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ORIGINAL ARTICLE

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The early association of water irrigation with negative pressure wound therapy does not more efficiently reduce the depth of the alkali infiltration progress into the burn

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Abstract

Water irrigation is an efficacious decontaminating method for dermis exposures to corrosive agents and hence has been widely applied to treat especially alkali burns. Nevertheless, once alkali has infiltrated the deep subcutaneous tissue, washing the tissue surface with water irrigation does not attenuate the damage progress. Therefore, significant efforts have been devoted to promising strategies aimed at removing the deeply infiltrated lye. According to a recent report, the negative pressure wound therapy (NPWT) reduces the pH value of the exudate from alkali-provoked burns thus accelerating wound healing. However, it remains to be ascertained whether or not NPWT coupled with water irrigation, that is, iNPWT, more effectively hinders the alkali injury deepening. In this study, we compared the effectiveness of an early application of water irrigation with or without NPWT in preventing the progressive deepening of the alkali burn in an animal model. Our histological examination results showed no appreciable difference in tissue injury depth, dermal retention, inflammatory cell infiltration, re-epithelization, and cellular function between iNPWT and water irrigation alone treatments. Thus, our results prove that the more expensive NPWT coupled with water irrigation does not more effectively hinder the alkali's injury deepening. Hence, iNPWT use should be more cautious in clinical practice.

KEYWORDS

alkali burn, NPWT, water irrigation, wound healing

Key Messages

- the present investigation is for the first time to explore the effectiveness of iNPWT in preventing the progressive deepening of the alkali burn in an animal model

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- 6 alkali burn wounds were created, early application of water irrigation with or without NPWT was conducted and histological analysis was performed thereafter
- histological examination results showed no appreciable difference in tissue injury depth, dermal retention, inflammatory cells infiltration, re-epithelization, and cellular function between iNPWT and water irrigation alone treatments

1 | INTRODUCTION

Chemical injuries are a common type of skin damage. In fact, the data from available sources show that from 2% to 5% of all skin dermis burn injuries are due to chemicals.[1,2] Among them, the alkali-caused injuries occur frequently and are likely to produce severe outcomes. Unless the alkali is quickly neutralised or removed, it keeps destroying the skin tissue, forming a progressively deepening ulcer leading to a way down partial thickness or a full-thickness burn wound.[3,4]

Thus, timely and effectively removing the contaminating lye is a most important early first aid strategy in alkali-caused burns. An early copious water lavage has been demonstrated both clinically and experimentally to effectively reduce alkali damage. Hence, the directly applied passive water flushing of the alkali-splashed skin surface is the standard procedure for managing this kind of chemical burn.[5,6]

However, once the alkali has seeped into the tissue, washing the tissue surface has almost no mitigating effect.[7] At this stage, surgical debridement is the main choice to remove the residual lye. Besides, to remove the alkali, continuous water washing must be started immediately and kept going until the chemical is totally removed from the burn wound. This procedure however entails an operational difficulty and a high risk of hypothermia.[3]

Recently, applying a continuous NPWT has emerged as a promising alternative to treat alkaline injuries. As a widely employed treatment for wound healing, NPWT was reported to reduce the pH value of the exudate of alkali-burnt patients, thereby promoting wound healing.[8] Also, an earlier study suggested that following thermal burn wounds debridement, a continuous NPWT treatment could significantly decrease the depth of cellular death in the stasis zone thus reducing skin tissue loss.[9] Moreover, some clinical cases with electrical burns treated with iNPWT during the acute phase showed an accelerated formation of granulation tissue and a mitigated inflammation.[3,7,10-12] Hence, it is reasonable to submit that joining NPWT to water irrigation might be more effective to control the deep-down progress of alkali-induced skin injuries.

Therefore, this experimental study aimed at exploring whether or not an early application of NPWT coupled with water irrigation (henceforth, iNPWT treatment) might be a better therapeutic strategy for alkali-caused burns management than water irrigation alone. Therefore, we designed and established an animal model of alkali-provoked skin injury, to which we applied at an early phase water irrigation with or without NPWT.

2 | MATERIALS AND METHODS

2.1 | Materials

We used the following materials: NaOH (Tianjinshi Baishi Chemicals, CN); filter paper (Cytiva, US); vacuum sponge (KCI, US); 3D films (3 M Corp., US); vacuum facility (Yuwell Co., CN); LDH staining kit (Solarbio, CN) and TUNEL Apoptosis Detection Kit (YEASEN, CN).

