Randomized Controlled Trial Comparing Silver-Impregnated Fibrous Hydrocolloid Dressings With Silver Sulfadiazine Cream Dressings for the Treatment of Fracture Blisters to Determine Time to Surgical Readiness

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Objectives: To investigate, in patients with fracture blisters, the time to surgical readiness in those treated with silver-impregnated fibrous hydrocolloid (SFH) dressings compared with those treated with topical silver sulfadiazine (SS) cream and to determine the direct costs associated with both treatments.

Design: A single-blind, randomized controlled trial.

Setting: The study was conducted at Tygerberg Hospital, a tertiary care facility, and Worcester Provincial Hospital, a secondary care facility, Western Cape, South Africa.

Patients: Patients >18 years of age with one or more fracture blisters overlying fractures requiring surgical fixation were considered for inclusion.

Main Outcome Measurements: The main outcome was the time to surgical readiness, after complete re-epithelialization of the affected site, in both groups. The direct cost associated with each treatment and the daily cost associated with hospital stay per day were recorded.

Results: At an interim analysis, 70 patients had been enrolled and completed the study protocol with 35 patients per group. Groups were balanced across patient and clinical demographic characteristics. A significant difference of 4 days (95% confidence interval: 2.9–5.1 days, $P < 0.001$) in the mean time to surgical readiness (SFH group, 5.3 days vs. SS group, 9.3 days) was observed. No difference between the time to surgical procedure as well as the total length of hospital stay between the 2 groups was observed.

Conclusion: This study reports that SFH dressings are a cost-effective treatment option for the management of fracture blisters evidenced by a significant accelerated time to blister re-epithelialization compared with a commonly described method of SS cream dressings.

Key Words: fracture blisters, treatment, re-epithelialization, silver sulfadiazine, fibrous hydrocolloid

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Fracture blisters are a fairly uncommon orthopaedic challenge, occurring in approximately 2.9% of all acute fractures.[1] Smith et al[2] defined fracture blisters as skin bullae representing areas of epidermal necrosis with separation of the stratified squamous cell layer from the underlying vascular dermal layer by edema fluid. They are hypothesized to form when posttraumatic edema causes a rise in interstitial pressure, resulting in vascular congestion and loss of cohesion between the epidermis and dermis and their subsequent separation. Fluid then collects at these separated areas with resultant local tissue hypoxia leading to epidermal necrosis and blister formation.[3,4] Risk factors for the development of fracture blisters include (1) areas of the body where the skin is thin without the underlying protection of muscle or adipose tissue, such as the ankle or elbow joint, (2) high-energy trauma, and (3) conditions that predispose to poor wound healing such as peripheral vascular disease.[1,3] Formation of these blisters can happen as early as 6 hours postinjury or as late as 3 weeks. The average time to development is 24–48 hours after the injury.[1,3]

The development of fracture blisters after trauma poses a significant burden to not only the patient but also the treating orthopaedic surgeon because they are associated with significant delays to surgery with resultant cost implications, the use of suboptimal surgical approaches, and subsequent wound complications.[5] Currently, no clear consensus exists in terms of blister treatment and the management of the underlying fracture with treatment modalities ranging from observation and surgical delay until fully re-epithelialized, aspiration and sterile dressings, and deroofment with the

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application of a topical antibiotic cream.[1–3] Globally, silver sulfadiazine (SS) dressings are the most commonly used method for fracture blister management and are the standard of practice used in our unit.[2,4]

Silver-impregnated fibrous hydrocolloid (SFH) dressings are widely used in the management of burn wounds, diabetic foot ulcers, and surgical wounds that have been left to heal by secondary intention.[6] The dressings are composed of sodium carboxymethylcellulose impregnated with 1%–2% ionic silver. The dressing fibers make contact with wound fluid by means of hydrophilic action and the fibers swell as they lock bacterial exudate and proteases away from the wound by means of vertical wicking, thus creating a large fluid absorption capacity.[6] The addition of ionic silver provides added broad-spectrum coverage of wound pathogens that can cause infection.[7]

Based on its mechanisms of action, SFH dressings could potentially be used in the management of fracture blisters; however, no such investigations have been performed.

