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The use of a novel burn dressing out of bacterial nanocellulose compared to the French standard of care in paediatric 2nd degree burns – A retrospective analysis

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ABSTRACT

Purpose: Paediatric burn care is a delicate discipline which benefits from special attention. Despite being highly effective, the current standard of care for second degree burns in the largest paediatric burn center in France – exposure to infrared light – involves long hospital stays, straining economic and professional resources, especially in times of a pandemic. The present study investigated this standard of care and compared it to the use of a bacterial nanocellulose dressing.

Materials and methods: A retrospective analysis of two groups has been performed: the control group assessed thirty consecutive children treated with the standard of care, and the intervention group assessed thirty consecutive children treated with the bacterial nanocellulose dressing. Parameters evaluated were: healed wounds, additional treatments, rate of infections, hospital length of stay, pain experience and overall satisfaction.

Results: The two groups did not differ significantly in terms of age and TBSA. A significant reduction in hospital length of stay ($p < .001$) and pain experience ($p < .001$) could be observed. In terms of healed wounds, additional treatments and infections, the two groups were equally matched ($p > .05$) with satisfactory results in both groups. Tendencies towards better results could be seen in the intervention group.

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Conclusion: The use of bacterial nanocellulose wound dressings is an important tool in the armamentarium of today's burn surgeons. Satisfying results were achieved, ameliorating burn care for children. Future studies are indicated to further support its value and assess the economic impact.

1. Introduction

The treatment of burns is a delicate discipline in pediatric patients. The children's often active yet pragmatic behavior patterns usually involve different approaches to care than in adult patients. Armand Trousseau hospital in Paris, France is the biggest burn center in the country treating approximately 8000 pediatric burn patients a year with about 800 hospitalizations. These numbers have increased since the early 2000's [1]. A technique that has been used to treat superficial dermal burns by this institution and other pediatric burn centers since the 1950s is the daily exposure to infrared light with additional antiseptic treatments [1]. This technique allows a non-painful treatment, with the exception of the antiseptic washing, and marks a possibility of spontaneous healing without the restriction of wound dressing and dressing changes [1]. Fig. 1 shows an infrared lamp which is used for treatment.

Despite the reported good results, one of the main disadvantages of this technique is the rather long hospitalization of the patients. Since no dressing is used, a release from the stationary care is only possible once the whole burn wound has healed or only small defects remain. This poses a tremendous challenge to burn care providers, since not only the respective infrastructure with sufficient lamps, but also the provision of sufficient beds and personnel has to be assured. Furthermore, the patients' families require specific care and accommodation, since not only patients from all over France, but also Overseas France and other countries are treated.

This development and the increasing demands on patient care lead to the search for alternative measures [2]. One of the major downsides when using a wound dressing compared to the infrared technique is the indication for frequent wound checks and often painful dressing changes that could irrevocably traumatize children in addition to the already traumatizing trauma itself [3]. Consequently, an alternative with a minimum of dressing changes is required.

Fig. 1 – The figure shows one of the infrared lamps used for the exposure method used at Armand Trousseau Hospital in Paris.

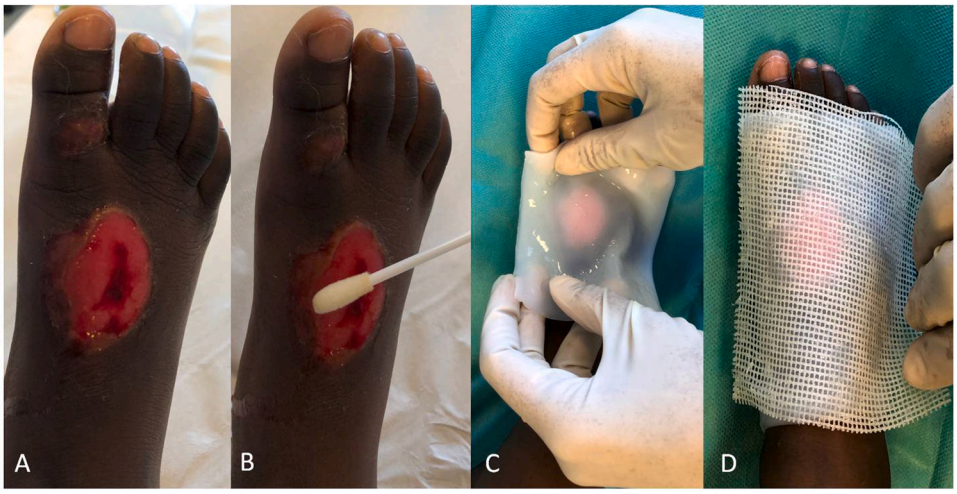

Fig. 2 – Depiction of the dressing regimen: In A the superficial dermal burn of the foot is shown after debridement. B shows the process of taking a swab for evaluation of bacterial colonization. C shows the application of the pre-soaked epicite^{hydro}. D shows the application of fatty gauze as secondary dressing.

