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Microbial cellulose dressing compared with silver sulphadiazine for the treatment of partial thickness burns: A prospective, randomised, clinical trial

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ARTICLE INFO

Article history:
Accepted 16 June 2018
Available online xxx

Keywords:
Burn
Wound dressing
Pain
Time for epithelialisation
Cellulose

ABSTRACT

Background: The current treatment for partial thickness burns at the trial site is silver sulphadiazine, as it minimises bacterial colonisation of wounds. Its deleterious effect on wound healing, together with the need for repeated, often painful, procedures, has brought about the search for a better treatment. Microbial cellulose has shown promising results that avoid these disadvantages. The aim of this study was therefore to compare microbial cellulose with silver sulphadiazine as a dressing for partial thickness burns.

Method: All patients who presented with partial thickness (superficial and deep dermal) burns from October 2014 to October 2016 were screened for this randomised clinical trial. Twenty patients were included in each group: the cellulose group was treated with microbial cellulose sheets and the control group with silver sulphadiazine cream 10mg/g. The wound was evaluated every third day. Pain was assessed using the Face, Legs, Activity, Cry, Consolability (FLACC) scale during and after each procedure. Other variables recorded were age, sex, percentage total body surface area burned (TBSA%), clinical signs of infection, time for epithelialisation and hospital stay. Linear multivariable regression was used to analyse the significance of differences between the treatment groups by adjusting for the size and depth of the burn, and the patient's age.

Results: Median TBSA% was 9% (IQR 5.5–12.5). The median number of dressing changes was 1 (IQR 1–2) in the cellulose group, which was lower than that in the control group (median 9.5, IQR 6–16) ($p<0.001$). Multivariable regression analysis showed that the group treated with microbial cellulose spent 6.3 (95% CI 0.2–12.5) fewer days in hospital ($p=0.04$), had a mean score that was 3.4 (95% CI 2.5–4.3) points lower during wound care ($p<0.001$), and 2.2 (95% CI 1.6–2.7) afterwards ($p<0.001$). Epithelialisation was quicker, but not significantly so.

Conclusion: These results suggest that the microbial cellulose dressing is a better first choice for treatment of partial thickness burns than silver sulphadiazine cream. Fewer dressings of the wound were done and, combined with the low pain scores, this is good for both the patients and the health care system. The differences in randomisation of the area of burns is, however, a concern that needs to be included in the interpretation of the results.

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https://doi.org/10.1016/j.burns.2018.06.007
0305-4179/

1. Introduction

1.1. *Dressings for superficial burns*

Burns are either superficial or deep, and excision and skin grafting is the procedure of choice for deep injuries. However, superficial burns are usually treated conservatively using different dressings [1]. Silver sulphadiazine cream was for a long time the standard treatment for partial thickness burns [2,3]. However, it needed frequent changes of dressings, which requires time and effort, is painful for the patient, and is an expense for health care providers [1,4]. Newer products, such as silver-coated gauze, hydrocolloid, foam, and fibre dressing, have been mixed with Nano-crystalline silver to ensure a more controlled release, which has been considered to be beneficial for infection control and healing time, although the current level of evidence for these favourable effects is low [1,5]. Some studies have shown that silver is toxic to regenerating keratinocytes, which can result in delayed healing, as well as adverse effects in the environment [1,5,6]. The search for alternative dressings is therefore important.

One option is biological membranous dressings, which allow less frequent changes of dressing, and do not have a toxic effect. A recent publication has shown promising results with a biocellulose dressing that contains polyhexanide for partial-thickness burns; they reported less pain and fewer changes of dressing than are necessary with silver-sulfadiazine [7]. There have also been some reports of the use of microbial cellulose [8], which reported that fewer applications were done, there were no reports of irritation by (or allergy to) the dressing material, and no pathogenic bacteria were isolated.

The aim of this study was to compare microbial cellulose with silver sulphadiazine as the dressing of preference for partial thickness burns.