2.2 | Animals

Animal care was provided according to all the relevant provisions of the Helsinki Accords. All experiments were conducted in keeping with the guidelines approved by the Ethics Committee of China Technology Industry Holdings Co., Ltd. (Shenzhen). Six SD rats weighing 190–220 g, bought from Beijing Vital River Laboratory Animal Technology Company, were adapted for 1 week before the experiments' start. Throughout the study, the rats were housed in a laminar air-conditioned room maintained at $23 \pm 2^{\circ}C$ at a relative humidity of $55 \pm 10\%$ with a 12 h dark/12 h light cycle. They had free access to food and water.

2.3 | Set up of an alkali-elicited animal skin burn model and treatments application

Figure 1 shows the experiment's schematic depiction. Briefly, the hair on the backs of each rat was cut using an electric shaver and a skin-hair-remover (Veet, CA). A

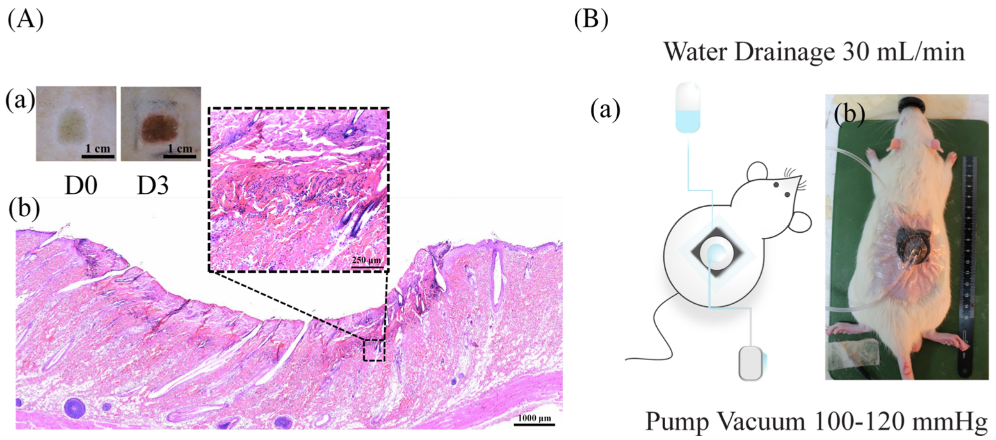


FIGURE 1 A, (A) Representative gross image of the rat alkali burn model at D0 and D3; and (B) HE stained sections of D3. B, (A) A schematic representation of iNPWT application. (B) The rat was applied with a KCI black sponge covered by 3 M film and attached to a negative pressure pump, generating a pressure between 100–120 mmHg. An injection hose was inserted into the surface of the skin to achieve a solution flow of 30 mL/min

3 M film with a centre square defect of 1 cm^2 was used to protect the skin edges. Alkaline injury was provoked by placing for 1 min a filter paper square (1 cm^2) saturated with 2.5% NaOH onto the shaved dorsal skin.[13] This procedure damaged the skin (Figure 1). Next, we used a randomised sampling method to divide the rats into two groups: water irrigation treatment alone (henceforth also named controls; $n = 3$) or iNPWT treatment ($n = 3$). Treatments started 5 min after the removal of the NaOH-saturated filter paper square. The rats underwent water irrigation or iNPWT[14] at an equivalent flow rate of 30 mL/min for 30 min. Thereafter, the wound conditions were monitored, and the rats were sacrificed on day 3 post-wounding for histological analysis.

2.4 | Wound's visible conditions and area measurements

Wound's gross pathological condition was monitored on day 1 and day 3 after injury through naked eyes. The following aspects of the wound were considered: erythema, oedema, and hair loss.[15] The eschar's square surface area was measured on pictures using image J1.53e software.

2.5 | HE and Masson staining and histological analysis

We conducted the histological analyses as previously described.[16] The wounded back skins, including 2–3 mm of wound's edge, were fixed with 4% paraformaldehyde, embedded in paraffin, sectioned, and mounted on slides. To assess the extent of tissue injury and the depth of dermal infiltration, the samples were stained with Haematoxylin and Eosin (HE) and Masson mixture.[17] After picture taking (TEKSQRAY, SQS-40P, CN), measurements[9] were performed using ImageJ 1.53e software and Fuji (image J1.53C) (NIH, US).