Several studies investigated the specifications of the ideal burn dressing, which should be non-adherent, absorbent and anti-infective but should also require few dressing changes that should be pain-free [4–6]. One of the recent developments of burn dressing research is a novel dressing made of biologically-produced nanocellulose containing 95% isotonic saline solution and therefore fulfilling most of the desired criteria [7]. One of its main advantages is the possibility of using it to create a composite dressing with either diagnostic [8] or therapeutic abilities [9,10] – ultimately being able to equip an anti-infective, cooling and non-adhesive wound dressing that requires a minimum of dressing changes.

The current study was motivated by the above-mentioned search for alternatives in pediatric burn care. We aimed at directly comparing the wound dressing made of bacterial nanocellulose to our current standard of care concerning the wound healing, length of hospital stay and caused pain. This study should critically examine and ultimately help to find an easily accessible and reproducible standard of burn care in pediatric patients.

2. Materials and methods

2.1. Study design

The experimental design was a monocentric, retrospective data analysis of two groups consisting of thirty children, each treated with 2nd degree burn at the burn unit of the Armand Trousseau Hospital in Paris, France. All patients' legal guardians agreed to participate in the data analysis and signed an informed consent. The study has been conducted according to the Declaration of Helsinki.

2.2. Inclusion criteria

All patients treated at the above-mentioned hospital with a 2nd degree burn (superficial or deep dermal) of less than 10% TBSA were screened. Thirty consecutive patients treated with the novel nanocellulose dressing epicite^{hydro} have been included. Additional 30 patients treated with the current standard of care (see below) were included to serve as control group. Patients had to be older than 12 months and younger than 18 years old to be included. All other patients, especially full thickness burn patients, or patients whose legal guardian refused inclusion have been excluded from the analysis.

2.3. Investigated parameters

Upon admission, patient data such as age, gender, cause of burn, and percentage of TBSA burnt as well as time to treatment (TTT) have been obtained. We investigated the amount of healed burns at day 15 (D15), the time to healing, and the rate of additional treatment, the duration of the hospitalisation (length-of-stay LOS), the pain level and the occurrence of infections. Pain level was obtained at the application and removal of the epicite^{hydro} in the intervention group, and daily during the antiseptic treatment in the control group using the EVENDOL [11] or VAS score, whereas the average for every patient was calculated. Occurrence of infection was obtained with an initial swab and afterwards by clinical assessment. Additionally, the overall satisfaction with the treatment of the patient and/or the family was evaluated with nominal question (yes/no).

2.4. Intervention and control treatment

2.4.1. Intervention group

Patients treated in the intervention group received a thorough cleaning of the burn and antispetic treatment before application of a nanocellulose dressing (epicite^{hydro}, QRSKIN GmbH, Würzburg, Germany) consisting of 95% isotonic saline solution, which had been soaked in a Chlorhexidine solution for 10 min. A secondary dressing of fatty gauze and finally dry gauze were applied to the epicite^{hydro}. The dressing regimen is depicted in Fig. 2. Pain management before and during the

treatment was conducted using medications of the first step of the WHO pain ladder in addition to nitrous oxide. The whole process was conducted under sterile conditions. Patients discharge was possible the same or the following day with planned consultations on day 4, 10 and 15. There was no planned dressing change of the epicite^{hydro}. The secondary dressing was changed upon necessity.

2.4.2. *Control group*

The control group received the standard of care which consisted of a daily exposure to an infrared lamp after thorough cleaning and antiseptic treatment of the burn. Details of the current standard of care at Armand Trousseau Hospital are published by Bach et al.[1]. Pain management before and during the treatment was conducted using medications of the first and third step of the WHO pain ladder as well as sedative or hypnotic medication.