2. Methods

All patients who were admitted to the Burn Unit in Plastic Surgery Department, Suez Canal University Hospital from October 2014 to October 2016 were screened for inclusion (Fig. 1). The study was approved by the local Ethics Committee at the trial site (21/09/2014). The trial registry number is ISRCTN14797020.

We included patients aged 5 years or over with any type of thermal injury that caused a superficial or deep partial thickness burn, and was recent (within the first 72 h). Those with full thickness burns, regardless of size, and women who were pregnant or breast feeding, were excluded from the study.

Potentially eligible patients (or their parents) were informed about the purpose, methods, effect, and possible complications of the study, and were given the opportunity to ask questions. If they agreed to participate, written informed consent was signed. Patients were randomly assigned (block randomisation, eight envelopes) to either the microbial cellulose group (experimental group) or silver sulphadiazine cream 10 mg/g (control group).

The following data were recorded during the first day: age, sex, percentage total body surface area burned (TBSA%), percentage superficial and deep dermal body surface area burned (BSA%), site, mechanism of burn, medical history, a baseline photograph of the burn, and assessment of pain by the Face, Legs, Activity, Cry, Consolability (FLACC) scale during wound care and after it. TBSA% and percentage superficial and deep dermal body surface area burned were recorded by the attending physician on admission by a detailed Lund & Browder chart. The depth of the burn was assessed by clinical examination including assessment of capillary refill and needle prick sensation.

The care of each wound was evaluated by the attending surgeon. A photograph of the burn was taken. Pain was assessed by the FLACC scale. Infection diagnosis was done by the attending physician and was based on the following clinical signs: an increase in white blood cell count above reference values after the first two days after injury, a considerable rise of plasma-C reactive protein concentration, fever exceeding 39°C, visible signs of local wound infection (rubor, tumor, calor) and severe wound pain. We considered full healing to have been achieved when the granulation tissue was totally covered with epidermis, and further evaluation

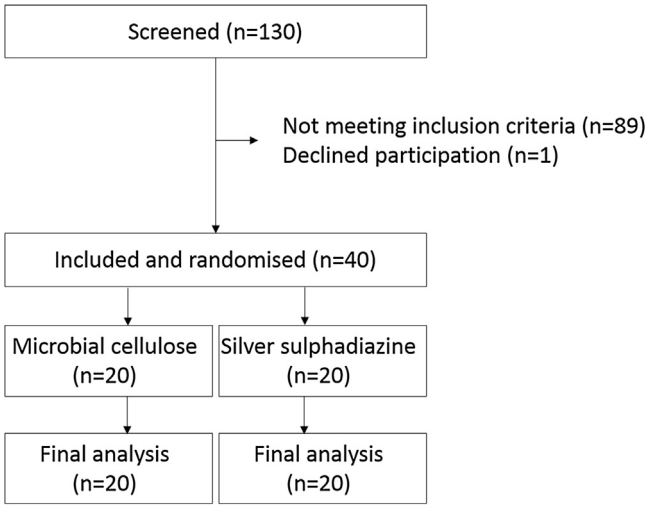

Fig. 1 – CONSORT flowchart.

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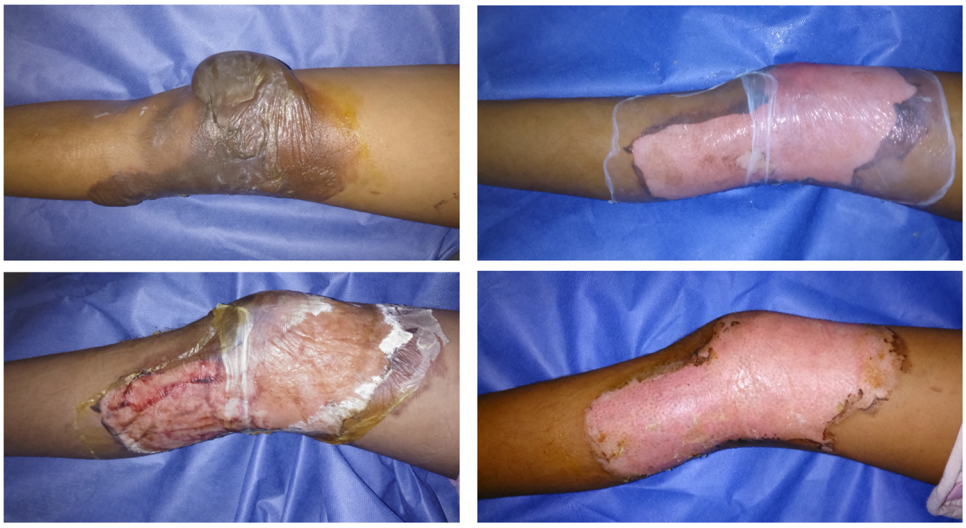

