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Comparative study of conventional and topical heparin treatment in second degree burn patients for burn analgesia and wound healing☆

Sobia Manzoor [a,1], Farid Ahmad Khan [a], Sohail Muhammad [b,*], Rehan Qayyum [c], Imran Muhammad [b,2], Umer Nazir [b], Muhammad Mustehsan Bashir [b,3]

[a] Plastic Surgery Department, Shaikh Zayed Medical Complex, Lahore, Pakistan
[b] Department of Plastic, Reconstructive Surgery and Burn Unit, King Edward Medical University, Mayo Hospital, Lahore, Pakistan
[c] Division of Hospital Medicine, Department of Internal Medicine, Virginia Common Wealth University School of Medicine, Richmond, VA, United States

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ABSTRACT

Objective: To compare clinical outcome of topical conventional with topical heparin treatment in 2nd degree or partial thickness (PTB) burn patients.
Methods: Patients, between the ages of 14 and 60 years with 2nd degree burns involving <20%. Total body surface area (TBSA) on front of chest, abdomen and upper limbs excluding hands and lower limbs were enrolled from September 2015 to August 2016. Patients were randomized to conventional or heparin treatment groups. Clinical outcome measured were healed wound size, pain scores and total consumption of analgesic medication required to relieve pain. Safety of the treatment and adverse events were also measured
Results: Out of 66 patient included in study mean (SD) age of participants was 27 (10) years, of which 59% were males. Mean (SD) TBSA burn was 14% (3) [23 (35%) had SPTB, and 43 (65%) had DPTB]. The burn injury was caused by flames in 68% and by hot liquids in 32% patients. There was no statistically significant difference in distribution of patients according to age, gender, TBSA burn, etiology or depth of burns in the two treatment groups. As compared to conventional treatment group, heparin treatment group had significantly better outcomes. Number of days needed for wound healing was significantly lower in the heparin group than the conventional group (SPTB 14±1 vs. 20±4 days; P-value <0.000 and for DPTB, 15±3 vs. 19 ±2 days; P-value <0.003). Mean pain score was also lower in the heparin group (for both SPTB and DPTB 3±1 vs. 7±1; P-value <0.000). Similarly, total consumption of analgesic medication was significantly less in the heparin group (53±27 vs. 119±15 mg; P-value <0.000 for SPTB

☆ The study was conducted at the Department of Plastic, Reconstructive Surgery and Burn Unit of the Mayo Hospital, Lahore, a hospital affiliated with the King Edward Medical University, Lahore, Pakistan.

* *Corresponding author at*: Department of Plastic, Reconstructive Surgery and Burn Unit, King Edward Medical University, Mayo Hospital, 86-A Habibullah Road, Garhi Shahu, Lahore, Pakistan.
E-mail addresses: drsobiamanzoor@yahoo.com (S. Manzoor), proffakhan@gmail.com (F.A. Khan), drsohail72@gmail.com, drsohail@kemu.edu.pk (S. Muhammad), rqayyum1@jhmi.edu (R. Qayyum), drimranmughal@gmail.com (I. Muhammad), drumer197@gmail.com (U. Nazir), drmustehsan@kemu.edu.pk (M.M. Bashir).
[1] 60-E, P.G.E.C.H.S Phase II, Collage Road, Lahore.
[2] Street No. 2, Mohala Arayain, PO Box, Ugoki, Sialkot.
[3] House No. 327-Block-H DHA, Phase 5, Lahore, Pakistan.

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and 46±6 vs. 126±12 mg; P-value <0.000 for DPTB). In both groups, no patient had wound infection, skin necrosis, leucopenia, thrombocytopenia, worsening renal function, or abnormal liver enzymes

Conclusion: Treatment of second degree or partial thickness burns (PTB) with topical heparin is superior to conventional treatment in terms of wound healing as well as for pain control. The treatment with topical heparin is well-tolerated and is without higher adverse effects.

1. Introduction

Second degree or partial thickness burns (PTB) are difficult to diagnose and treat. They are further divided into superficial partial thickness burns (SPTB) and deep partial thickness burns (DPTB) depending upon the extent of dermal involvement. SPTB and DPTB burns differ in appearance, ability to heal, and potential need for excision and skin grafting [1]. Clinical judgment remains the most reliable method for diagnosing these burns. Recently the introduction of laser Doppler imaging has improved burn care by accurate assessment of burn depth [2,3].