2.5. *Statistical analysis*

Data has been analyzed using means, median, standard deviation and other variables of descriptive statistics. To describe inferential statistics, student's *t*-test had been used. Data was tested for normal distribution using the Kolmogorov-Smirnov-Test. Significance has was set to $p < .05$. Given the small sample size, *Cohen's* d as indicator of effect size was calculated for non-significant results [12].

3. Results

3.1. *Study population*

In total, 60 patients have been included in the retrospective data analysis (30 per group). The mean age was 3.4 years (+/- 3.0 years) and the mean TBSA was 4.0% (+/- 1.94%). The TTT was 1.5 days on average (+/- 1.5 days) and the cause of burn was scald in 95% (57/60) and contact burn in 5% (3/60) of cases.

The differences between the age ($p = .147$) and the TBSA ($p = .444$) were not statistically significant; neither were the differences in ttt ($p = .738$) or cause of burn ($p = .561$). Details of the study population can be found in Table 1.

3.2. *Healed Burns at D15 and time to healing*

Twenty-six of the 30 burns in the intervention group (86.67%) had healed at D15. Twenty-three of the 30 burns in the control group had healed at D15 (76.67%). The difference is not significant ($p = .330$). The total time to healing in the intervention group was 14.6 days (+/- 8.98), and in the control group 17.4 (+/- 9.60). The difference in time to healing does not differ significantly ($p = .256$). The effect size for time to healing was 0.301. Figs. 3–5 show three cases of the intervention group whose burns had healed. Fig. 6 shows a case of the control group that had healed at D15.

3.3. *Additional grafting*

Two of 30 burns in the intervention group underwent an additional split thickness skin graft (6.67%). Four of 30 burns in the control group received an additional split thickness skin graft afterwards (13.33%), with a fifth one that should have be grafted, but the parents refused to consent (16.67%). The difference is not significant ($p = .235$), and the effect size is 0.316.

3.4. *Duration of hospitalisation*

The average LOS was 1.67 days (+/- 0.98) in the intervention group and 11.10 days (+/- 2.96) in the control group. The difference is significant ($p < .001$).

3.5. *Pain level*

The average pain level in the intervention group was 2.86 of 10 (+/- 1.5). The average pain level in the control group was 5.84 of 10 (+/- 1.14). The difference is significant ($p < .001$).

3.6. *Occurrence of infections*

All initially performed wound swabs were negative. Further along, no sign of infection was seen in the control or intervention group. The rate of infections is therefore 0%.

3.7. *Satisfaction*

The patient and/or his family were overall satisfied with the treatment in 96.67% (29/30) of cases in the intervention and in 90% (27/30) of cases in the control group. The difference is not significant ($p = .309$), and the effect size 0.271.

The results are summarized in Table 2.

4. Discussion

Paediatric burn care is a delicate discipline with particular caution taken to not cause additional burdens of the treatment. In this retrospective analysis, we could show no significant difference of healed burn wounds at D15 when comparing our current standard of care with the application

Table 1 – Summary of the study population. TBSA = Total body surface area, TTT = Time to treatment, d = day.

	n	Age (mean)	% TBSA	TTT (d)	Burn cause
Intervention	30	4	3.72	1.56	Scald 28/30 (93.33%) Contact 2/30 (6.67%)
Control	30	2.86	4.23	1.43	Scald 29/30 (96.67%) Contact 1/30 (3.33%)
p-value		.147	.445	.738	