The aim of this study was to investigate, in patients with fracture blisters, the time to surgical readiness in those treated with SFH dressings compared with those treated with topical SS cream. A secondary aim was to determine the direct costs associated with both treatments.

MATERIALS AND METHODS

A single-blind, randomized controlled trial was conducted at 2 sites between July 1, 2018, and February 29, 2020. Patients older than 18 years who had one or more fracture blisters overlying fractures that required surgical fixation were considered for inclusion. Patients were excluded if they (1) did not require surgical fixation or (2) had known povidone-iodine, silver, or sodium carboxymethylcellulose allergy. All patients provided informed consent, and ethical approval and institutional permission were obtained, and the study was conducted under the guidelines of the Declaration of Helsinki as well as the national Good Clinical Practice guidelines.

Patients were randomized using block randomization in a 1:1 ratio with blocks of size 4 that were randomly permuted. Allocation concealment was performed using opaque envelopes, and each envelope was drawn from an opaque container when required. The principal investigator was responsible for the application of the treatment and daily evaluation. Patients were not informed about which treatment group they were assigned to; however, based on the difference in treatment modalities, it was not possible to fully blind patients as to their specific treatment.

Patients meeting the inclusion criteria were recruited, and basic patient demographics, injury characteristics, and blister descriptive data were collected (Fig. 1A). In both treatment groups, skin preparation of the blisters was performed with povdone-iodine solution, and blisters were deroofed using an 18-gauge needle (Fig. 1B), after which the chosen intervention was applied, and then covered with sterile gauze dressings. Patients in the SS group received new dressings daily, whereas patients in the SFH group had their blisters inspected daily, but the dressing was only removed once the blister had re-epithelialized. Patients were deemed ready for surgery once the blister had fully re-epithelialized (Fig. 1C). The time to complete re-epithelialization, and thus surgical readiness, was recorded. Because of the high burden of orthopaedic trauma cases awaiting theater at our unit, patients did not necessarily go to theater on the day that re-epithelialization was deemed complete.

The costs involved in the individual dressings, based on the amount of equipment and products required to treat the blisters, included SFH being 0.90 USD per day and SS being 0.73 USD per day. The cost associated with hospital stay (hospital stay per day) was calculated according to the Uniform Patient Fee Schedule (UPFS) fee schedule using a level 2 patient fee at 69.90 USD per day. The direct cost, based on treatment (SS or SFH) and hospital stay, was calculated.

Sample Size

For the 2 treatments that are being compared (SS and SFH), the primary outcome, time to surgical readiness, is based on clinical evaluation measured in days. An equal allocation was planned. From the literature, the SS treatment takes on average 7.7 days to readiness with a range of 4–21 days. From a pilot study performed in a local setting, the SFH

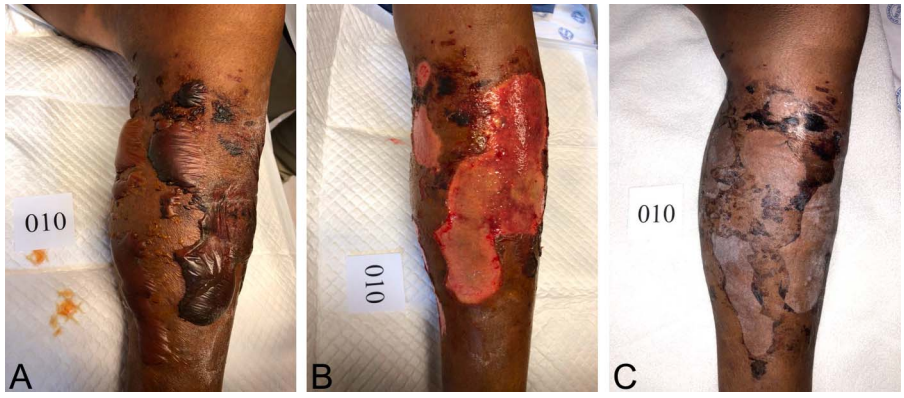

FIGURE 1. A, Fracture blister pre-intervention, (B) deroofed fracture blister, and (C) re-epithelialized fracture blister. **Editor's Note**: A color image accompanies the online version of this article.