Conventional topical treatment of SPTB wounds includes wound wash and application of petroleum-based antimicrobial ointments. Conventional topical treatment of a small DPTB includes application of topical broad spectrum antimicrobial agents to minimize wound colonization. Application of antimicrobial agents is continued until wound heals by secondary intention, however, wounds that do not appear to be healing well are prepared with normal saline-(NS) soaked dressings for grafting. However extensive DPTB (>20% total body surface area burns [TBSA] are excised to a viable depth and then skin grafted [4,5].

Severe pain is hallmark of PTB. Conventional topical treatment for PTB is painful, complex, and uncomfortable for patient. Recently topical un-fractionated heparin treatment has been introduced as safe, cheap, and effective treatment for burns. Indeed there are a number of reports of use of heparin, topically or systemically, in the treatment of second degree burns [6–8]. However evidence of its effectiveness is weak and there is paucity of data from satisfactorily controlled trials to determine its effectiveness. Therefore, the aim of the present study was to compare clinical outcome (pain, total consumption of analgesic medication required to relieve pain and wound healing time) of topical conventional with topical heparin treatment in 2nd degree burn patients.

2. Methods

2.1. Study design, participants and randomization

This randomized controlled clinical trial was conducted at the Department of Plastic Surgery and Burn Unit of the Mayo Hospital, Lahore, Pakistan, a hospital affiliated with the King Edward Medical University. Patients were enrolled from September 2015 to August 2016. The study protocol was approved by the Institutional Review Board (84/RC/KEMU) and was registered at the Clinical Trials. gov (NCT01489540). The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Patients, between the ages of 14 and 60 years with 2nd degree scald or flame burns involving <20%TBSA (determined by Wallace rule of nine) on front of chest and abdomen, upper limbs excluding hands and lower limbs excluding feet were enrolled from the Emergency and Outpatient Departments (OPD) using non-probability consecutive sampling technique (patients fulfilling inclusion criteria were enrolled continuously till completion of sample). Patients were assessed by consultant burn surgeon clinically and confirmed by LASER Doppler (The mean perfusion units for superficial partial thickness burn was 866±443) and for deep partial thickness burn was 342±118). Patients with 2nd degree burns involving >20% TBSA or those who presented more than 72 h after injury were excluded. Patients with third or fourth degree burns, facial burns, chemical or electrical burns, history of hemorrhagic diathesis or heparin intolerance, and liver or renal disorder were also excluded.

After obtaining written informed consent, we collected demographic, clinical (total body surface area burn [TBSA], depth of burn, mechanism of injury, time since injury), and laboratory data. Patients were randomized to conventional treatment or heparin treatment groups using computer generated random number table. Pretreatment photographs were taken and size of burn wound was measured in in.^{2} using transparent graph paper. All patients received intramuscular tetanus toxoid, omeprazole 20 mg daily, and acyclovir 400 mg every 8 h as per protocol of our Burn Unit.

2.2. Interventions

Conventional treatment group: Polymyxin B sulphate 10,000 IU, Bacitracin Zinc 5000 IU and (Polyfax™ Skin Ointment, GlaxoSmithKline) 3–5 gm × percent TBSA burn was applied on SPTB, while thick layer of Silver Sulphadiazine 1% cream (Dermazin™ Novartis Pharma) was applied on DPTB. Application was performed twice daily after wound wash until wounds healed. Burn wounds that failed to heal within 21 days were re-evaluated by the treating consultant surgeon. Wounds found to be suitable for healing by secondary intention were continued on the same treatment. Wounds that did not appear to be healing well were treated with normal saline-soaked dressings and, when ready, underwent skin grafting.