Fig. 2 – A burn before cleaning, with cellulose sheets applied, after one week, and the healed picture after two weeks.

was made by the attending surgeon as before. Percentage of area excised (if any), time to epithelialisation, and duration of hospital stay were recorded.

2.1. *Cellulose group (microbial cellulose)*

Wounds were cleaned with normal saline and any bullae or debris removed. Microbial cellulose (Epiprotect® S2Medical AB, Sweden) sheets were applied under aseptic conditions, covered by plastic film and an elastic bandage (Fig. 2). In case of facial burns cellulose was used alone (Fig. 3). Every week the bandage was removed and the cellulose dressing was inspected through the plastic film. In cases of partial detachment from the wound the cellulose was replaced by a new sheet. If signs of infection were present, the cellulose was replaced by a new sheet. If the wound (totally or partially) was deeper than it appeared at the primary assessment (had become full thickness) it was excised and grafted or sutured if necessary.

2.1.1. *Control group (silver sulphadiazine cream 10 mg/g)*

Wounds were cleaned with normal saline and any bullae or debris removed. Silver sulphadiazine cream 10 mg/g (1%) (Dermazine®, Sandoz) was applied under aseptic conditions, covered with sterile gauze, and an elastic bandage applied. Silver sulphadiazine was changed every second day. If the wound (totally or partially) was deeper than it appeared at the primary assessment (had become full thickness) it was excised and grafted or sutured if necessary.

2.1.2. *Statistics*

All data were collected on a study case report form, and any that were missing had to be explained.

Data were analysed with the help of STATA (STATA v12.0, Stata Corp. LP College Station, TX, USA). Descriptive data are presented as median (25th–75th centiles) unless otherwise stated. Probabilities of less than 0.05 were accepted as significant. Distribution was tested with the Lilliefors test for normality. The significance of differences between groups

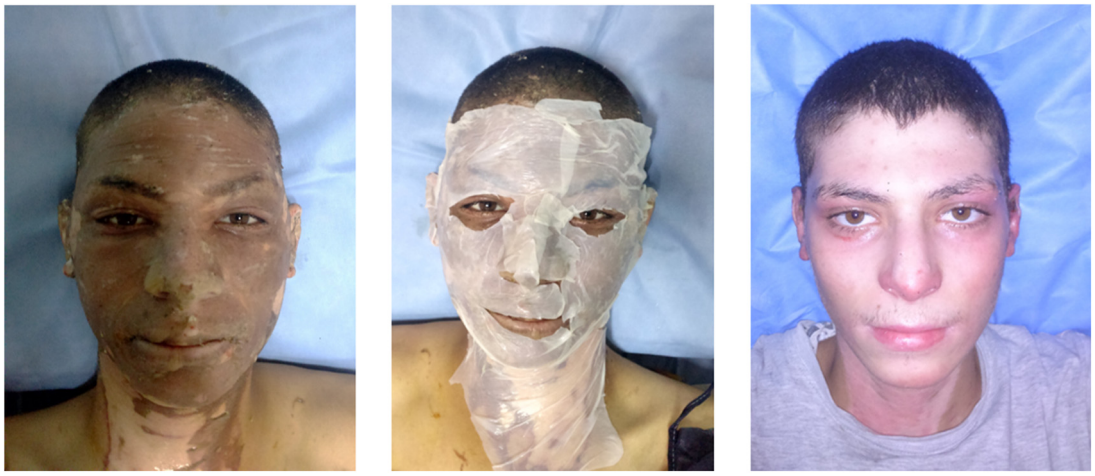

Fig. 3 – A facial burn before cleaning, with cellulose sheets applied, and the healed picture after 28 days.

