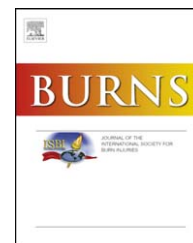


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The optimal duration and delay of first aid treatment for deep partial thickness burn injuries

Leila Cuttle^{a,*}, Margit Kempf^a, Pei-Yun Liu^a, Olena Kravchuk^b, Roy M. Kimble^a

^a Royal Children's Hospital Burns and Trauma Research Group, University of Queensland, Department of Paediatrics and Child Health, Royal Children's Hospital, Herston Rd, Herston, Queensland 4029, Australia

^b University of Queensland, School of Land, Crop and Food Science, St Lucia, Queensland 4072, Australia

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ABSTRACT

Using our porcine model of deep dermal partial thickness burn injury, various durations (10 min, 20 min, 30 min or 1 h) and delays (immediate, 10 min, 1 h, 3 h) of 15 °C running water first aid were applied to burns and compared to untreated controls. The subdermal temperatures were monitored during the treatment and wounds observed weekly for 6 weeks, for re-epithelialisation, wound surface area and cosmetic appearance. At 6 weeks after the burn, tissue biopsies were taken of the scar for histological analysis. Results showed that immediate application of cold running water for 20 min duration is associated with an improvement in re-epithelialisation over the first 2 weeks post-burn and decreased scar tissue at 6 weeks. First aid application of cold water for as little as 10 min duration or up to 1 h delay still provides benefit.

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1. Introduction

The current recommendation for the first aid treatment of burns from the Australian and New Zealand Burn Association [1], is to cool the burn wound with cold running tap water for 20 min, up to 3 h after the injury has occurred. However, the published first aid experiments that these guidelines are based on are conflicting and it is surprising that these recommendations could be made from the evidence to date. The conflicting results are probably due to the studies being conducted in different animal models, using different depth and mechanism of injuries and examining different outcome measures (such as edema, Evans blue dye perfusion, mortality and histological damage).

If pain is used as an outcome, most people advocate application of cold treatment until no pain is felt on removal of the cold [2], and this has been described as 30 min—

several hours [3,4]. However, when examining edema as an outcome, one study found that the longest duration of treatment tested (2 h at 0 °C) was found to be most beneficial [5]. Another study using Evans blue dye perfusion found that although there was benefit for up to 4 h duration of cooling, the effect was not much better than cooling for 30 min [6]. They recommended that first aid should be applied for at least 30 min duration, but for up to 3 h was acceptable. Most recently, Bartlett et al. [7] found that a duration of 20 min in a porcine burn model lead to less injury measured histologically 9 days after injury.

Delays after which positive effects can still be seen are reported as <2 min [8], <5 min [9,10], <30 min [6], 30 min [11,12], 45 min [13], <60 min [14], 60 min [15], 2 h [16] or 3 h [17]. Many studies report that immediate treatment is the most beneficial, however positive effects are still seen after periods of delay.

* Corresponding author. Tel.: +61 7 3636 9067; fax: +61 7 3365 5455.

E-mail address: L.Cuttle@uq.edu.au (L. Cuttle).

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In this study, we used our clinically relevant [18,19] porcine burn model [20,21] which has previously been used to test other first aid treatments such as temperature [22] and alternative therapies [23]. This time we tested various durations and delays of first aid (15 °C running water) on deep partial thickness burns. Our aim was to determine the optimum duration of first aid and the delay after the burn for which first aid is still effective. The outcomes we measured were: wound re-epithelialisation, subdermal temperatures, change in wound and scar area over time, histology of the scar and cosmetic appearance of the scar. The endpoint was 6 weeks after the burn, allowing us to examine the full re-epithelialisation process and scar appearance.