takes on average 6.4 days to readiness with a range of 5–10 days. From this information, the SD of the readiness times in each treatment was calculated from the range. Using the non-normal approximation, which uses the range/6, the SS SD is 2.8 days, and for SFH, the SD is 0.83 days. Rounded figures of 3 and 1 day were used in the sample size calculation. The sample size for a 2-sample *t* test with unequal variances with 90% power and a significance level of 5% for a superiority hypothesis was 128 participants in total.

Statistical Analysis

Data were analyzed using Stata (v15 StataCorp LLC, TX). Descriptive tables of means, SDs, frequencies, and percentage were compiled reflecting the result by arm. The 2-sample *t* test with unequal variances was used to compare the continuous outcomes including the primary outcome. For the primary outcome, the mean difference and 95% confidence intervals were calculated. An interim efficacy analysis at 50% of the study completed was planned using the Haybittle–Peto stopping rule.

RESULTS

An interim analysis was performed after a total of 70 patients (55% of the study information) had completed the study protocol with 35 patients in the SS and SFH groups, respectively (Fig. 2). The primary outcome was assessed, and the recommendation was to stop the trial for efficacy.

The mean age for the development of fracture blisters was equally distributed across both groups with both being

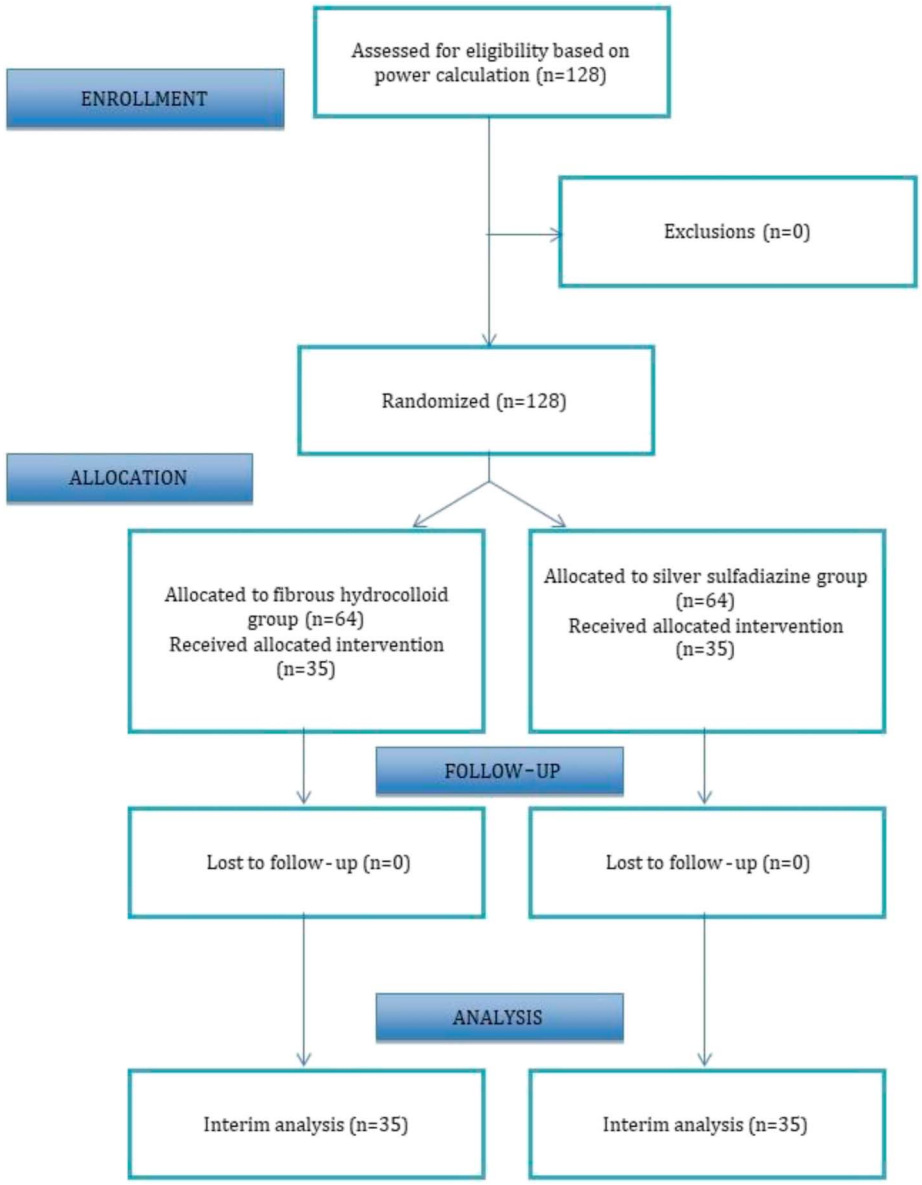

FIGURE 2. Flow diagram of recruitment and randomization processes. **Editor's Note**: A color image accompanies the online version of this article.

TABLE 1. Patient and Fracture Demographics

	SFH (n = 35)	SS (n = 35)
Age (y) (mean ± SD)	42.0 ± 2.2	41.1 ± 2.1
Sex (male/female) (%)	54.3 (19)/45.7 (16)	71.4 (25)/28.6 (10)