2.6 | Immunohistochemistry staining

To assess re-epithelialization, we performed Cytokeratin 14(CK14) (Santa Cruz Biotechnology Cat# sc-53253, RRID: AB_2134820) IHC staining according to the manufacturer's instructions (IHC kit; MXB technologies, CN) and as previously described.[18] Tissue sections were fixed, blocked, and incubated overnight at 4°C with the anti-CK14 antibody (1:500 dilution). The incubation with a secondary antibody from the IHC kit was performed at RT for 45 min. Next, a DAB detection Kit (MXB technologies, CN) was used followed by Counter staining with Haematoxylin. The sections were viewed under a light microscope.

2.7 | TUNEL staining

To stain TdT-mediated dUTP Nick-End Labeling (TUNEL) cells, we used the TUNEL Apoptosis Detection kit (YEASEN, CN) following the manufacturer's protocol. Counterstaining with 4′,6-diamidino-2-phenylindole (DAPI) (YEASEN, CN) was performed to visualise nuclei. Sections were photographed under a fluorescence microscope (Olympus, IX70, JPN).

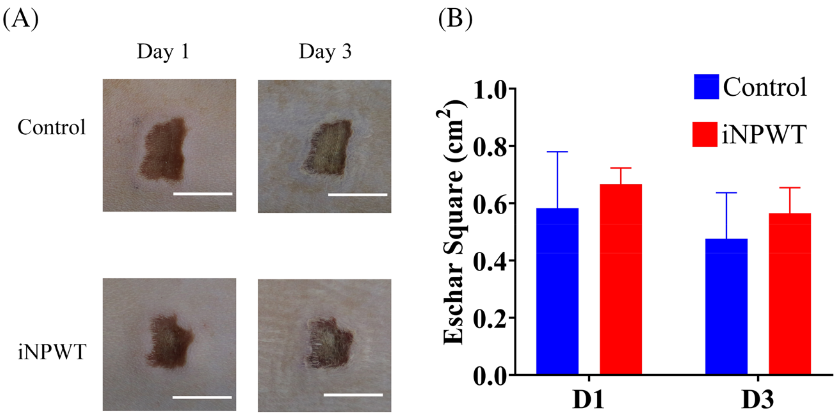


FIGURE 2 A, Representative gross image of the differently treated burn wounds on day 1 and day 3. Scale bar, 1 cm. B, Quantification of the surface areas of the eschar formation at post-burn day 1 and day 3. $P > 0.05$

2.8 | LDH staining

Lactate dehydrogenase **(**LDH) is a key metabolic enzyme that is active only in viable cells.[19] To confirm whether partial cellular damage had occurred, LDH staining was done according to the kit instructions (Solarbio Life Science, CN). In brief, the skin tissue was embedded in OCT (Sakura, Japan), and sectioned at 6 μm thickness (Thermal Scientific, US). With no prior fixation, the slices were incubated in LDH5 solution, placed in a 37°C incubator for about 15 min, then sealed with Glycerin gelatin (Servicebio, CN). The sections were photographed under a light microscope.

2.9 | Statistical analysis

Data for all experimental groups were presented as means ± standard deviation (SD). Statistical comparisons were performed using the student's *t*-test analysis of variance. Statistical significance was defined as *p* values lower than 0.05.

3 | RESULTS

3.1 | In vivo wound healing analysis

On day 1 after burn injury, all the rat wounds exhibited a visible eschar (Figure 2). Moreover, the eschar surface area of the control (water irrigation only) group, that is, 0.58 ± 0.2 cm^2 did not differ from the eschar area (0.67 ± 0.1 cm^2; $P > 0.05$) of the iNPWT-treated group. All rats in both groups had a visible erythema around the eschar and the wounds' edges were edematous. Besides, no hair was visible within the wounds. The same evidence of injury could be observed on day 3 post-burn (Figure 2) when again the control group eschar surface area (0.48 ± 0.2 cm^2) did not differ ($P > 0.05$) from that (0.57 ± 0.1 cm^2) of the iNPWT-treated group.

3.2 | Re-epithelization of the wounds

On post-burn day 3, the CK14 IHC staining showed that the re-epithelialization of the wounds of the mice treated with iNPWT was like that of the control group (Figure 3). The wound healing rate of the control group was 97.5 ± 2.3%, while in the iNPWT-treated group was 91.7 ± 4.6% ($P > 0.05$ between the two groups).