Heparin treatment group: Topical dose of heparin (PINE injection 5000 I.U./ml, Vail contains 5 ml, Houns. Co, Ltd) was calculated by the following formula: 4200 IU of heparin- × percent TBSA burns. The aqueous heparin solution for topical use was prepared by adding 5000 IU of heparin to 25 ml of normal saline and using 22.5 ml of this solution per percent

TBSA burns. Each treatment session started with a thorough wound wash, followed by three cycles of aqueous heparin solution sprayed aseptically on the burn wound using a spray bottle with 5–10 min interval between cycles. Treatment sessions were repeated twice daily. The dose of heparin aqueous solution used was reduced to 75% of calculated dose on day 3 and 50% on day 5 (last treatment day). The blisters, when present, were filled and rinsed with heparin aqueous solution twice daily with each treatment session consisting of three cycles and 5–10 min intervals between cycles. Blisters were treated until the blister collapsed, usually on day 2 or 3. Between the heparin sessions wounds were dressed with normal saline soaked gauzes. All patients were monitored daily for any adverse effects of heparin including bleeding from wound or alteration in laboratory parameters such as platelet count, serum aspartate aminotransferase, and serum calcium level for 5 days. After 5 days, normal saline soaked gauze dressings were continued. Wounds that failed to heal within 21 days were re-evaluated and categorized based on their expected response to treatment. Wounds found to be suitable for healing by secondary intention were continued with normal saline soaked dressings. Wounds that did not appear to be healing well underwent skin grafting when ready.

Outcomes. Outcome measures were healed wound size after 21 days in square inches, percentage of wound healed within 21 days, numbers of days required to achieve 70% healing (defined as >70% re-epithelialization), days required to achieve 100% healing with or without grafting, days required from 21st day after randomization to healing without grafting (defined as complete re-epithelialization of remaining wound), days required from 21st day after randomization for the wound to the time when ready for skin graft (defined as wound covered with granulation tissue with epithelialized margins). Wounds were examined daily and above outcomes were determined by the same consultant burn surgeon who was not blinded to the group allocation. Photographs were taken at various intervals to document the wound healing status.

Table 1 – Study population characteristics.

	Conventional treatment group (n=30)	Heparin treatment group (n=30)	P value
Female	11	16	0.32
Flame burns	24	21	0.60
Age (years)	27 (10)	28 (10)	0.56
Total body surface area burn (%)			
SPTB, n=19	12 (3)	14 (3)	0.157
DPTB, n=41	14 (3)	14 (3)	0.112
Initial wound size (in.^{2})			
SPTB, n=19	322 (75)	375 (60)	0.098
DPTB, n=41	370 (64)	362 (82)	0,088

Table 2 – Outcomes in the conventional and heparin treatment groups.

Outcomes	Superficial partial thickness burn			Deep partial thickness burn		
	Conventional treatment n=9	Heparin treatment n=10	P value	Conventional treatment n=21	Heparin treatment n=20	P value
Primary outcomes						
Wound healed at 21 days (In.^{2})	245 (109)	366 (83)	<0.014	243 (54)	318 (63)	0.000
Wound healed in 21 days (%)	73 (17)	100 (0)	<0.003	69 (18)	92 (17)	0.000
Days required to achieve 70% healing	20 (4)	14 (1)	<0.000	19 (2)	15 (3)	0.003
Days required to achieve 100% healing with or without grafting	25 (4)	19 (4)	<0.006	28 (3)	20 (4)	0.000
Days required after 21st day to healing without grafting	5 (4)	0	–	4 (1)	4 (0)	0.840
Days required after 21st day for the wound to be ready for grafting	0	0	–	9 (2)	7 (1)	0.008
Secondary outcomes						
Pain score mean (SD)	7 (1)	3 (2)	0.000	7 (1)	3 (1)	0.000
Analgesic requirement (mg)	119 (15)	53 (27)	0.000	126 (12)	46 (6)	0.000
Safety outcomes						
Wound site bleed, n (%)	0 (0)	1 (10)	0.330	1 (5)	1 (5)	0.973
Skin discoloration, n (%)	7 (77)	1 (10)	0.003	17 (80)	1 (5)	0.000
Pseudo-eschar, n (%)	9 (100)	0 (0)	0.000	21 (100)	0 (0)	0.000
Skin allergy, n (%)	4 (44)	0 (0)	0.018	4 (19)	1 (5)	0.138

All patients were also assessed three times a day for pain requiring analgesic medication based on the Numeric Visual Analog Score (NVAS). Only those with pain score >4 were given intravenous (IV) injection tramadol 10mg as needed. Total consumption of analgesic medication (defined as total amount of IV tramadol required to relieve pain from day 0 to day 5) was noted in mg/day.

Safety of the treatment and adverse events: Following safety outcomes were measured: wound site bleeding (defined as blood oozing for more than 10min and required dressing), thrombocytopenia (defined as platelet count <150,000/ml), wound infection (defined as wound with foul smell and covered with pus or slough), and heparin allergy (defined as itching, burning or numbness over the wound after application of heparin).