Hygiene (good/fair/poor) (%)	68.6 (24)/28.6 (10)/2.9 (1)	74.3 (26)/25.7 (9)/0.0 (0)
Spanning external fixator applied (yes/no) (%)	17.1 (6)/82.9 (29)	14.3 (5)/85.7 (30)
Type of fracture (open/closed) (%)	14.3 (5)/85.7 (30)	0.0 (0)/100.0 (35)
Associated injuries (yes/no) (%)	20.0 (7)/80.0 (28)	2.9 (1)/97.1 (34)

Data are presented as mean ± SEM or as frequencies with counts indicated in parentheses.

within the fourth decade. The distribution of categorical variables was also similar in both treatment groups (Table 1).

The different mechanisms of injury were equally represented in both groups with the most common mechanism of injury resulting in the development of fracture blisters being a mechanical fall, including those from a height or standing position (see **Table**, **Supplemental Digital Content 1**, http://links.lww.com/JOT/B325, which illustrates the differences in mechanism of injury between the SFH and SS groups). Gunshot wound injuries, a common mechanism of fracture causation in the study setting, only resulted in the development of fracture blisters in a single patient in this study.

Fracture types observed were predominantly located to the lower limbs with the exception of a single patient who developed fracture blisters after a distal humerus fracture (see **Table**, **Supplemental Digital Content 2**, http://links.lww.com/JOT/B326, which illustrates the differences in fracture types between SFH and SS groups). Fracture types were equally distributed between both treatment groups, with ankle fractures accounting for most fracture types observed in 37.1% (n = 13) and 40.0% (n = 14) of patients in the SFH and SS groups, respectively. Tibia shaft fractures accounted for 31.4% (n = 11) in each treatment group.

