed a monotonic trend ($P < .01$; page test in ref. [22]). However, the changes from baseline were not significant in trial centers 200 and 300, but significant in center 400 (Wilcoxon test, $P = .01$). Pain therapy showed partially significant center differences possibly caused by low administration of anti-inflammatory and antirheumatic agents in centers 200 and 300 ($P < .01$), but high rates of analgesics classified as diphenylpropylamine derivates ($P < .01$) in center 400, which were administered in the first 24 hours.

DISCUSSION

Burns are serious traumatic injuries, and wound infection is still one of the leading causes of substantial morbidity and mortality in burn patients. For deep partial and full thickness burns, STSG is the current gold standard of care. Infection impairs wound healing and, therefore, impedes adequate skin grafting, with a subsequent increase in the risk of sepsis.[2] Thus, there is a need for a reliable protocol for the prevention of wound infection in burns after STSG.

Burn wounds treated with PWX did not show any sign of infection and erythema during the postoperative course. The median time to complete re-epithelialization was 7 days, thus, burn wounds entirely healed after one to three administrations of the gel. Furthermore, PWX demonstrated good safety and tolerability as no treatment-related adverse events occurred except for two patients where graft site pruritus was possibly caused by the investigational product. At this point, it has to be taken into account that pruritus is a frequently encountered symptom following burns and that higher intensity of itching has been associated with the depth of wounds and specific body locations.[23]

Table 2. Overview of adverse events ($N = 51$)

Parameter		*N*	(%)	E
		12	(23.5)	28
Serious	No	11	(21.6)	27
	Yes	1	(2.0)	1
Causal relationship	Unlikely	10	(19.6)	26
	Possible	2	(3.9)	2
Intensity	Mild	7	(13.7)	23
	Moderate	4	(7.8)	4
	Severe	1	(2.0)	1
Outcome	Resolved, no sequelae	10	(19.6)	26
	Resolved with sequelae	-		-
	Present at final visit	2	(3.9)	2
	Death	-		-

N = number of patients; % = percentage of patients; E = number of events. Twelve patients on 51 evaluable patients occurred 28 adverse events: one serious adverse event not related to the product and 27 adverse events have been reported as described in the table.

Table 3. Details of all adverse events

All adverse events (E)	28
Cardiac disorders	**1**
Tachycardia	1
Eye disorders	**1**
Eye irritation	1
Gastrointestinal disorders	**4**
Constipation	2
Gastrointestinal pain	1
Nausea	1
General disorders and administration site conditions	**7**
Axillary pain	1
Catheter site hypesthesia	1
Catheter site phlebitis	2
Chills	1
Implant site pruritus	2
Injury, poisoning and procedural complications	**1**
Post procedural haemorrhage	2
Transplant failure	1
Metabolism and nutrition disorders	**1**
Hyperglycemia	1
Musculoskeletal and connective tissue disorders	**4**
Arthralgia	1
Back pain	1
Pain in extremity	2
Nervous system disorders	**1**
Dizziness	1
Psychiatric disorders	**1**
Anxiety disorder	1
Renal and urinary disorders	**1**
Anuria	1
Respiratory, thoracic and mediastinal disorders	1
Pneumonia	**1**
Skin and subcutaneous tissue disorders	**2**
Pruritus	2
Vascular disorders	**1**
Hypertension	1

The bold values mark the sum within the "disease group".

Itching and pruritus were recorded in two patients at the donor site where PWX was not applied. Therefore, these cases are likely to be related to the underlying disease.

PWX has been successfully used for the cleansing and moistening of acute and chronic wounds as well as for prevention of biofilm formation. It has a broad spectrum of activity against Gram-positive and Gram-negative bacteria, biofilms, and fungi[17,18] with no known resistances,[24] and can be applied over an extended period due to its low-grade toxicity. Polyhexanide-based products have been shown to be less cytotoxic than other antimicrobials.[13,25] Furthermore, PWX has a suitable viscosity for burn patients allowing easy application to large surface burn wounds. In addition, the gel is colorless and clear which facilitates visualization and assessment of the affected wound area. Several clinical trials have demonstrated the efficacy of Prontosan® used on chronic wounds.[26] Prontosan® Wound Irrigation Solution has been found to reduce bioburden, aid wound healing[13,25] and reduce the time to wound closure in a randomized, controlled clinical study including 142 patients.[27,28] Additionally, a comparative retrospective trial with 112 patients has shown Prontosan® Wound Irrigation Solution to reduce infection rates and decrease wound healing time.[29] In both an in vitro study and an animal model, Prontosan® has been reported to be effective against biofilms.[30,31] Biofilms are associated with the development of antibiotic-resistant organisms and are refractory to the immune system. In burns, biofilm has been shown to be significant for developing wound infections and subsequent sepsis.[32] Therefore, the effectiveness of a topical agent against biofilm and the formation of biofilm is crucial. In this context, the short duration of treatment and absence of wound infections in our study represent a marked advantage for the additional application of PWX to the grafted site in comparison with the standard care for STSGs consisting only of vaseline gauze dressing.