2.3. *Statistical analysis*

Assuming expected difference in means of healed wound area in square inches between the two group as 70 square inches and standard deviation of 75 square inches, we needed 25 subjects in each group to achieve a power of 90% at alpha of 0.05. Assuming a 30% loss to follow-up in each group, we decided to enroll 33 subjects in each group.

Data were summarized as mean and standard deviation (SD) or proportion as appropriate. Independent sample T-tests were used to compare size of healed wound at 21 days, percentage of wounds healed in 21 days, number of days required to achieve 70% healing, number of days required to achieve 100% healing with or without grafting, days required from 21st day to healing without skin graft, days required from 21st day to when wound was ready for skin graft, pain score and total consumption of analgesic medication. Chi-square tests were used to compare distribution of patients according to gender, etiology and depth of burns in the two groups. A P-value of ≤0.05 was considered significant.

3. Results

Of the 370 patients assessed for the study, 66 patients met inclusion criteria and provided consent. The mean (SD) age of participants was 27 (10) years, of which 39 (59%) were males. Mean (SD) total body surface area (TBSA) burn was 14% (3) [23 (35%) had SPTB, and 43 (65%) had DPTB]. The burn injury was caused by flames in 45 (68%) and by hot liquids in 21 (32%) patients. There was no statistically significant difference in distribution of patients according to age, gender, TBSA burn, etiology or depth of burns in the two treatment groups (Table 1). Two patients in the heparin group and one patient in the conventional treatment group were lost to follow-up by 21st follow-up day. After the 21st follow-up day, three

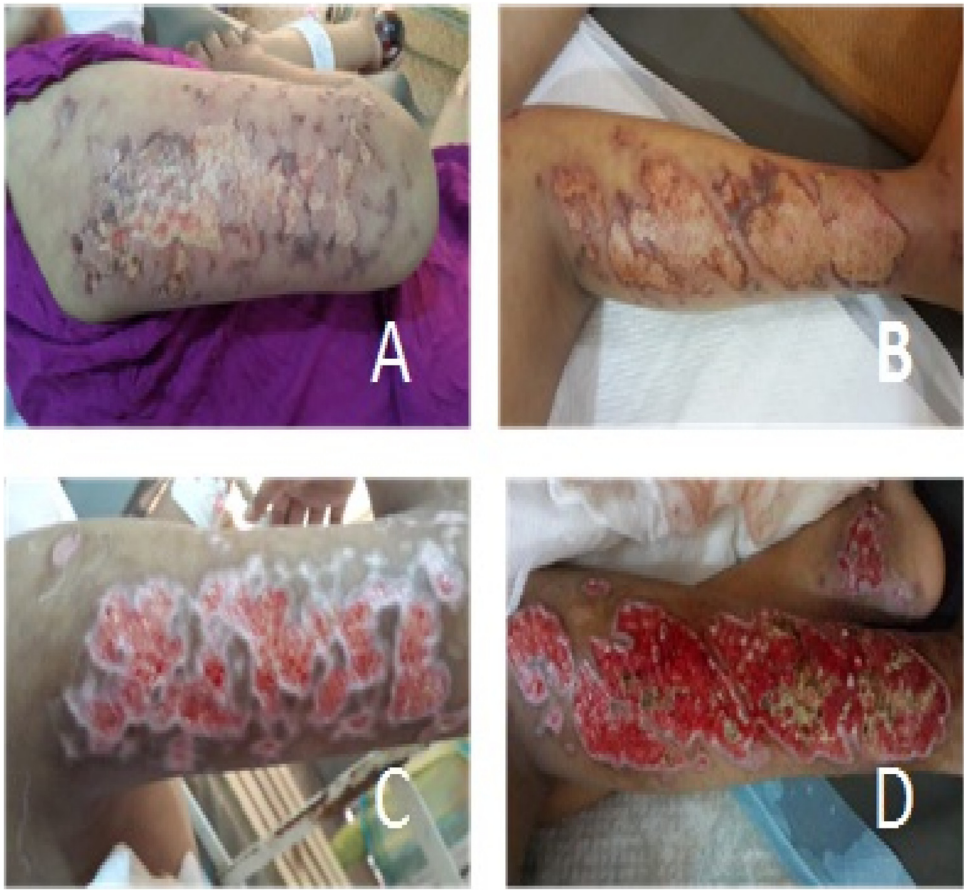

Fig. 1 – Patient sustaining scald. (A) Partial thickness Burn (PTB) wound on lateral aspect of right arm (1st post burn day). (B) Same patient with PTB wound on postero-lateral aspect of right leg (1st post burn day). (C) Wound of right arm on 21st day after conventional treatment. (D) Wound of right leg on 21st day after conventional treatment.

additional patients were lost to follow-up, 2 in the conventional treatment group and 1 in the heparin group.