3.3 | Tissue loss and dermal collagen alkali infiltration

The dermal collagen denaturation caused by alkali exposure was revealed via Masson stain and measured through digital microscopy. As Figure 4 shows, at the post-burn day 3, only parts of the dermis collagen persisted in the control and iNPWT-treated groups, as most of it had been liquefied and necrotised. Statistical analysis indicated that the dermal collagen percent retention of the control group (12.9 ± 5.8%) did not significantly ($P > 0.05$) differ from that of the iNPWT-treated group (11.2 ± 2.0%). These data indicated that the iNPWT treatment did not hinder the alkali deep-down infiltration more effectively than did water irrigation alone.

In the NaOH-treated skin, the burn depth examination on day 3 (Figure 5) showed that a moderate degree of necrosis had occurred. The tissue damage depth was confirmed by depth profiling in the tissue sections. The control group maximum depth of tissue loss was 32.4 ± 23.4%, while that of the iNPWT-treated group was 40.3 ± 9.3% ($P > 0.05$ between the two groups).

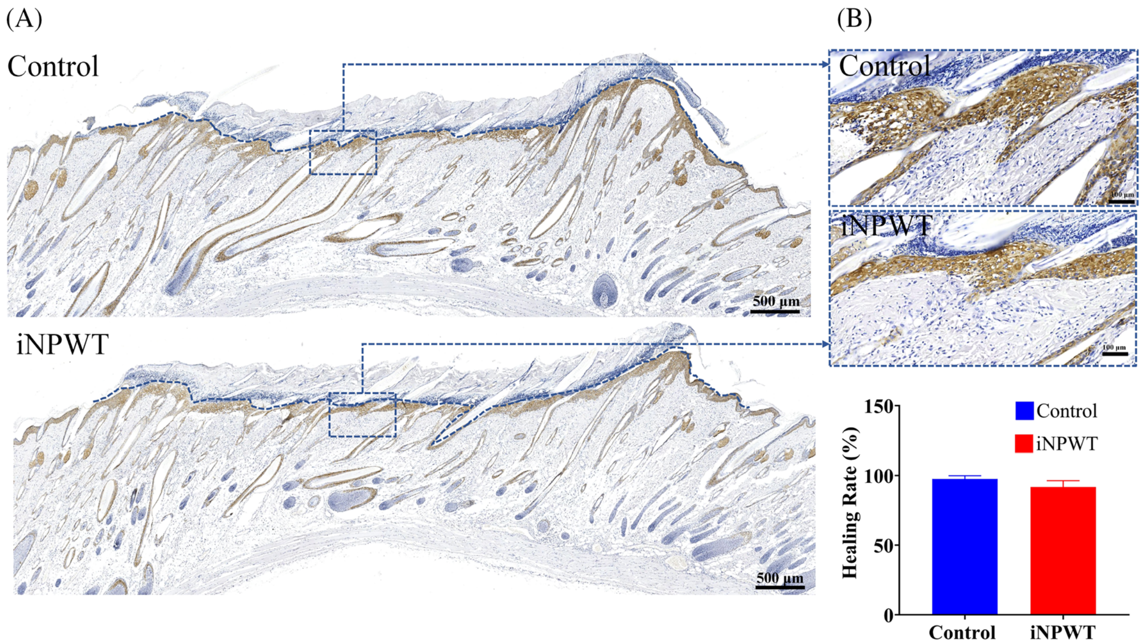


FIGURE 3 A, Representative CK14 IHC staining microscopic image at post-burn day 3. B, High-power microscopic image of CK14 IHC staining and quantification of the epithelialization percentages of wounds at post-burn day 3. $P > 0.05$