2. Materials and methods

2.1. Animal surgery

All animal work was approved by the institutional animal ethics committee and all animals were treated in a humane manner. Forty Large White juvenile pigs of 15–20 kg (approximately 8 weeks of age) were used for the study. Anaesthesia was induced with an intramuscular dose of 13 mg/kg ketamine hydrochloride (Ketamine 100 mg/mL, Parnell Laboratories, Alexandria, Australia) and 1 mg/kg xylazine (Xylazil 20 mg/mL, Ilium, Troy Laboratories, Sydney, Australia) and was maintained with isoflurane via a size 4 laryngeal mask airway [24]. The hair on the back and flanks was clipped and the skin rinsed with clean water prior to wounding. Buprenorphine hydrochloride at 0.01 mg/kg (Temgesic 0.3 mg/mL, Reckitt Benckiser, West Ryde, Australia) was administered as an analgesic on induction.

Core body temperature was measured with a digital rectal thermometer (MC-110B, Omron Corporation, Japan) at regular intervals. To measure the subdermal temperature during burn creation and first aid treatment, a temperature probe was inserted under the skin. A 14 gauge 2.1 mm × 45 mm cannula was inserted obliquely from outside the wound area and advanced under the dermis, through the fat layer until the tip was in the centre of the burn area. The needle was removed from the cannula and a type K thermocouple (Radiospares Components Pty Ltd., Smithfield, Australia) was inserted and taped into position. The probe was inserted by this method under the skin to minimise the possibility of direct heat transfer from the burning device and to minimise damage to the tissue. A digital 54II Fluke thermometer (Fluke Australia Pty Ltd., North Melbourne, Australia) automatically collected and logged temperature measurements every 15 s once the burning device was applied and during the course of the first aid treatment.

Wounds were created using a technique described previously by our group [20]. A bottomless bottle sealed with plastic wrap was filled with 300 mL of sterile water and heated in a microwave oven until it was approximately 95 °C. The temperature of the water inside the bottle was monitored with a digital thermometer (N19-Q1436 Dick Smith, Australia, range –50 °C to 100 °C (±0.5%)) and when the water was at 92.0 °C, the device was placed on the pig flank. The device was held in place by the same person each time for 15 s. Two burns were created on each animal, one on each flank.

2.2. Administration of first aid

After the burns had been created, a photograph was taken and the treatment was commenced at the relevant time. Running water at 15 °C was applied at a rate of 1.6 L/min from a cooling water bath (Grant S26, Jencons (Scientific) Limited, Leighton Buzzard, UK) through plastic tubing connected to a water pump. The animals were positioned on a table which allowed the water to drain away underneath. Hot water bottles were applied to the body of all animals during cold water treatment and during the 1 h and 3 h delay periods to minimise risk of hypothermia. After the treatment period, the wounds were dressed with Jelonet™ (inert paraffin gauze, Smith & Nephew, Hull, UK) and Melolin™ (Smith & Nephew, Hull, UK) and secured with Fixomull® retention tape (BSN Medical, Hamburg, Germany). The animals were then put into custom-made garments to protect the dressings and wounds over the 6-week period.

2.3. Dressings and sedation

For weekly dressing changes, the animals were sedated with an intramuscular dose of ketamine/xylazine (13 mg/kg ketamine/1 mg/kg xylazine). Dressings were removed and the wounds were washed with 0.4% chlorhexidine solution and cotton gauze. The wounds were examined and a clinical description of the wound was noted, observing characteristics such as wound exudate, scar profile and presence of hair. Photographs were taken of the wound using a Canon EOS 400D digital SLR camera (Canon Australia Pty Ltd., North Ryde, Australia). The perimeters of the wounds were traced using a Visitrak™ device (Smith & Nephew, Hull, UK) which calculates the total area of the wound in cm². The Visitrak™ device was also used to calculate the amount of wound re-epithelialisation as a percentage of total wound area by tracing the outlines of wet skin areas (un-re-epithelialised skin). The animals were euthanized at 6 weeks after the burn with 15 mL of sodium pentobarbitone (lethabarb 325 mg/mL, Virbac (Australia) Pty Ltd., Peakhurst, Australia). Representative tissue biopsies approximately 1 cm³ were collected from the burn (seven areas) and unburned normal areas (two areas) and fixed in 10% formalin for paraffin embedding.

