Comparative Study between Topical Heparin and Nebulised Heparin in the Management of Thermal Burn Patients in a Tertiary Care Hospital, Tirupati

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ABSTRACT

BACKGROUND

Burn treatment is complex and involves many components. Topical solutions that contain antiseptic, antibiotic, and growth factor properties are effectively used in superficial burns. Heparin satisfies all the parameters. Routes of heparin administration described are subcutaneous, topical, intravenous, and inhalation. In this study, the need was felt to evaluate the efficacy of various heparin routes such as topical against nebulised heparin.

METHODS

100 consecutive thermal burn patients were studied prospectively under two groups i.e., topical heparin (T group) and nebulised heparin (N group). Hospital stay, final scar outcome, wound infection rate, secondary procedures, pain medication, dressings and antibiotics required were compared.

RESULTS

It was found that the T patients complained of less pain and received less pain medication, fewer dressings and antibiotics compared to N group. Significantly less IV fluids were infused to T group 36 vs 64 litres compared to N group ($P < 0.01$). T group had fewer secondary procedures 6 vs 14 compared to N group. The number of days in hospital for T was significantly less (over all $P < 0.0001$). 14 patients (28 %) in the topical group were discharged from the hospital in 10 days or less compared with 8 patients (16 %) in the nebulised group ($P < 0.001$, S). 38 out of the 50 H patients (76 %) were discharged in less than 3 weeks compared with 22 nebulised group patients (32 %) ($P < 0.001$, S).

CONCLUSIONS

Usage of Heparin is safe, needs no monitoring by bleeding time (BT), clotting time (CT), or partial thromboplastin time (PTT). The final scar outcome with parameters such as scar itchiness, texture, the wound infection rate, secondary procedures like a skin graft, post-burn contractures release were fewer in burn patients treated with topical heparin.

KEYWORDS

Topical Heparin, Nebulised Heparin, Hospital Stay, Scar Outcome, Secondary Procedures, Pain

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DOI: 10.18410/jebmh/2021/318

How to Cite This Article:
Challapalli SR, Gandikota VP, Chilakala A, et al. Comparative study between topical heparin and nebulised heparin in the management of thermal burn patients in a tertiary care hospital, Tirupati. J Evid Based Med Healthc 2021;8(21):1685-1690. DOI: 10.18410/jebmh/2021/318

Submission 04-02-2021,
Peer Review 14-02-2021,
Acceptance 08-04-2021,
Published 24-05-2021.

BACKGROUND

Burn treatments have been described since ancient times. The majority of ancient burn care consisted of topical therapies and can be traced back to centuries. Burn treatment is a complex understanding and involves many components like dressings, infection control, fluid resuscitation, and surgeries. This necessitates the development of newer management methods within our means to reach the common endpoint of reducing morbidity and mortality. Topical solutions that contain antiseptic, antibiotic, and growth factors properties are effectively used in superficial burns.

The management of burn wound is quite challenging as there should be continuous change in the treatment strategy depending on the host response to the injury and the treatment given. For this reason, a single agent that can provide adequate pain relief and accelerated wound healing is necessary. Heparin satisfies all the parameters. In addition to anticoagulation, heparin has anti-inflammatory, neo-angiogenic, and collagen restoring properties.[1-12] Heparin inhibits early inflammatory response by inhibiting coagulation by fibrinolytic activation, thereby decreasing the acute lung injury score.

Moreover, heparin regulates cell proliferation, prevents free radical-induced cell injury. The heparin administration routes described are topical, intravenous, subcutaneous, and inhalation in the management of thermal injuries.

Objectives

1) To evaluate the efficacy of various heparin routes such as topical against nebulised heparin in the management of thermal burns. Focus should be mainly on the better pain control, improved healing, improved functional and cosmetic outcomes.
2) To compare the outcome of burns, patients treated with topical heparin against nebulised heparin have to be evaluated in the following each group.
   - The rate of formation of scars and contracture.
   - Pain management.
   - Length of stay in hospital.
   - Healing time.

METHODS

The study design was prospective type and its population comprised of patients presenting to the Emergency Department and OPD of General surgery, SVRRGG Hospital, Tirupati with thermal burns and the sample size being 100.The study was conducted for one year (2019 - 2020) from the time of approval of the Institutional Ethics committee.

Inclusion Criteria

- Patients presenting with thermal burns between the age group of 18 to 60 yrs.
- Thermal burns of 1st, 2nd, and 3rd degree up to 35 %.