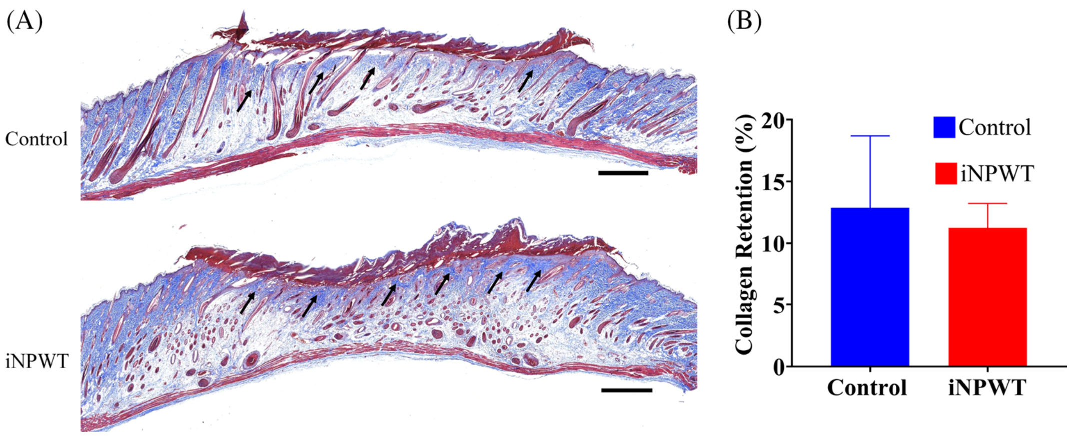
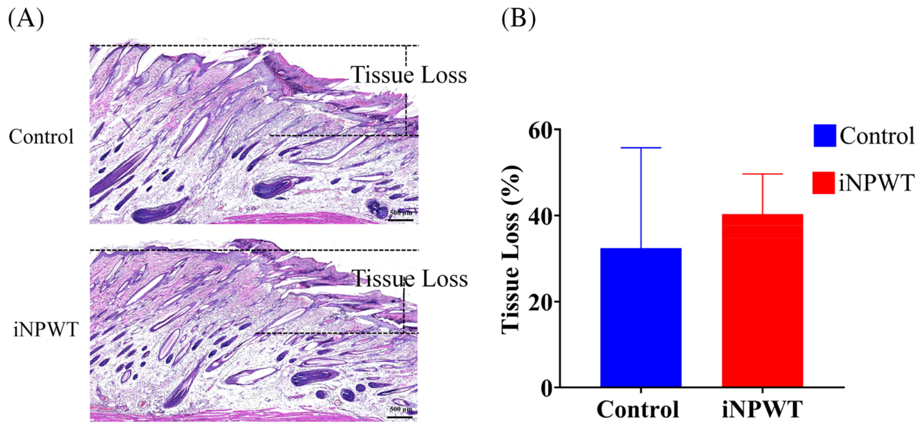


FIGURE 4 A, Post-burn day 3 Masson staining of the wound tissue sections. The retained collagen was marked with arrows. Scale bar, 1 mm. B, The percentage of the collage retention area at day 3 after injury. $P > 0.05$

FIGURE 5 A, Post-burn day 3 HE stains of the wound sections. B, The percentage of tissue loss at day 3 after injury. $P > 0.05$



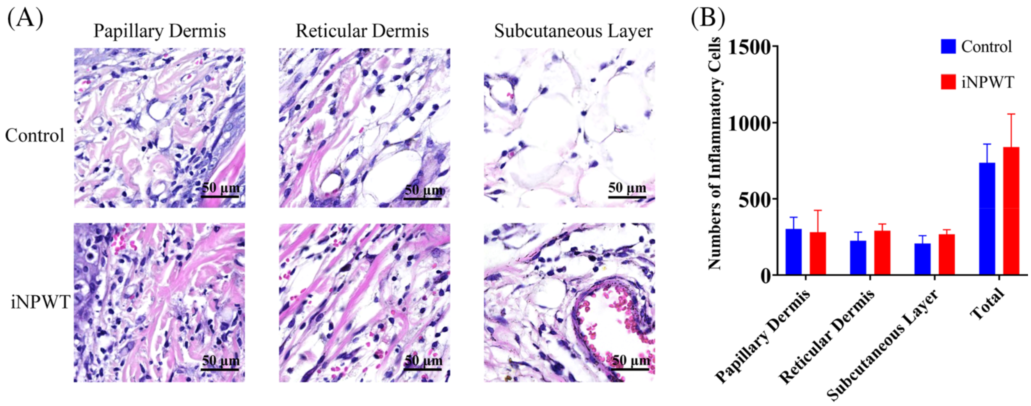


FIGURE 6 Inflammatory cells in different layers of the burn wound skin. Scale bar, 50 μm. $P > 0.05$

3.4 | Burn wounds' inflammation assessment

The inflammatory cell numbers in the wounds' dermal papillary layer, dermal reticular layer, and subcutaneous layer were determined in HE-stained day 3 post-burn tissue sections (Figure 6). In the control group, the inflammatory cells' number in the papillary dermis was slightly higher (303.3 ± 76.5) than in the iNPWT group (281.7 ± 143.1). The opposite was true in the reticular dermis (226.0 ± 55.6) and subcutaneous layer (208.0 ± 51.0) of the control group *versus* the iNPWT-treated group (291.0 ± 44.6 and 267.3 ± 31.0, respectively). However, none of these differences was statistically significant ($P > 0.05$). Also, the total number of inflammatory cells infiltrated in the burn wound area did not statistically differ ($P > 0.05$) between the control (737.3 ± 122.0) and iNPWT-treated (840.0 ± 216.7) groups.