2.4. Histology: light microscopy

Paraffin sections of 4 μm thickness were stained with haematoxylin and eosin (H&E) and digital images captured through a Nikon EP600 microscope fitted with a Spot RT slider cooled CCD camera (Nikon Australia Pty Ltd., Lidcombe, Australia). The thickness of the skin and the amount of organising granulation tissue (OGT) was measured digitally from the images using Image Pro Plus v4.1.29 software (Media Cybernetics Inc., Silver Spring, USA) in a blinded manner.

2.5. Assessment of cosmetic appearance

The wounds were examined at post-mortem in a blinded manner by three experienced burn observers and graded using a point scale scoring system, which was established with the use of example wound photographs, similar to the Manual for Matching Assessment using Photographs with Scars (MAPS)

system [25]. There was a good agreement (within 0.1 point on 5 point scales) among assessors.

2.6. Statistical analysis

The statistical analysis of this study was conducted with Minitab[®] R15 (Minitab Inc., Chicago, 2005). The general linear model procedure, and the combinations of rank tests and Levene's test of the difference in variances were used. In all tests individual animals were presented as experimental units and wounds as sub-units. The healing effects and standard errors of effects were calculated for each treatment group using data from each animal replicate in that group. A meta analysis was conducted for the control and first aid (immediate application of running cold water for 20 min) treatments combined from the delay and duration studies. In the analysis, the duration and delay studies were included as a random effect in the model, to account for minor differences in animal weights and skin thickness between the trials (which did not significantly affect results). The level of significance of every individual test was set at 5% ($p < 0.05$), and the actual p -values were additionally derived to account for multiple testing.

3. Results

3.1. Animal operations

One animal was euthanized during the surgery and four wounds were excluded as they had superficial areas (>5% total

area was red). The average pig weight at scald creation was 21.7 ± 1.0 kg (mean \pm SE). The average scald area was 45.4 ± 3.0 cm².

3.2. Duration

With longer durations of cold water, the skin subdermal temperature continued to decrease (Fig. 1A). At the end of the treatment period, the average subdermal temperatures were 29.1 ± 1.01 °C, 28.2 ± 0.83 °C, 26.1 ± 0.22 °C and 23.7 ± 0.26 °C for 10, 20, 30 min and 1 h durations, respectively, compared to the untreated control after 20 min (36.1 ± 0.21 °C). During the 1 h treatment with cold water, the core body temperature dropped 2.7 ± 1.1 °C despite the application of hot water bottles, compared to the control, which dropped 0.5 ± 0.3 °C. At 2 weeks after burn, re-epithelialisation was higher for the 20 min treatment compared to control, although this was not quite significant ($p = 0.05$, Fig. 1B), with other durations (both shorter and longer), giving less benefit. However, after 2 weeks (i.e. at week 3 and thereafter), this beneficial effect on re-epithelialisation compared to control disappeared. No significant difference was found in the average wound size between the treatments over the 6 weeks ($p = 0.34$), or the contraction of the wounds from scalding to week 6 ($p = 0.76$). There was no significant difference in the average %OGT ($p = 0.34$) or average OGT thickness ($p = 0.78$) among the treatments (Fig. 1C), however the distribution of %OGT was significantly different among the treatments, with control wounds having consistently higher median %OGT ($p = 0.03$), while first aid treated wounds had a larger proportion of cases