As compared to conventional treatment group, heparin treatment group had significantly better outcomes (Table 2). Number of days needed for wound healing was significantly lower in the heparin group than the conventional group (SPTB 14 ±1 vs. 20±4 days; P-value <0.000 and for DPTB, 15±3 vs. 19±2 days; P-value <0.003) Figs. 1–4. As compared to conventional treatment group, mean pain score was also lower in the heparin group (for both SPTB and DPTB 3±1 vs. 7±1; P-value <0.000). Similarly, total consumption of analgesic medication was significantly less in the heparin group (53±27 vs. 119±15 mg; P-value <0.000 for SPTB and 46±6 vs. 126±12 mg; P-value <0.000 for DPTB).In both groups, no patient had wound infection, skin necrosis, leucopenia, thrombocytopenia, worsening renal function, or abnormal liver enzymes. Far fewer patients had other adverse effects in the heparin group than in the conventional therapy group except for wound site bleed (Table 2). We observed bleeding episodes in 2 patients treated with topical heparin as compared to one patient in the conventional treatment arm (P-value=0.55). However, the bleeding was minor in nature and was during dressing changes which was managed conservatively.

4. Discussion

This randomized controlled trial compared the outcome of topical conventional and topical heparin treatment in 2nd degree burn patients. The study found that heparin therapy was associated with not only faster healing of the second-degree burns, as evidenced by the wound size, number of wounds healed, or days needed to heal, but was also associated with decreased pain and analgesic drug needs. This beneficial effect was not associated with an increase in adverse effects. In fact, heparin treatment group had lower risk of skin discoloration, pseudo-eschar formation, or skin allergy. Thus, we show that treatment of second degree burns is associated with better outcomes and lower adverse effects (Figs. 1–4).

Silver sulfadiazine (sulfonamide) is found to be the most commonly used topical antimicrobial agent. It has bactericidal activity against a broad spectrum of gram-positive and gram-negative bacteria as well as being effective against yeast. By preventing infection it affect wound healing. Its application always lead to formation of yellowish-gray pseudoeschar which needs removal during daily wound wash to prevent infection. Few studies had outlined some rare complications like skin necrosis and leucopenia (temporary drop in white blood cell) in initial 24–48 h of application of silvazine and may affect renal and hepatic function [9].

We found in our study that silver sulfadiazine had no role in decreasing burn wound pain and removal of eshcar was mostly painful and ordeal process which resulted in increases in pain rather than decrease. A large proportion of patients had mild itching and burning sensation for 15–20 min after application however we did not encounter complications like skin necrosis, leucopenia, hepatic or renal dysfunction.