There is a paucity of clinical studies addressing the use of polihexanide in the field of burn injury. A prospective trial with 14 patients requiring STSGs has revealed that meshed skin grafts treated with polihexanide have shown by far the best re-epithelialization compared to meshed skin grafts treated with povidone-iodine and silver nitrate in which deep tissue necrosis and marked fibrin discharge have been observed.[33] The deep partial thickness burns treated with polihexanide have re-epithelialized without any further debridement after an average of 10 days with

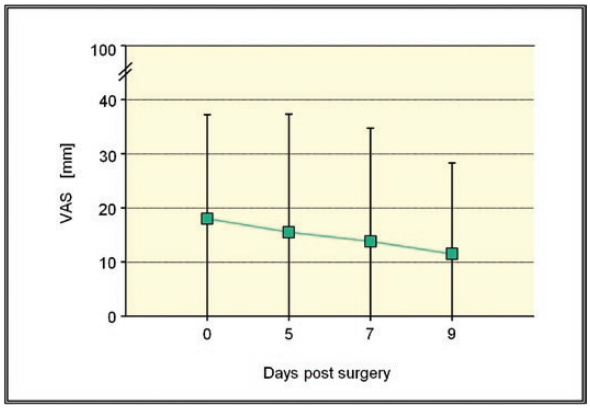

Figure 4. The course of pain evaluated by VAS is shown for all patients. The assessment showed a decreasing tendency of postoperative pain at graft sites which was significant ($p < .02$). *VAS*, visual analog scale.

notable pain reduction. Regarding the higher number of investigated patients in our study, the PWX treatment showed an increased healing tendency. In addition, a randomized controlled study reported significantly better and faster pain reduction while treating deep partial thickness burn wounds with a polihexanide-containing bio-cellulose dressing when compared to silver sulfadiazine cream.[34] Although silver-based agents, such as silver nitrate and silver sulfadiazine, provide excellent antimicrobial protection and decrease rates of superinfections, poor wound penetration and several electrolyte-associated side effects have to be taken into consideration when used in burn patients.[12,13]

Moistening of wounds with hydrogels has been shown to improve re-epithelialization.[35] Again, there is a paucity of studies analyzing the use of hydrogels in burn wounds as most of the trials conducted have focused on the treatment of donor sites after skin grafting.[36] Several studies have investigated the use of polyvinylpyrrolidone-iodine (PVP-I), a well-established topical antiseptic, for its effect on re-epithelialization in patients receiving meshed skin grafts. In a randomized, controlled study 36 burn patients have been treated with PVP-I hydrogel covered with chlorhexidine gauze or chlorhexidine gauze only until complete healing.[35] The wound dressing has been changed on postoperative day 3 and then once a day. Graft loss has occurred in 35.7% of the burn patients treated with chlorhexidine gauze only compared to 5% of the patients treated additionally with PVP-I hydrogel. Furthermore, the re-epithelialization rate in this study has been approximately 97% after treatment with PVP-I hydrogel until postoperative day 11 compared to 82% after treatment with chlorhexidine gauze only. With chlorhexidine gauze only, complete re-epithelialization has not occurred until day 13 following meshed skin grafting. Comparable studies conducted by Vogt et al. and Hauser et al. have revealed similar results.[37,38] Meshed skin grafts of 167 patients have been dressed either with PVP-I hydrogel covered with impregnated vaseline gauze (n = 83) or impregnated vaseline gauze only (n= 84). Wounds receiving PVP-I hydrogel have shown significantly faster re-epithelialization than wounds treated with vaseline gauze dressing alone. In another clinical trial, investigators have compared the intraindividual use of PVP-I hydrogel with a regular silver sulfadiazine cream in 43 patients with partial-thickness burn wounds. Eligible patients have been required to present with two separate burn wounds of comparable size, location, and treatment prior to the screening visit to allow for an intraindividual comparison. Daily treatment with PVP-I hydrogel and vaseline gauze dressing has resulted in significantly faster re-epithelialization of the target wounds compared to the control group.[39] However, due to the characteristic color of PVP-I, blinding of the clinical assessment of the wounds was not possible. In comparison, fewer graft losses occurred in our clinical trial and the median time to complete re-epithelialization was shorter than in the studies mentioned.

However, several limitations of the study need to be discussed. The lack of a control group and baseline data on infections are restrictions of this trial. This study is the first observational study to document the outcomes of deep partial thickness and full thickness burns treated with Prontosan® Wound Gel X for moistening and cleansing. Therefore, the goal was to evaluate the safety and efficacy of the gel. For this purpose, a small patient cohort was planned to get a clear safety and tolerability profile of the product. With the data provided by this study, future random control trials can be designed.

Another limitation of the survey is the photo-planimetric measurement of graft re-epithelialization. The clinical assessment of the wound healing was only supported at one of the three trial centers by the digital image analysis. The method revealed some technical problems and proved to be unsuitable for representing the re-epithelialization progress accurately. Though mesh expansion ratios were consistent within the study centers, differences in the actual placing of the STSGs on top of the debrided burn wounds resulted in varying photo-planimetric measurements throughout the postoperative course of re-epithelialization. Hence, extending the meshed skin graft influenced the resulting measurement, and, since the baseline value was “false positive,” the

difference in progress was small. Thus, the photoplanimetric assessment of the epithelialization progress was highly user dependent although being reliable in assessing open interstices. To avoid mistakes in the analysis, photo documentation, as well as manual placement of the STSGs, have to be strictly standardized to avoid mistakes in the analysis. Thus, more work is needed to establish an objective measurement of graft re-epithelialization.

CONCLUSION

In conclusion, PWX was shown to be safe and well tolerated for use in burn wounds requiring STSG. Clinical assessment was found to be a reliable parameter for evaluating the healing of skin grafts whereas the photo-planimetric method possessed significant technical issues, at least in this study. Due to an open study design, the efficacy of the investigational product could be compared only with historical data. However, this study could serve as the basis of a sample size calculation for future randomized, controlled clinical trials.

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