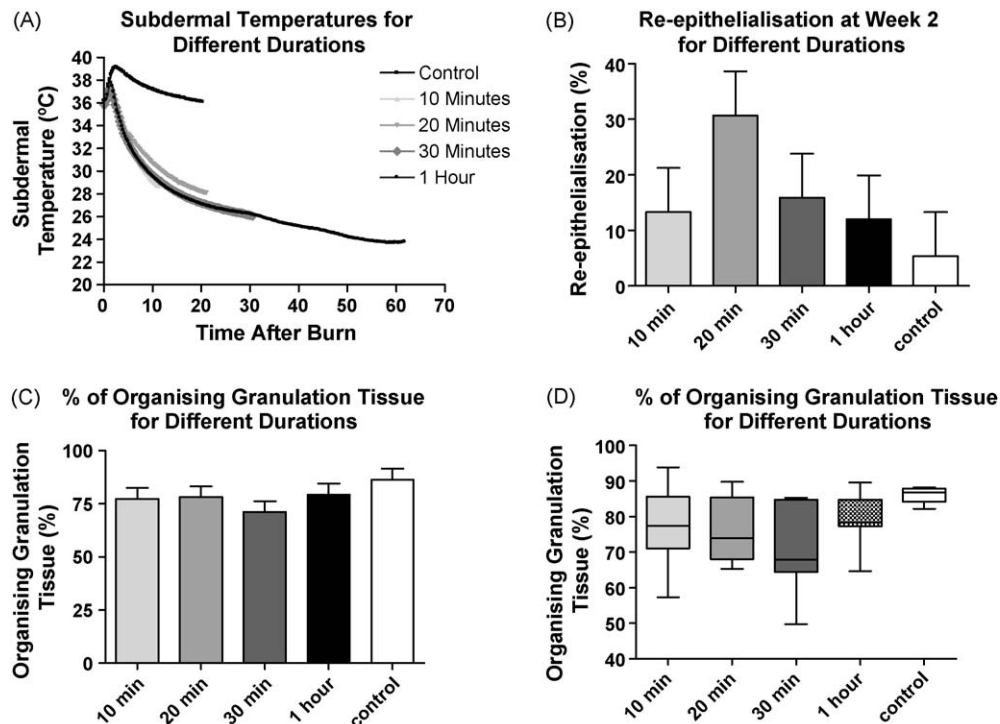


Fig. 1 – Clinical outcomes measured when first aid is applied to a burn wound for different durations (10 min, 20 min, 30 min and 1 h compared to an untreated control). (A) The subdermal temperature decreased more the longer the first aid was applied. (B) Re-epithelialisation was faster for the 20 min treatment at 2 weeks post-burn ($p = 0.05$ in comparison to the control). (C) There was no significant difference in the average % organising granulation tissue (scar tissue) between treatments, however the controls had higher median %OGTs ($p = 0.03$) (D).

with lower %OGTs ($p = 0.03$) (Fig. 1D). There was no significant difference in the cosmetic appearance of the scar at week 6 among the treatments ($p = 0.68$).

3.3. Delay

The control subdermal temperature returned to normal ($36.5 \pm 0.10^\circ\text{C}$) approximately 20 min after the burn was created. As the temperature continued to drop, when treatment was delayed for 1 and 3 h, the subdermal temperature was lower by the end of the 20 min treatment period ($23.7 \pm 1.03^\circ\text{C}$, $24.2 \pm 0.43^\circ\text{C}$, respectively) compared to immediate and 10 min delays ($26.0 \pm 0.40^\circ\text{C}$, $26.1 \pm 0.82^\circ\text{C}$, respectively) (Fig. 2A). During the 3 h delay period, the core body temperature dropped an average of $2.0 \pm 0.9^\circ\text{C}$ before treatment commenced. At 2 weeks post-burn, the re-epithelialisation appeared higher for the immediate treatment compared to control ($33.3 \pm 9.5\%$ for immediate, 14.6 ± 6.7 for control) although this was not quite significant ($p = 0.07$, Fig. 2B). However, after 2 weeks, the 3 h delay treatment re-epithelialised significantly faster compared to control (85.8 ± 12.4 for 3 h delay, 59.2 ± 12.4 for control, $p = 0.04$ at 3 weeks), whereas the positive effect of immediate treatment diminished from week 3 onwards compared to control ($p > 0.10$, Fig. 2C). There was a significant difference in wound