3.5 | Cellular activity and apoptosis

As for LDH staining, the eschar had no viable structure. However, the skin beneath the scar was viable and exhibited an intense LDH activity in both the control and iNPWT-treated groups (Figure 7). As for TUNEL staining, quite a few apoptotic cells could be seen under the eschars in the day 3 skin sections pertaining to both groups (Figure 8).

4 | DISCUSSION

The present study aimed at ascertaining whether or not an early application of NPWT plus water irrigation as compared to water irrigation alone might improve the lye elimination from the burned skin.

Generally, water irrigation is considered to be a safe and effective treatment for controlling alkali-elicited skin damage.[6] However, its limitation is that it cannot hinder the damage progress once the alkali has penetrated the subcutaneous tissue.[4] Thus, the timely and effective alkali removal matters a lot as regards the evolution of alkali-induced burns. A recent clinical study[8] showed that an NPWT's application drained an exudate with a higher pH from alkali-elicited wounds than from (silver sulfadiazine dressing change) controls, suggesting that NPWT could more efficiently remove the deep-down penetrated lye. Also, Morykwa's[9] study using an experimental pig model showed that partial-thickness thermal burn injuries treated with a negative pressure within the first 12 h did not worsen further. Another study revealed that following an alkali injury the subcutaneous pH gradually increased during the first 10 min to sharply peak at 32 min, and gradually decreased thereafter. By 90 min, the pH level tended to stay stable since no more tissue remained the lye could react with.[3] These data inspired us that water irrigation plus NPWT might be a better treatment strategy to control alkali's progressive deep-down tissue damage.

Our present results show that (*i*) iNPWT-treated animals had, from both histology and gross anatomy standpoints, the same degree of deep-down tissue damage as the water irrigation alone-treated animals (Figures 2 and 5); (*ii*) in both groups the re-epithelization was achieved at day 3 after injury (Figure 3); and (*iii*) the two groups did not differ in dermal collagen retention (Figure 4) or inflammatory cells infiltration (Figure 6). So, why did our data diverge from those reported in Huang C's study?[8]

According to practical mechanisms, NPWT can take away the wound's exudate only after the scab removal. Huang C's report[8] found that the pH value of the NPWT group's exudate was higher than that of the silver sulfadiazine treated group, which might have indicated that the NPWT removed the lye penetrated into the tissue. However, the patients included in that trial[8] did not receive scab incision surgery, which means that scabs will act as barriers preventing NPWT from sucking the deep-down penetrated lye out of the tissue. Besides the pH value of sulfadiazine silver

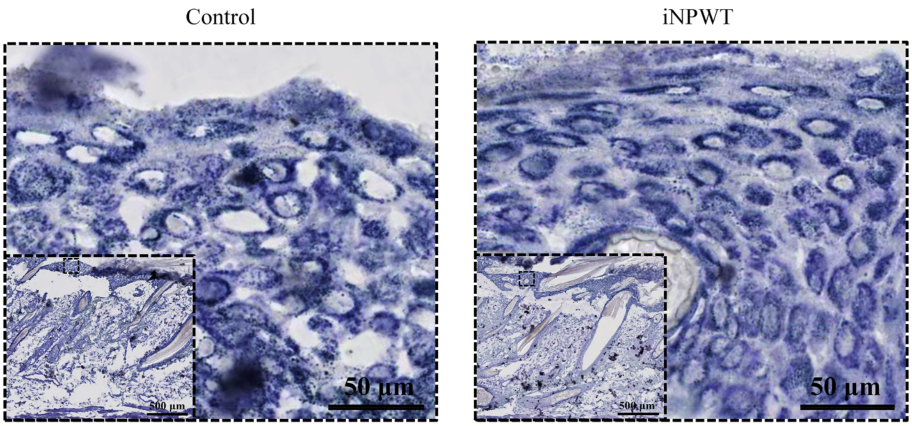


FIGURE 7 LDH-staining of dead/live rat skin cells at post-burnt day 3. The blue-purple precipitate/particle marks the LDH enzyme activity