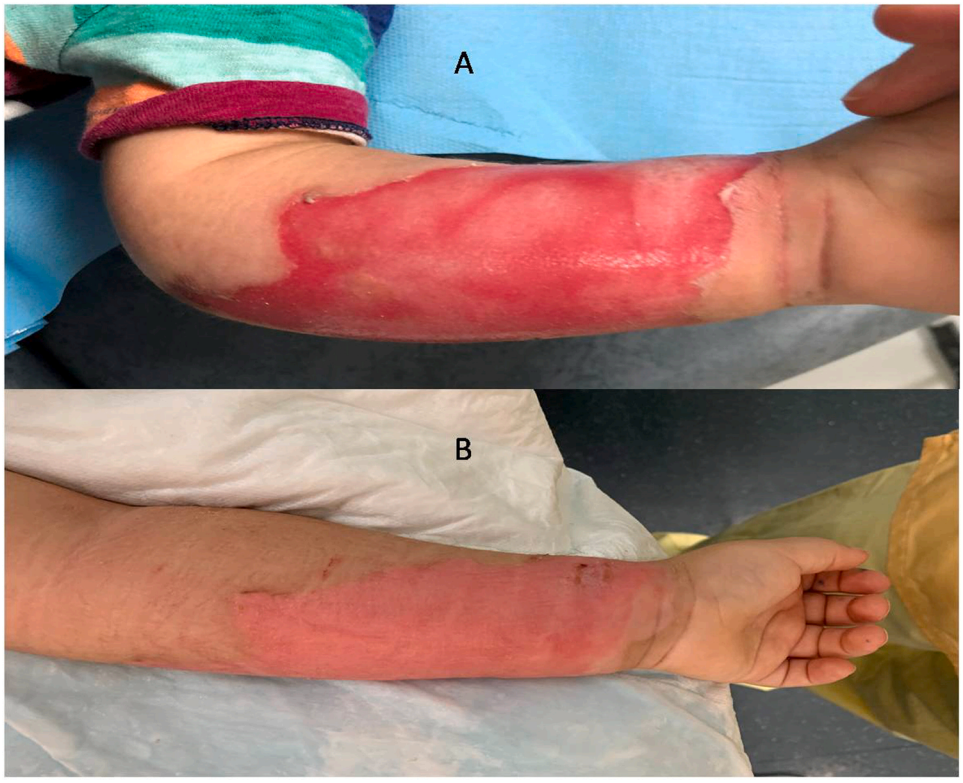

Fig. 3 – The figure shows a superficial dermal burn of the volar forearm after debridement (A) and 15 days after treatment with epicite^{hydro} (B).

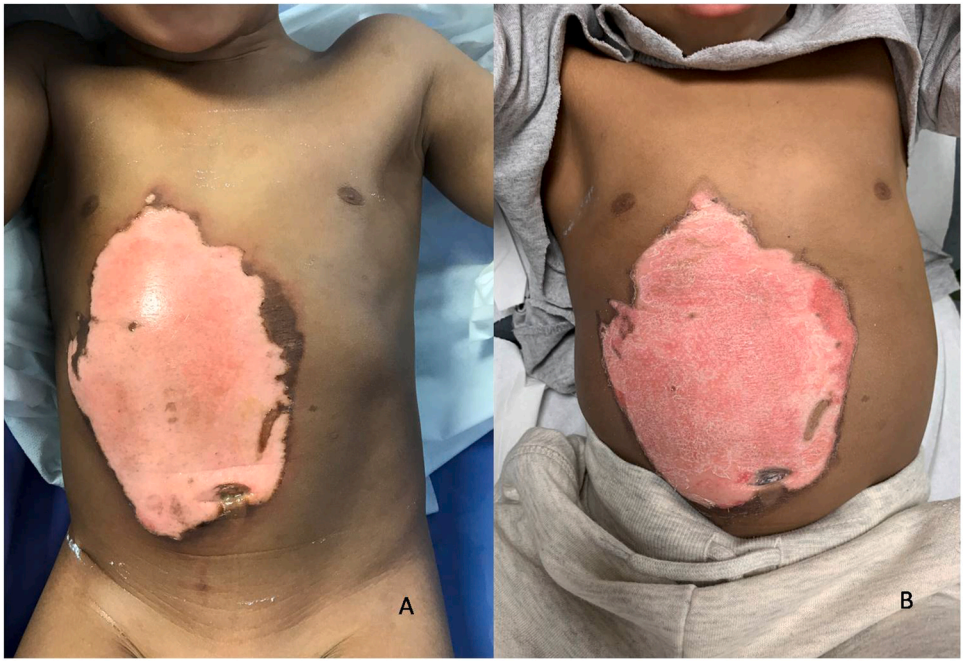

Fig. 4 – The figure shows a superficial dermal burn of the ventral epigastrium and lower thorax after debridement (A) and 15 days after treatment with epicite^{hydro} (B).