size between the treatments over the 6 weeks ($p = 0.04$), with the 1 and 3 h delay treatments having less contracted wounds compared to control at week 6 ($p = 0.03$). There was no significant difference in the average %OGT ($p = 0.71$) or average OGT thickness ($p = 0.74$) among the treatments (Fig. 2D), however the distribution of %OGT was significantly different among the treatments with control wounds having consistently higher %OGT (except for one wound out of 10, which healed with less than 80% OGT) while delayed first aid treated wounds had a larger proportion of cases with lower %OGTs ($p = 0.04$). We found no significant difference in the cosmetic appearance of the scar at week 6 among the treatments.

3.4. Meta analysis of first aid treatment

For this analysis, all the control data from the experiments was combined into the control group and the data for 20 min duration (from the duration study, which was applied immediately) and data for the immediate delay (from the delay study, which was applied for 20 min duration) were combined for the first aid treatment group. We found no significant differences between control wounds and animals in both duration and delay studies. The animals and wounds in the first aid treatments were also similar in both studies.

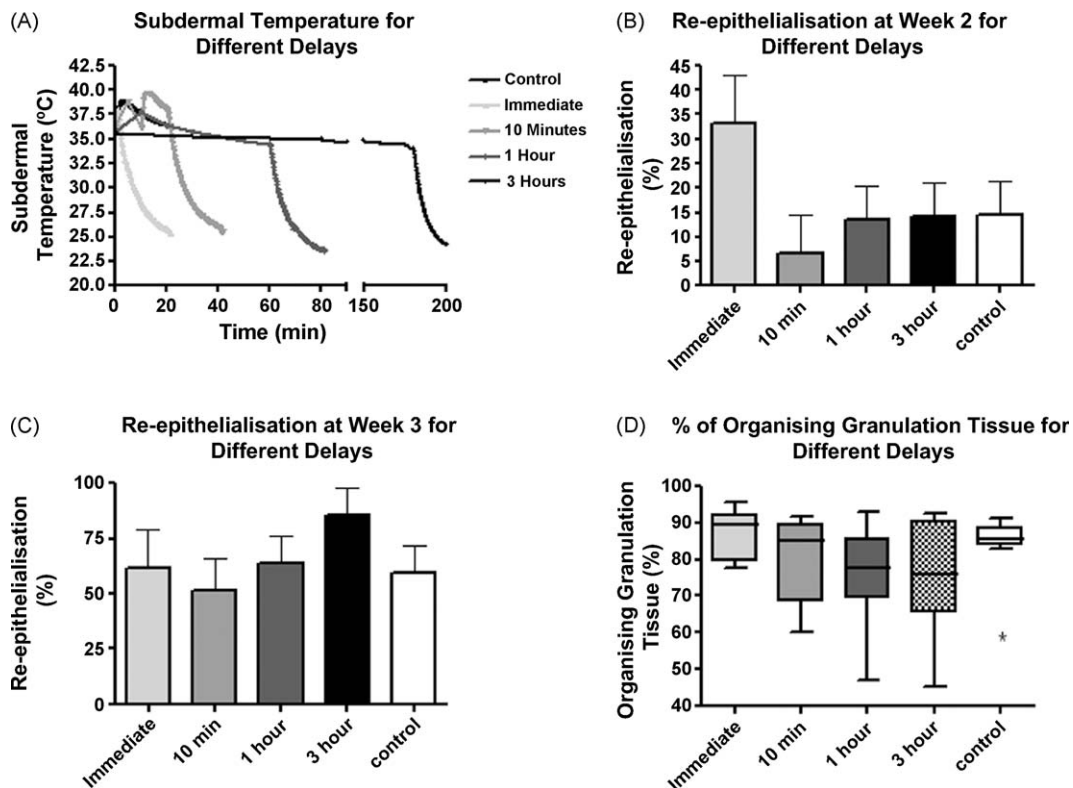


Fig. 2 – Clinical outcomes measured when first aid is applied to a burn wound after different delays (immediate, 10 min, 1 h, 3 h compared to an untreated control). (A) The subdermal temperature decreased further after longer delays. (B) Re-epithelialisation was faster for the immediate treatment at 2 weeks post-burn (although this was not quite significant, $p = 0.07$), and this effect disappeared after this time ($p > 0.10$). (C) Re-epithelialisation was faster for 3 h delay treatment at 3 weeks post-burn. (D) There was no significant difference in the average % organising granulation tissue (scar tissue) between treatments, however the controls tended to have higher %OGTs. There was only one control wound (out of 10) which healed with $<80\%$ OGT, this is indicated with an asterisk.