Please cite this article in press as: A. Aboelnaga, et al., Microbial cellulose dressing compared with silver sulphadiazine for the treatment of partial thickness burns: A prospective, randomised, clinical trial, Burns (2018), https://doi.org/10.1016/j.burns.2018.06.007

Table 1 – Details of patients.

	Total (n=40)	Cellulose (n=20)	Control (n=20)	p Value
Age (years)	22.0 (13.0-37.5)	23.0 (14.5-37.5)	22.0 (11.0-37.5)	0.76
TBSA%	9.0 (5.5-12.5)	7.0 (4.0-9.5)	10.0 (9.0-15.0)	0.01
Superficial dermal burn BSA%	5.0 (0.0-8.0)	4.5 (1.5-7.0)	6.5 (0.0-10.0)	0.56
Male sex	20	7	13	0.06
Flame burns/scalds	31/9	15/5	16/4	1.00[a]
Site of burn:				
Trunk	14	3	11	0.01
Face	13	9	4	0.09
Leg	12	6	6	1.00
Arm	9	4	5	1.00[a]
Hand	6	2	4	0.66[a]
Neck	2	2	0	0.49[a]

Data are median (25th–75th quartile) or number of patients. Mann–Whitney U test and chi square test.
[a] Fisher's exact test.

was assessed using the Mann Whitney U, and the chi square, tests. Linear multivariable regression was used to assess the effect of the wound dressing on duration of hospital stay, as well as time to epithelialisation, both adjusted for age, and the size and depth of the burn. Linear multivariable panel regression was used to analyse the effect of the dressing on the pain score from three wound care procedures, adjusted for age, and the size and depth of the burn.

3. Results

We studied 40 patients (20 in each group). The median age for the whole group was 22 years, half were male, and median TBSA% was 9% (IQR 5.5–12.5) which were mostly superficial dermal burns. Thirty-one were caused by flames, and the most common burned site was the trunk, followed by the face and lower extremities. The control group had larger total burns (TBSA %) than the cellulose group, they were more frequently burned on the trunk, and there was a tendency of a smaller proportion of facial burns. Other than that there were no baseline differences between the groups (Table 1). Nine of the patients had their burns excised, and eight were given skin grafts. The first operation was done on median day 25 (IQR 21–31) after admission.

Microbial cellulose was mainly applied to the face, followed by the lower and upper extremities, covering a median of 6.5 BSA%. Three of the patients had it applied to more than one site (face, neck, chest, arm, and hand). More changes of dressing were done in the control group (Table 2). Of the patients in the cellulose group 15 had one cellulose dressing and five had two. Three patients underwent operations, of whom one had the burn excised, and two received split-thickness skin grafts. The median duration of hospital stay was 16 days and the time for epithelialisation was 17 days in the whole group, with no differences between the two study groups (Supplemental Table 1). The control group had higher pain scores both during and after wound care (Table 3 and Fig. 4). They also had more infections, although there was no significant difference between the groups (Supplemental Table 1).

3.1. *Adjusted results (multivariable regression analysis)*

The fact that the control group had bigger TBSA% entailed further analysis to adjust for the differences between the

Table 2 – Treatment of the burn.

	Total (n=40)	Cellulose (n=20)	Control (n=20)	p Value
Number who underwent operation	9	3	6	0.26
Excised area (BSA%)	4 (1-5)	4 (1-10)	3 (1-5)	0.71
Patients with split thickness skin graft	8	2	6	0.24[a]
Number of dressings	2.0 (1.0-10.5)	1.0 (1.0-2.0)	9.5 (6.0-16.0)	<0.001
BSA% covered with cellulose		6.5 (4.0-7.0)		
Sites where cellulose applied:				
Face		9		
Leg		5		
Arm		4		
Neck		2		
Hand		2		
Trunk		2		

Data are median (25th–75th quartile) or number of patients. Mann–Whitney U test and chi square test.
[a] Fisher's exact test. BSA%=percentage body surface area.