The mean number of fracture blisters overlying a fracture was 5.3 ± 0.8 in the SFH group and 3.5 ± 0.4 in the SS group with no difference observed between the mean size of each blister between the groups (see **Table**, **Supplemental Digital Content 3**, http://links.lww.com/JOT/B327, which illustrates differences in blister specific information between the SFH and SS groups). Clear blister types predominated between both treatment groups with 45.7% (n = 16) in the SFH group and 60.0% (n = 21) in the SS group. The average time to the development of fracture blisters after an injury was similar between the treatment groups, and surgical incision required for fracture fixation was avoidable for the overlying fracture blisters in only 20.0% (n = 7) patients in the SFH group and 17.1% (n = 6) in the SS group.

At the interim analysis of 55% of the study information, a significant difference of 4 days (95% confidence interval: 2.9–5.1 days, $P < 0.0001$) in the mean time to surgical readiness was observed with the SFH group requiring a mean of 5.3 days compared with the SS group, which required a mean of 9.3 days (Table 2). The *P* value of the primary outcome was lower than the Haybittle–Peto *P* value boundary of 0.001, and hence, the trial was stopped for efficacy. No difference between the time to surgical procedure and the total length of hospital stay between the 2 treatment groups was observed (Table 2).

The average daily rate was 0.73 USD for SS dressing and 0.90 USD for SFH dressing. A substantial difference in cost between the 2 treatment groups for the hospital stay cost, based on the mean time to re-epithelialization, was observed with the SFH patients costing on average 370.47 USD compared with the SS patients, costing on average 650.07 USD, thus with an overall total treatment cost until surgical readiness of 375.24 USD for SFH and 656.86 for SS, respectively (Table 3). The total treatment cost until discharge, which was based on the total hospital stay and daily dressing costs, was similar between the 2 treatment groups at 868.58 USD for SFH and 901.54 USD for SS as expected in our setting because of the high trauma burden and availability of theater time.

DISCUSSION

The aim of this study was to investigate, in patients with fracture blisters, the time to surgical readiness in those treated with SFH dressings compared with those treated with topical SS cream. To the best of our knowledge, this is the

TABLE 2. Time to Surgical Readiness and Surgical Procedure as Well as Total Length of Hospital Stay for Treatment Groups

	SFH (n = 35)		SS (n = 35)		Difference	
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean (95% CI)	*P*
Time to surgical readiness (d)	5.3 ± 2.6	4.7–6.0	9.3 ± 2.0	8.5–10.2	4.0 (2.9 to 5.1)	<0.001
Time to surgical procedure (d)	10.5 ± 5.5	8.6–12.3	11.6 ± 2.9	10.6–12.6	1.2 (−0.9 to 3.3)	0.268
Length of stay (d)	12.3 ± 6.4	10.1–14.5	12.8 ± 3.0	11.8–13.8	0.5 (−1.9 to 2.9)	0.688

Data are presented as means ± SDs, with 95% confidence intervals indicated.
CI, confidence interval.

TABLE 3. Treatment Costs Involved of Fracture Blister Interventions

	SFH (n = 35)	SS (n = 35)
Dressing cost based on the mean time to re-epithelialization (USD)	4.77	6.79
Hospital stay cost based on the mean time to surgical readiness (USD)	370.47	650.07
Total treatment cost until surgical readiness (USD)	375.24	656.86

Data presented as approximate costs in USD (exchange rate calculated on April 29, 2020 at 1.0 USD = 18.14 ZAR). Daily dressing costs: SFH, 0.90 USD per day; SS, 0.73 USD per day.

first randomized controlled trial that compared the efficacy of these 2 interventions and whether there is a novel and cost-effective method to accelerate surgical readiness in these patients.