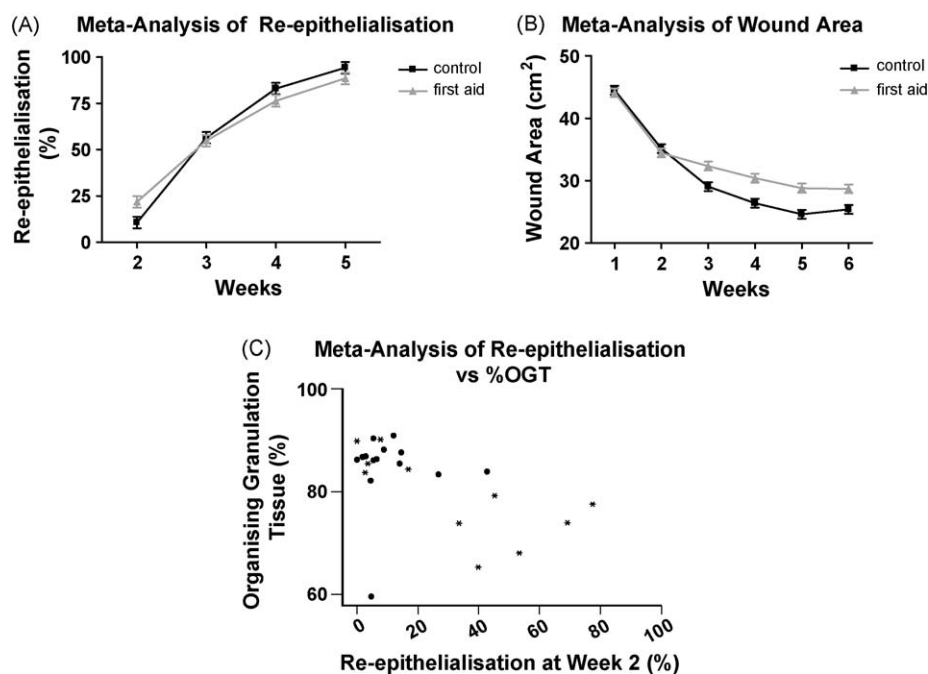


Fig. 3 – Meta analysis of data comparing untreated controls to first aid treatment (cool water applied immediately for 20 min duration). **(A)** Re-epithelialisation is better for the first aid treated group at week 2, but this effect does not last. **(B)** The untreated control wounds have greater contraction over the 6 weeks, compared to the first aid treated wounds. **(C)** A scatterplot shows first aid treatment (asterisks) has higher re-epithelialisation at week 2 and lower %OGT, compared to controls (filled circles).

The combination of data in this way enabled us to compare data for the untreated control to the recommended first aid guidelines of immediate application for 20 min duration.

In the meta analysis, the trend of improved re-epithelialisation seen in the duration and delay results reached significant levels. The first aid treated wounds showed significantly different re-epithelialisation profiles compared to control ($p = 0.012$), with higher re-epithelialisation at week 2 ($p = 0.04$); however after week 2, the rate of re-epithelialisation was slower for the first aid group compared to the control group (Fig. 3A). There was also a difference in wound contraction between first aid treatment and control, with the control wounds being significantly more contracted at week 6 ($p = 0.01$) (Fig. 3B). Although there was no significant difference in the average %OGT ($p = 0.22$) or the OGT thickness ($p = 0.90$) between control and first aid treatment, the distribution of %OGT was significantly more variable in the first aid group ($p < 0.01$), with the control %OGT being consistently close to a high value of 85%. Applying first aid treatments did not worsen the healing outcomes, and there was a significantly higher proportion of wounds that re-epithelialised faster by week 2 and/or had less OGT ($p < 0.01$) (Fig. 3C).