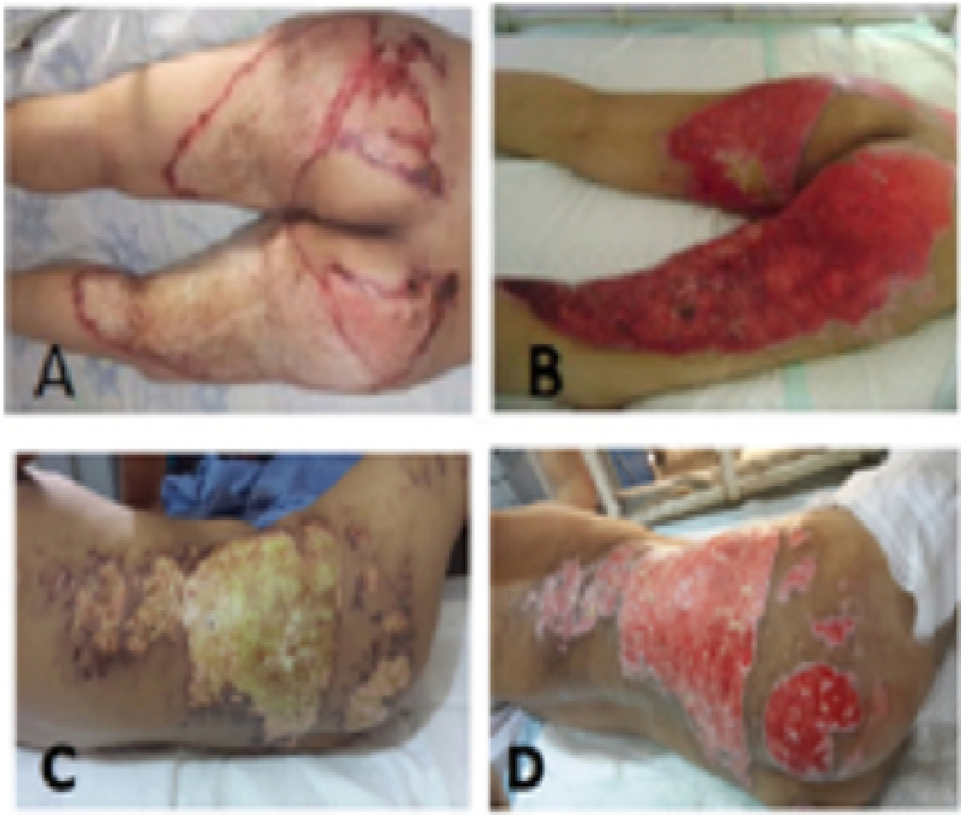

Fig. 2 – (A) Case 1, sustaining partial thickness Burn (PTB) wound involving both buttocks and posterior thighs (1st post burn day). (B) Case 1, Wound on 28th day after topical conventional treatment. (C) Case 2, partial thickness flame burn involving right side of chest, back and thigh. (D) Case 2, wound on 26th day after topical conventional treatment.