The main finding of this study was a significant reduction in the mean time to surgical readiness characterized by re-epithelialization of the blisters overlying the fracture site in the SFH arm of 4 days or a 43% reduction in the time of the SS arm of 9.3 days. The time taken to complete re-epithelialization has been differently reported across different investigations with some reporting an inability to determine the exact time for blister re-epithelialization to occur and others reporting re-epithelialization of a fracture blister averaging between 6 and 21 days.[1] In turn, Uebbing et al[3] reported that clear-filled blisters take approximately 12 days to heal, whereas hemorrhagic blisters take approximately 16 days to heal. This is substantially longer than what is reported in this study. Similarly, Strauss et al also reported shorter times to definitive surgery with a mean delay to definitive surgical care reported as 7.7 days (ranging from 0 to 20 days). However, the authors reported that blister beds continued to be treated with SS dressings twice daily after the surgery until the blister had completely healed, which implies that full re-epithelialization had likely not occurred by the time that definitive surgery was performed.[8] Therefore, their results are not necessarily directly comparable with this study.

The second finding of this study was that there was no significant difference to the time to definitive surgical procedure with both groups being similar, the SFH and SS groups with 10.5 days and 11.6 days respectively. In addition, no difference between the duration of hospital stay was observed between the groups. This is however not a surprising finding, given the study setting. Because of a very high trauma burden in our institution, performing surgery immediately once patients are ready for surgery is not routinely possible as there are often more urgent surgical cases taking preference. Therefore, the main outcome of this study was considered the time to surgical readiness since; once the fracture blisters had re-epithelialized, immediate surgery was not routinely possible and subsequently, as expected, similar timing to definitive surgical procedures was observed between the groups. It should be noted that the applied interventions were stopped as soon as re-epithelialization had occurred.

An interesting finding of this study was that a mean time of 36 hours passed before fracture blisters developed. This finding is in agreement with the reported information from several other studies, with a mean time to the development of fracture blisters of 24–48 hours reported by Varela, Smith, and Wallace.[1,2,4] All 3 authors also reported that in rare cases after extremely high-energy trauma, fracture blisters developed as early as 6 hours after the injury.[1,2,4] Therefore, after injuries where a high index of suspicion exists for the development of fracture blisters, surgery should be preferably performed within 24 hours, before which fracture blisters are likely to develop, to prevent unnecessary delays. Early surgical intervention would help to avoid possible incisions through fracture blisters and also help to reduce the formation of fracture blisters by relieving high pressures within the soft tissues, hematoma evacuation as well as reducing further soft tissue edema by providing fracture stabilization.[2] This approach is however not always feasible, especially in high-volume or low-resourced units where there may be significant delays to definitive surgery. For this reason, a fracture blister treatment that is widely available and cost-effective, that could potentially shorten the overall duration of a hospital stay by ensuring an accelerated time to re-epithelialization is ideal.

Although the direct treatment costs of SFH per day are more expensive than SS, in settings where definitive surgery is performed as soon as re-epithelialization of the fracture blister occurs, the costs involved in patient care could potentially be significantly lower with the use of SFH. This is clear from the substantial difference in the cost of hospital stay and dressings, between the 2 groups, with the SFH group saving an average of 275 USD per patient. It should be noted that this study considered only the direct costs associated with treatment, namely a hospital bed and the dressing costs, and that it would be necessary to consider the costs of implants used for definitive fracture fixation, as this would affect the overall cost to the treatment of the patient, something outside the scope of our investigation.

Limitations of this study include an observed imbalance between the number of fracture blisters between the 2 treatment groups. It is however unlikely that this would have influenced the results in any way as the time to re-epithelialization was calculated when all blisters had re-epithelialized. Furthermore, the SFH group, despite having more fracture blisters, re-epithelialized at a faster rate in comparison with the SS group, contrary to what would have been expected the number of blisters influence the outcome. The principal investigator was responsible for the application of the treatment and daily evaluation, and this could lead to a bias in the assessment of re-epithelialization of the blisters.

CONCLUSION

This study reports that SFH dressings, commonly used in the management of burn wounds and diabetic foot ulcers, is a cost-effective treatment option for the management of fracture blisters evidenced by a significant reduced time to fracture blister re-epithelialization when compared with a commonly described method of SS cream dressings.

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