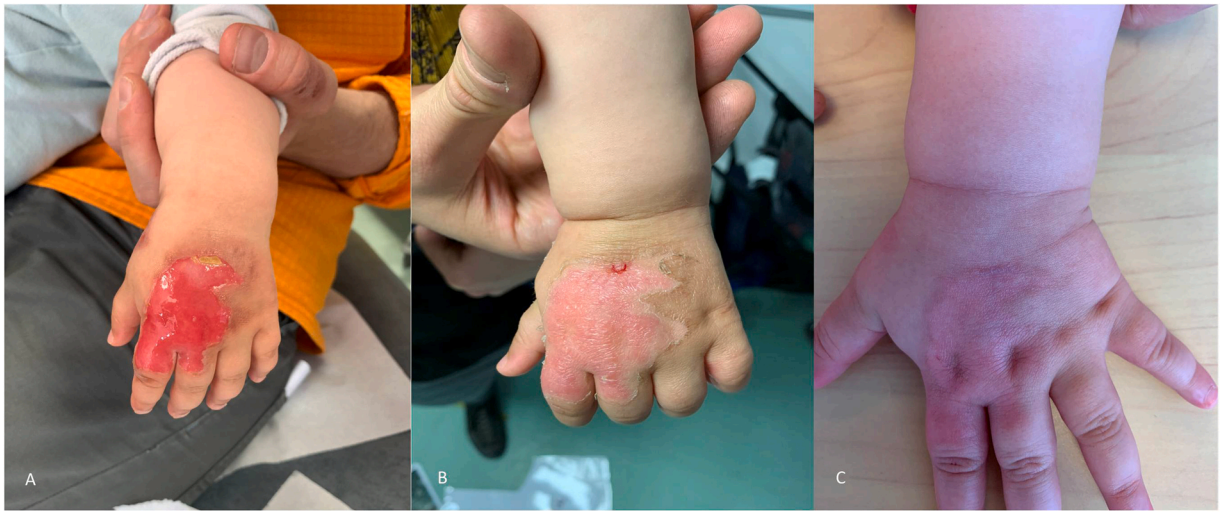

Fig. 5 – The figure shows a superficial dermal burn of the dorsal hand after debridement (A), 15 days after treatment with epicite^{hydro} (B) and at a follow-up 6 weeks after burn (C).

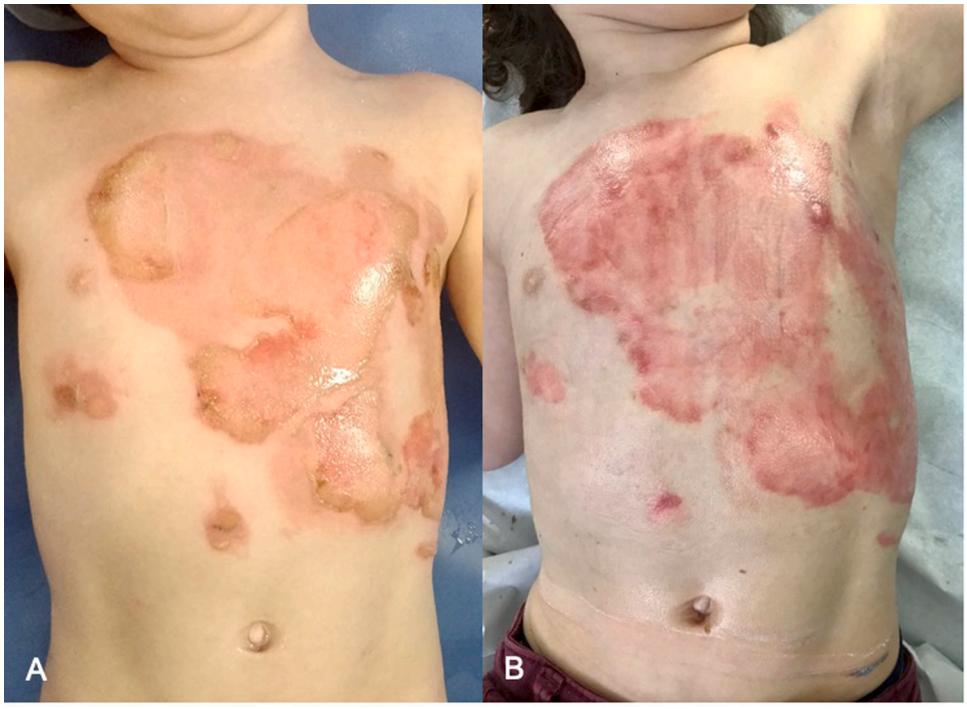

Fig. 6 – The figure shows a superficial dermal burn of a left hemithorax after debridement (A), and 15 days after daily exposure to an infrared lamp (control group).

of a biological nanocellulose dressing while drastically decreasing the LOS and also reducing the pain perceived.

The intervention and control group had the same prerequisites with no difference in age, TBSA burnt, TTT and cause of burn in between the groups. Consequential, our results can be considered valid.