4. Discussion

This study shows beneficial effects on re-epithelialisation and amount of scar tissue when first aid treatment is applied

to burns and specifically, when cold water is applied immediately, for 20 min duration. Although many clinicians promote the immediate treatment of burns (probably predominantly for analgesia), this report actually demonstrates a significantly positive effect of immediate treatment. The optimal duration of first aid treatment of 20 min has also been confirmed by others using a similar porcine burn model [7]. It was interesting that the positive effects of this treatment on re-epithelialisation were only significant for the first 2 weeks post-burn in the meta analysis and that after this time, results were similar to the untreated control. Faster wound healing within the 2-week period after burn is known to reduce the possibility of scarring [26] and this effect can be seen here with the first aid treated wounds having less chance of high %OGT or scar tissue, although the average amount of %OGT was not significantly lower than controls. This effect may also suggest that more superficial burns (which heal faster) would benefit more greatly from first aid compared to deep burns as they would be almost certainly healed by the second week, before the effect of first aid “wears off”.

In this study we also found a beneficial effect on re-epithelialisation after 1 or 3 h treatment delays. Others using a similar porcine model have also reported benefit measured histologically after 1 h delayed treatment [15]. Ofeigsson also reported from his studies that although rats with 45 min delayed cooling appeared initially less healthy than immediately treated animals, they still showed positive healing after 3–4 weeks [13], which is similar to the delayed beneficial

effect seen here at 3 weeks. They found a slight dose-related effect (with 3 h showing more benefit than 1 h), which suggests that this effect is related to anaesthesia and decreased pain sensation. As the animals were under general anaesthetic during this delay period, this may have resulted in less pain-mediated release of inflammatory mediators, and therefore an improved re-epithelialisation rate. The relationship between pain, inflammatory processes and wound healing is not well understood and more research is required in this area. However, it is difficult to state that a delay in first aid treatment of up to 3 h provides benefit, without further study controlling for the effects of anaesthetic. More work is planned to verify this result and investigate the mechanisms at work.

The contradiction in previously reported studies concerning optimal duration and delay may be due to several factors other than the difference between burn models used. Here we saw that the positive healing effect of recommended first aid disappeared after 2 weeks post-burn. As many studies are conducted within this time frame (usually for only a few hours post-burn), the outcome measures may not truly reflect the healing of the treated burn wound. It is also important to consider that previous studies, especially those which reported benefits after delayed treatment, may also have been affected by anaesthesia-related effects. The studies conducted here are the longest longitudinal first aid studies and demonstrate the importance of examining several different outcome measures and longer-term follow-up of wound healing and scar formation.

In terms of the recommended guidelines for first aid duration and delay, immediate application of 15 °C running water for 20 min is associated with an initial improvement in re-epithelialisation and decreased scar tissue after 6 weeks. In general though, the effect of first aid is mild compared to other clinical burn therapeutic strategies we have measured previously [27,28] and this made it difficult to measure any major or significant differences between different treatment durations and delays. It may also help to explain why there is so much controversy in the literature regarding optimal first aid conditions. However, from the studies here it appears that using cold water treatment for as short as 10 min duration or for up to 1 h (and maybe longer) delay post-burn still is better than nothing in terms of giving a better wound outcome. Many people only apply first aid for the analgesic effect (and this should also be taken into account when determining the duration of first aid treatment), however first aid definitely also provides wound healing benefits and for this reason it should be widely promoted.

Conflict of interest

There are no conflicts of interest for any of the authors.

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