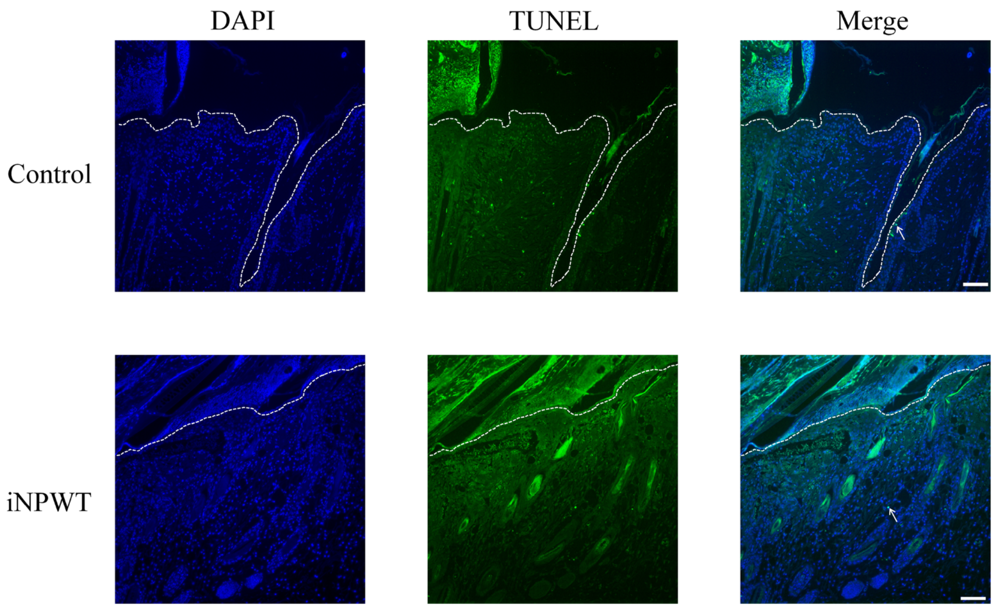


FIGURE 8 TUNEL-staining of apoptotic rat skin sections at post-burnt day 3. Positive cells are marked with white arrows. Scale bar, 100 μm

is about 5.5–7.0. Thus, a lower pH value of the control group's exudate may not correspond to a smaller removal of the lye but to a neutralisation of the exudate by the silver sulfadiazine. Silver sulfadiazine did not function as a good control, which might have misled the authors' conclusions. Moreover, in that trial[8] the patients might have come in contact with lye of different pHs and their hospital acceptance times might have differed. Besides, the alkali-elicited tissue necrosis is direct and fast. An earlier study[3] showed that the subcutaneous pH peaks by 32 min and are closely related to the entity of tissue damage. At this point, the patients may already be suffering from deep partial-thickness or full-thickness burns. Our belief is that Huang C's study[8] did not show that negative pressure therapy could indeed draw out the deep-down penetrated alkali. In fact, Huang C's application of NPWT to alkali wounds did not differ in mitigating oedema, intensifying perfusion, and advancing wound healing than did long-term negative pressure therapy applied to thermal burn wounds or chronic wounds.[20-22] Their results did not prove that an early application of NPWT can stop alkali from penetrating the burn's bed. Therefore, an early application of water irrigation associated with NPWT does not improve the therapeutic upshot of alkali-elicited burns. In addition, some studies have revealed that NPWT application will increase the therapy costs and patients' economic burden.[23] Also, most of the studies about NPWT use for burns therapy were of the observational kind or small-scale RCTs, and hence lacked sufficient evidence.[3,7,10-12]

Taken together, our data demonstrated for the first time that associating NPWT with water irrigation soon after an alkali-induced injury does not more effectively reduce the skin injury's depth. For sure there are limitations to our study because of the small sample size, small wound size, and short window of observation. Also, rat skin is very different from human skin in many ways, thus we should carefully interpret the animal data to guide clinical practice.

Still, our study has enticed us to develop more efficient future strategies for the prevention and therapy of alkali-provoked injuries while clearly signifying that the use of iNPWT in clinical practice should be more cautious.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study is available from correspondence author upon request.

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