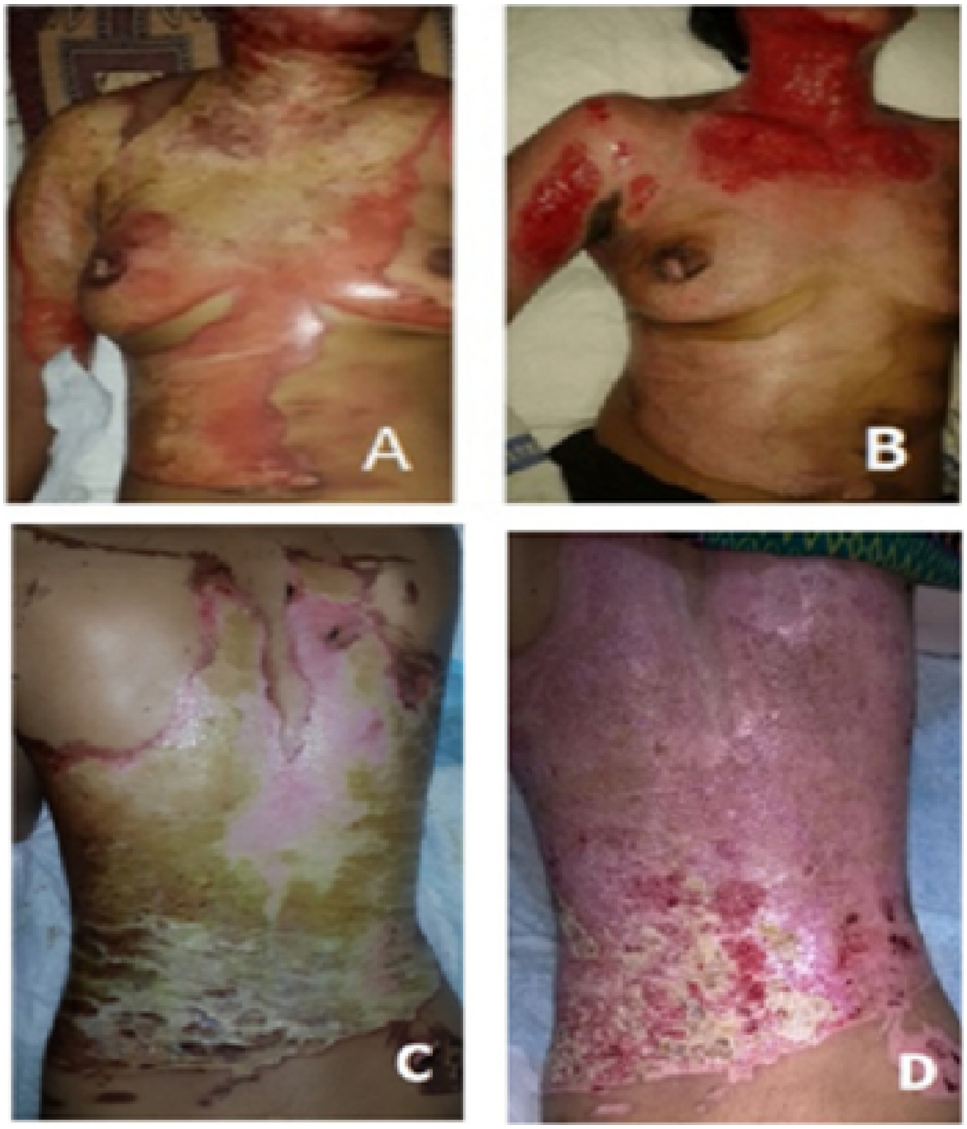

Fig. 3 – (A) Case 1, patient suffered from flame burn sustaining partial thickness Burn (PTB) wound involving neck, chest, abdomen and right arm (1st post burn day). (B) Case 1, wound on 16th day after treatment with topical heparin. (C) Case 2, patient suffered from flame burn sustaining partial thickness Burn (PTB) involving back. (D) Case 2, wound on 14th day after treatment with topical heparin.

Polyfax Ointment (10,000IU Polymyxin B Sulphate+500IU Bacitracin Zinc/gram) is described as amphipathic molecules having antibacterial activity against gram positive and gram negative bacteria. These molecules interact with the lipopolysaccharide in the bacterial cell membrane inhibiting cell wall development. An allergic reaction (rash, itching) had been reported in literature with topical Polyfax application however none of our patients developed any such complication [10].

Normal saline dressing functions in part as an osmotic dressing which encourage healing and promote the formation of healthy red granulation tissue. Application of simple normal saline soaked gauze dressing is cost effective, easily available and has no known cytotxic side effects. With evaporation of water the dressing becomes hypertonic. The hyperosmolarity of the normal saline dressing provides an osmotic gradient for absorption of wound fluid and desloughing, contributing to its effectiveness as moist wound dressing promoting granulation and epithelialization [11].

Our findings have strong biological plausibility and are consistent with the evidence from cellular and animal studies. Heparin is naturally found in the body. In 1960, Dr. Saliba described its effectiveness in burn patients and highlighted it as an anti-inflammatory and an angiogenic drug [12]. Heparin has been shown to modulate several phases of wound healing. It has a chemotactic effect on endothelial cells, with resultant stimulation of neovascularization and improvement of blood circulation subjacent to the burn, events that are important in inducing repair mechanisms [10]. In PTB patients, the deeper layers of skin develop ischemic injury due to vasoconstriction mediated by local generation of compounds, such as thromboxanes and possibly by vascular thrombosis within dermis. Heparin has been shown to increase survival of deeper layers