Exclusion Criteria

- Chemical or electrical burns in history.
- Personal or family history of haemorrhagic diathesis.
- Personal or family history of Heparin intolerance.
- History of liver disease or renal failure.
- Thrombocytopenia.

General Treatment of Group T & Group N

A total of 100 patients were enrolled for the study. With the use of random number tables, the study population was randomly allocated into two groups - Group N and Group T, initially assessed and the estimation of total burn surface area was done.

Rule of 9 was used for calculating the total burn surface area. vital signs, air entry examination was done. All the patients had IV lines secured with an 18 G cannula.

Sedation with Inj. Pentazocine with Promethazine was administered to an adult. Prophylactic tetanus toxoid was administered. Prophylactic systemic antibiotics were given to all the patients, including either single or combination of ampicillin, gentamycin, amikacin, cefotaxime, ceftriaxone, and metrogyl in the standard dosages. Emergency baseline investigations were done; the wound swab was taken on the day of admission.

IV fluid requirement was calculated by using Modified Parkland formula (4 x TBSA x wt in kg). The 2nd degree superficial burns were clinically diagnosed based on the tactile and pressure sensation, presence of Redness, Blisters, Blanching. The deep 2nd degree burns were clinically diagnosed based on the failure to blanch on pressure and mottled appearance of wound.

Topical Heparin Group [T]

Topical heparin spray is prepared by adding 20.8 ml of 5000 IU / ml of heparin to 500 ml of Normal saline to make 200 IU / ml concentrated solution. The heparin requirement dose is calculated based on the percentage of burns taking. Each 15 % 1 lakh IU of Heparin, and accordingly, the solution is prepared. With iv needle and Set, Heparin solution is sprayed on occlusive saline dressing of single layer gauze pads which help by providing an adequate moist environment and avoids wastage of heparin and coagulation profile is checked every alternate day.

Debridement of blisters was not done. A small hole was made with the needle and 200 IU / ml heparin was introduced into a blister, fluid in the blister was made to drain spontaneously.The procedure was repeated 2 - 3 times; residual volume of heparin was left within the blister after withdrawal of the needle.

Nebulised Heparin Group [N]

Nebulised heparin 10,000 units given 4 - hourly, alternating with nebulised 0.5 % albuterol (a beta-agonist) and either 20 % N-acetyl cysteine (NAC) 4 - hourly.

Measurement of Outcome

Healing Time

Epithelialization was certified by either the chief or a senior faculty

Pain

Visual analogue pain scale of 1 – 10 was used for pain estimation, reading was taken on day 2 & 4, and the average was recorded.

Duration of Hospital Stay Scar Assessment

The scar assessment was done by using the Vancouver scar scale.[9]

Statistical Analysis

we have entered the data into MS-EXCEL, and statistical analysis has been done using IBM SPSS version 22.0 for categorical variables; the data values were represented as percentages and numbers. Differences between the groups were tested by using the chi-square test derived in Epi Info - 6 software. The data value was shown as the Mean difference between the two groups; we used the students t-test. All the P values having less than 0.05 were considered statistically significant.

RESULTS

The number of patients were the same in both groups. The age of patients in both groups was not significantly different.

Sex and Age Distribution	Topical Group	Nebulised Group
Male	18 – 45 – 14 (28 %)	18 – 45 – 16 (32 %)
	46 – 60 – 6 (12 %)	46 – 60 – 10 (20 %)
Female	18 – 45 – 18 (36 %)	18 - 45 – 16 (32 %)
	46 - 60 - 12 (24 %)	46 - 60 – 8 (16 %)

Table 1. Sex and Age Distribution

TSBA & Nature of Burns	Topical Group	Nebulised Group
Up to 15 %	Scald 10 (20%)	Scald 12 (24 %)
	Flame 18 (36%)	Flame 18 (36 %)
15 to 35 %	Scald 6 (12%)	Scald 8 (16 %)
	Flame 16 (32%)	Flame 12 (24 %)

Table 2. TSBA & Nature of Burns

Analgesics per day	Topical Group	Nebulised Group
1 - 2 times	50 (100 %)	20 (40 %)
3 - 4 times	Nil (no calculation)	30 (60 %)

Table 3. Patients' Requirement of Analgesics

	Topical Group	Nebulised Group
Average amount of IV fluids (litres)	36	64
Requirement of secondary procedures	6 (12 %)	14 (28 %)

Table 4. Requirements of Intravenous Fluids & Requirement of Secondary Procedures (P < 0.01)