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Table 3 – Multivariable regression analysis for pain score during and after wound care.

	During			After		
	Coefficient	p Value	95% CI	Coefficient	p Value	95% CI
Superficial dermal BSA %	0.19	0.002	0.07–0.31	0.10	0.01	0.02–0.17
Deep dermal BSA %	0.15	<0.001	0.08–0.22	0.09	<0.001	0.05–0.13
Cellulose[a]	−3.38	<0.001	−4.28 to −2.47	−2.17	<0.001	−2.72 to −1.62
Age (years)	−0.02	0.12	−0.05 to 0.01	−0.01	0.15	−0.03 to 0.00
Constant	5.04	<0.001	3.66–6.42	3.06	<0.001	2.21–3.90

Multivariable panel regression, model (between) R^2 0.73, $p < 0.001$ for both models. Patients n = 40. Pain score values of three procedures/visits, n during = 120, n after = 119.
[a] Control group is reference.

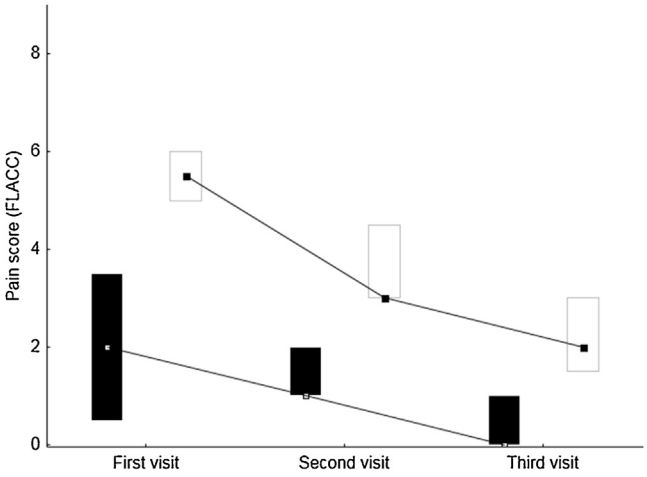

Fig. 4 – Pain score FLACC (The Face, Legs, Activity, Cry, Consolability scale) after wound care. Cellulose group = black bars, control group = white bars. Median and 25th–75th centiles (quartiles).

groups. The multivariable regression model for the pain score showed that the cellulose group had (mean) 3.4 lower score points during wound care and (mean) 2.2 lower score points afterwards, after adjustment for the size and depth of the burn, and the patient's age (Table 3).

The multivariable linear regression model showed that duration of hospital stay was (mean) 6.3 days shorter in the cellulose group after adjustment for size and depth of the burn and age. It also showed that each BSA% of deep dermal burns increased the duration by (mean) 1.1 days (Table 4). The multivariable regression model for time for epithelialisation showed that each BSA% of deep dermal burns prolonged the duration by (mean) 0.6 days, but younger age was associated with shorter duration of epithelialisation. It also showed that the cellulose group epithelialised (mean) 4.3 days quicker, although the difference was not significant (Table 5).

4. Discussion

The results of the study showed that patients with partial thickness burns treated with microbial cellulose had a shorter

Table 4 – Multivariable regression analysis for duration of hospital stay.

	Coefficient	p Value	95% CI	β
Superficial dermal BSA%	0.11	0.80	−0.73 to 0.94	0.04
Deep dermal BSA%	1.10	<0.001	0.63–1.56	0.70
Cellulose[a]	−6.34	0.04	−12.47 to −0.21	−0.26
Age (years)	−0.20	0.06	−0.40 to 0.01	−0.26
Constant	19.77	<0.001	10.31–29.24	

Model R^2 0.45, $p < 0.001$, n = 39.
[a] Control group is reference.