The first and most important parameter in our opinion concerned the question: Is there a difference in healing time when deviating from the to-date successful standard of care at Armand Trousseau hospital? We investigated this question by assessing the rate of healed wounds at D15, two weeks after commencement of treatment. Given the fact that two weeks is a relatable time frame for 2nd degree burns to heal, good results could be seen: 76.67% of burns in the control group had healed. In the intervention group, the rate even rose to 86.67%. The time to healing in both groups was 17.4 (+/- 9.60) and 14.6 (+/- 8.98) days respectively. Despite the difference not being statistically significant, a tendency can be seen to a faster healing with the nanocellulose dressing, which is supported by the effect size of 0.301. While this

Table 2 – Summary of the results. D15 = day 15, LOS = length of stay.

	Total Healing (D15)	Time to healing [days]	Additional treatment	LOS (days)	Pain (x/10)	Infected wounds	Overall satisfaction
Intervention	26/30 (86.67%)	14.6 (+/- 8.98)	2/30 (6.67%)	1.67	2.86	0	29/30 (96.67%)
Control	23/30 (76.67%)	17.4 (+/- 9.6)	5/30 (16.67%)	11.1	5.84	0	27/30 (90%)
p-value	.330	.256	.330	< 0.001	< 0.001		.309

effect might seem rather small, as theoretically an effect size of higher than 0.5 is considered large [12], *Gignac and Szodorai* argue, given the feasibility in medical studies, empirically, an effect size > 0.3 should be considered as large effect [13]. Future studies with large sample sizes are necessary, to further investigate the effect. Similar results have been achieved by two other groups that investigated the use of nanocellulose in paediatric burns: Most wounds in these two studies had already healed after 10 days [14,15], in our study a mean time to healing of 14.6 days was achieved. In vitro and preclinical studies using chlorhexidine could show a negative effect of wound healing (delay) [16,17]. While these results could not be shown in in vivo studies [18,19] and its efficacy is undoubted [20], increased adverse events were found in newborns [21], hence suggesting an increased susceptibility of younger patients. Despite no clear consensus for or against chlorhexidine can be found [22], we cannot rule out a confounding factor of the disinfection protocols with possible influence of repeated scrubbing [23] or slow release of chlorhexidine, which can be assumed from other studies investigating the release of other antiseptics from BNC [10]. Alternatives for chlorhexidine could be found for instance in povidone-iodine, polyhexanide, or octenidine dihydrochloride. Further studies should evaluate the healing rate with more patients, and different disinfectants possibly detecting a significantly faster wound healing, which could be expected given the in-vitro evidence of BNC supporting wound healing [25,26]. A similar interpretation can be deduced from the rate of additional treatment: in our investigation, only 2 of 30 patients in the intervention group underwent additional skin grafting. This rate of 6.67% is even lower than the one reported by Cattelaens et al.(18%) [14]. However, they reported 23.21% of burns to be at least deep dermal while our study protocol did not take into account a further differentiation. While the difference compared to the control group is not significant ($p = .235$), a trend can be assumed based on the five patients in this group who needed additional treatment, further supported by the effect size of 0.316. Further studies with more patients and exact differentiation of burn depths might clarify this trend and ultimately yield a significant difference.

In addition to the overall healing, the LOS in stationary care is probably one of the most interesting aspects to be analyzed in our study. Since the infrastructural necessities of our standard of care require a long stationary care, the intervention should yield a drastic reduction in LOS in order to be considered successful. We could observe a reduction of almost ten days on average in the intervention group compared to the control group (1.67 vs. 11.10 days, $p < .001$). The short LOS is even shorter than the one reported by Cattelaens et al. [14] in whose study children stayed in hospital for an average of 6.7 days (superficial burns only 5.7). These differences might occur due to different hospital policies, limited experience with these novel wound dressings or even differences in cost coverage. Since the other group did not specify the criteria for a release from stationary care, we cannot reveal the cause with certainty. Given the retrospective nature of our study, we can most surely exclude a selection bias having led to this significant reduction in LOS. However, the reduction of LOS should to be regarded

cautiously, given the inherent longer stay in the control group, as daily treatments were done and thus discharge was only possible after almost complete wound healing. Another group having recently come to similar conclusions is the group around Maurer et al. [27]: They could show a similar reduction in hospital LOS ($p < .001$) Apart from the distress caused by a prolonged hospital stay not only for the patients themselves [28] but also for their caregivers, and in our case infrastructural bed management [29], an additional cost reduction could be achieved, ultimately assessing the intervention as being a successful alternative [30]. In critical and challenging times, as we all have experienced during the COVID-19 pandemic, prolonged hospital stays are an additional risk as well [31]. The patients being quickly equipped with the "final" wound dressing and a consecutive short hospital stay allows for follow-up treatments close to a patient's home and the use of telemedicine for additional assessments, thus not requiring any procedural change in case of tight capacities.