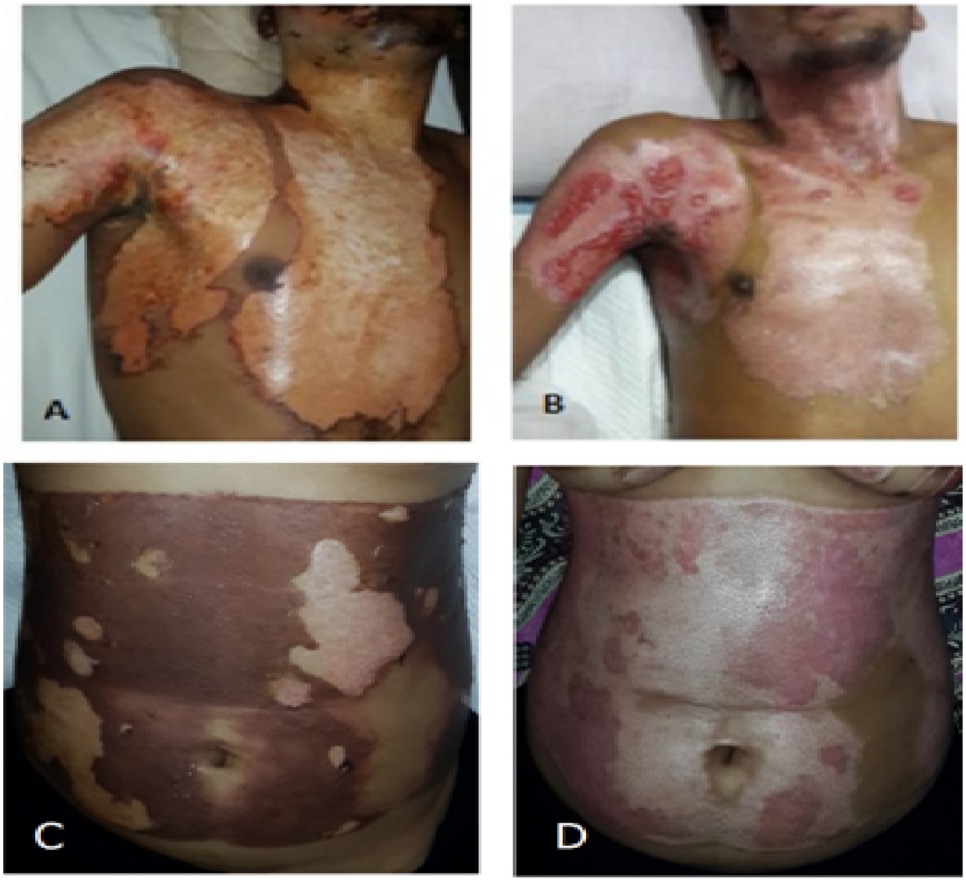

Fig. 4 – (A) Case 1, post flame burn partial thickness Burn (PTB) wound involving neck, chest and right arm (1st post burn day). (B) Case 1, wound on 14th day after treatment with topical heparin treatment. (C) Case 2, post flame burn partial thickness Burn (PTB) wound involving abdomen. (D) Case 2, wound on 13th day after treatment with topical heparin treatment.

of skin through its vasodilatory and antithrombin effects. Furthermore, epithelization by proliferation of these surviving de-epithelized island cells is induced with heparin thus making superficial and deep burns to heal in shorter periods of time [13–15]. our study found that heparin therapy was associated with faster healing of the second-degree burns (both SPTB and DPTB) as compared to those treated with conventional therapy.

Several clinical studies report that topical application of heparin on second degree burn significantly reduce pain and provide pain relief within 10-15 min. Ferreira Chacon et al. similarly, concluded that topical application of heparin in spray form was also effective in alleviating pain in patients with superficial second-degree burns [16]. The analgesic effect of heparin may be due to its inhibition of pro-inflammatory products that act on free nerve endings. Topical heparin application is also associated with less requirement of analgesic medication with additional benefit of reduced frequency of analgesic-induced complications [17,18]. Our study reinforced above findings showing significantly less pain scores and less analgesic requirement in 2nd degree burn patients (both SPTB and DPTB) treated with heparin as compared to those treated with conventional therapy.

Complications of topical heparin in our study were similar to those delineated in the literature. However, frequencies of these complications were significantly less in heparin group than conventional treatment group. Various studies had outlined bleeding episodes from wound site with topical heparin likely due to heparin's anticoagulant effect [12].

Our study has several strengths and limitations. This was a randomized-controlled trial eliminating the possibility of selection bias in treatment allocation. We were unable to blind the treating physician or the patient due to the nature of the treatment. A sham-treatment would have been ethically challenging in this setting. The small size of our study is one potential limitation; however, we found significant benefit of heparin treatment which was apparent in most outcomes even at this small sample size. Furthermore, this is a one center study which limits its generalizability. Another limitation is that the conventional treatment included only topical antibiotics and silvadine has been shown repeatedly to impede wound healing. Perhaps it could have delayed wound healing in conventional group than the accelerated healing observed in heparin group. This can only be demonstrated with another control group without heparin.

In conclusion, we show that treatment of Second degree or partial thickness burns (PTB) with topical heparin is superior to conventional treatment in terms of wound healing as well as for pain control. The treatment with topical heparin is well-tolerated and is without higher adverse effects. Our findings, if

confirmed in future randomized controlled trials have a potential to alter the current treatment paradigm of PTB treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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.2018.05.010.

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