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Table 5 – Multivariable regression analysis for time to full epithelialisation.

	Coefficient	p Value	95% CI	β
Superficial dermal BSA%	−0.58	0.08	−1.23 to 0.08	−0.27
Deep dermal BSA%	0.64	0.001	0.27–1.02	0.53
Cellulose[a]	−4.28	0.08	−9.12 to 0.56	−0.22
Age (years)	−0.18	0.03	−0.34 to −0.01	−0.29
Constant	27.56	<0.001	20.15–34.96	

Model R^2 0.44, $p < 0.001$, n=39.
[a] Control group is reference.

duration of hospital stay, lower pain scores both during and after wound care, and they needed fewer changes of dressing. There was also a tendency for epithelialisation to be quicker in the cellulose group.

4.1. *Frequency of changes of dressing*

Frequent changes of dressing are a problem in burn care, mainly because they cause pain, but also because more dressings means more costs and more infections. The less often the dressing is changed the better, according to many authors [6,9,10], and we also found this to be the case in the cellulose group.

4.2. *Time for epithelialisation and duration of hospital stay*

In the cellulose group epithelialisation was complete in four fewer days than in the control group after adjustment for the differences in TBSA%, although not significantly so. A bigger study group would be needed to show if there was a difference between the groups, as was shown in another study [11]. The adjusted duration of hospital stay for the cellulose group was six days shorter than that in the control group, indicating that more patients could be managed as outpatients, which would provide better social and economic outcomes. The patients in this study were kept as in-patients for several reasons, including the long distances they would have to travel, and the cost of attending for appointments, which can jeopardise follow up with serious consequences, particularly among children [12]. The reported time needed for epithelialisation varies among studies, which makes the comparison more difficult because of the range of factors that affect outcome, but our median time to epithelialisation was comparable with that reported in several studies [11,13,14].

4.3. *Pain scores*

The cellulose group had lower adjusted pain scores both during and after wound care which is similar to the results of studies in which different membranous dressings were tested on burns [6,13]. The FLACC score was used for both adult patients and children in the current study because many patients had difficulty in interpreting a Visual Analogue Scale. Other reports have confirmed that it can be used for adult patients with cognitive dysfunction as well as for critically ill patients [15].

A thorough review of different dressings in the treatment of superficial burns in children [6] concluded that membranous dressings are superior to cream-based dressings in many ways. Microbial cellulose fulfils these criteria by being a biological membranous dressing with no risk of transferring infections (which is a risk with the use of allografts and xenografts). In addition, cultural and religious beliefs could limit the use of allografts, and particularly xenografts.

4.4. *Limitations*

The study had some limitations in that it is a single centre study that included a limited number of patients, which made it impossible to detect some significant differences. The differences in randomisation of the area of burns is a concern as it suggests that some bias can have been introduced. The tendency of higher proportion in the control group of all burn sites, except for the face, can be explained by the fact that the larger the burn, the more sites can be affected, but we have no explanation for the tendency of difference in proportion of facial burns. The study lacks long term follow up of the scar, which could be interesting and can be the subject of a future study. The comparison of a sheet dressing and a water-based cream may be unfair, because the nature of the cream dressings is that it necessitates frequent change of dressings. Further comparisons can be done in future between different sheet and membranous dressings.

5. Conclusion

Our results suggest that microbial cellulose would be the better first choice of dressing for partial thickness burns than silver sulphadiazine cream. The fewer dressings used, together with the low pain scores, are advantageous for both patients and the health care system.

The differences in randomisation of the area of burns is, however, a concern that needs to be included in the interpretation of the results.

Funding

This work was supported by and done at the Plastic Surgery Unit, Surgery Department, Suez Canal University, Ismailia, Egypt. No specific grants from funding agencies in the public, commercial, or not-for-profit sectors were received. The cellulose dressing material used in the study was donated by the manufacturer. The company played no part in the design of the study, collection and analysis of the data, decision to publish, or preparation of the manuscript.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.burns.2018.06.007.

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