Another highly relevant aspect we could assess in this study is the reduction of experienced pain. The intervention group showed an average pain level of 2.86, while the control group showed an average level of 5.84 (of 10, $p < .001$). It is needless to say that a reduction of pain is worth striving for, especially with children [3]. In a recent study by Nischwitz et al., it was shown that pain management is an aspect which can sometimes be underestimated in burn patients – especially in the developing world [6,32]. Given that fact, in a market plentiful stocked with different advanced wound dressings, a pain reduction by a dressing itself is even more important. Of course, another fact influencing the pain score we have obtained is that the standard of care utilises daily manipulations (antiseptic treatments) which are usually painful and stressful in the early stages of wound healing, while the control group underwent manipulation only once. The use of modern wound dressings usually reduces the number of dressing changes, hence supposedly also the pain experienced. The reduction of dressing changes is one of the main advantages of modern burn dressings, which is why many modern burn centres are already using these dressings with great success. The early antiseptic treatment and the following 'wound-sealing' by the wound dressing showed a 0% infection rate in our study, therefore justifying the single antiseptic treatment at the beginning. This rate goes along with the recently published studies by Resch et al., Cattelaens et al., and Maurer et al. [27], who showed no relevant increase in infections and/or complications in their respectively treated groups either.

Ultimately, we assessed the overall satisfaction of the treatment by patients and/or their families. In both groups, a tremendous overall satisfaction was achieved (96.67% vs. 90%). The difference was not statistically significant, nor could a large effect be shown (effect size < 0.3). This judgement might support the use of both modalities in burn care, despite possibly being influenced by not only the treatment modality itself, but also the overall impression of the hospital and the interpersonal experience with doctors, nurses and other caregivers.

This study also shows some limitations. On the one hand, the retrospective nature of the study is a downside, but on the other hand, it can lead to the definite exclusion of a selection bias. The insignificant differences in age and TBSA in our two groups further support this fact. Another disadvantage is the small case number that yielded in some tendencies without being statistically significant. Future studies should investigate the actual duration of healing with these two treatments and should further differentiate between burn site and objectively measured depth. An additional interest should also be the economic aspect in these studies. A cost reduction is without a doubt achievable, not only by the reduction of LOS itself and the associated healthcare costs, but also by minimizing the hospitalization of the families probably far away from home, not being able to work and possibly pay for the lodging. Yet, our study did not investigate this aspect, which could lay the ground for tremendous benefits and savings that deserve to be investigated in further studies. Another noteworthy aspect is the fact, that the LOS reduction we found, was predictable: The burns included in this analysis were 2nd degree burns of limited TBSA, which nowadays are usually treated in an outpatient setting. Therefore, the choice of control group, which nevertheless is the current standard of care despite being considered antiquated by most modern burn centres, was supposed to have a higher LOS, since daily treatments are necessary, and discharge is only possible, once the wounds have healed.

Finally, the rate of healed wounds, rate of additional treatments and the low rate of infections yield the intervention equally matched the currently used standard of care, while the short length of stay and pain reduction make the treatment with epicite^{hydro} an important and relevant treatment alternative in the armamentarium of a burn surgeon.

5. Conclusion

The current standard of care at the largest paediatric burn unit in France was compared to the use of a novel epidermal substitute made of bacterial nanocellulose in 2nd degree burns in 60 children in this study. We could show a significant reduction in hospital LOS and pain by the usage of epicite^{hydro} while being equally matched in terms of healing and infection rate with tendencies towards a higher healing rate at day 15 with epicite^{hydro}.

The use of advanced wound dressings is a highly relevant and important modality in the armamentarium of today's burn surgeons, that should be further investigated and developed in future studies to promote wound healing, regenerative medicine and burn care overall.

Conflict of interest statement

The authors declare to have no conflict of interest. Epicite^{hydro} wound dressings were provided by QRSKIN GmbH free of charge. No funding occurred for this study, QRSKIN GmbH did not influence the structure or content of this study in any way.

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