Duration of Hospital Stay (days)	Topical Group	Nebulised Group
Up to 10 days	14 (28 %)	8 (16 %)
Up to 20 days	24 (48 %)	14 (28 %)
Up to 30 days	10 (20 %)	20 (40 %)
More than 30 days	2 (4 %)	8 (16 %)

Table 5. Distribution of Patients by Duration of Hospital Stay (P < 0.001)

Complications	Topical Group	Nebulised Group
Aspiration pneumonia	1 (2 %)	0
Wound infection	2 (4 %)	8 (16 %)
Septicaemia	0	1 (2 %)
Pain estimate by the visual analogue scale on average	3	5
Bleeding	0	0
Mortality	0	3 (6 %)

Table 6. Complications

DISCUSSION

The treatment of burns need a complete understanding of pathophysiology of burns which is a complex process. This is mainly attributed to the inflammatory mediators released. There will be microcirculation impairment, tissue oedema, inadequate tissue perfusion and failure of nutrients to the tissue. burn injury is hyper metabolic state with increased resting energy expenditure rate higher than the normal levels.

This increased basal metabolic rate causes devastating sequel at both cellular and systemic levels leading to impaired immune system, delayed wound healing, increased wound infection rate. This cumulatively leads to development of sepsis, which plays an important role in morbidity and mortality of burns. Heparin is a potent anti-inflammatory agent which inhibits enzymes and cytotoxic mediators released from proinflammatory cells, responsible for augmentation of inflammatory cytokines such as elastase, cathepsin G, eosinophil peroxidase, eosinophil cationic protein, major basic protein, interleukin-8, and stromal-derived factor-1.[2]

On the other hand, heparin sulphate enhances the recruitment of inflammatory cells, since endothelial surface Heparin sulphate decreases adhesion. HS can also be recognized as a sensor of tissue injury, thanks to the interaction with TLR-4 on leukocytes. This action regulates the release of proinflammatory cytokines by macrophages and significantly enhances the maturation of dendritic cells. Mentioned phenomenon is confirmed by the upregulation of Major histocompatibility-II, CD 40, ICAM-1, CD 80, CD 86, and reduced antigen uptake. Heparin sulphate are recognized as pivotal players in angiogenesis, cell growth, migration, and differentiation. Heparin sulphate, abundant in acute wound fluid 24 – 72 h after injury, bind heparin binding growth factor (Hb - EGF), which can act as a mitogenic agent for fibroblasts, smooth muscle cells, and epithelial cells.

Moreover, after skin damage, heparin sulfate proteoglycan, syndecan-4, is upregulated within the granulation tissue on fibroblasts and endothelial cells, which may suggest that syndecan-4 regulates wound healing and related angiogenesis. Heparin sulphate interacts with hepatocyte growth factor, which regulates cell growth, motility, and morphogenesis of epithelial or endothelial cells and stimulates epithelial repair and neovascularization. Heparin sulphate also influences fibroblast growth factor responsible for cell proliferation, differentiation, signal transduction, and angiogenesis. Heparin sulphate, which interacts with TGF – β 1 and potentiate its activity, are

indispensable for adhesive and contractile signalling, that results in myofibroblast formation and wound closure.

The study was conducted in a uniformly controlled manner without bias in patients' initial selection and any performance deviation. one year was the duration of the study. The same nurses, doctors, and ancillary staff treated all the topical and nebulised patients in the same burns unit, using the same facilities.

The subjects in the study included the first 100 consecutively admitted burn patients out of the 194 patients who had the same characteristics and parameters as regards age (18 - 60 yr.) and presentation that was mode, burns in less than 35 % of Total body surface area (TBSA).

First, the second-degree superficial and deep, the third degree was chosen as the degree of severity. A total of 100 patients were enrolled for the study. With the use of random number tables, the study population was randomly allocated into two groups - Group N and Group T

Pain medication was administered once or twice a day to all topical patients and 40 % of nebulised group patients. Sixty percent of nebulised group patients and no topical patients received pain medication as often as 3 to 4 times a day (P not calculable) (Table III). The reduced use of pain medication and associated reduced side effects permitted topical group patients. The key feature that was preventing extension of burn wound leading to a better outcome in patients treated with heparin was quicker revascularization of ischemic tissue. The neoangiogenic effects of heparin were presumed responsible for these improvements.

No of patient's difference between the Nebulised (40 / 50, 80 %) and Topical (38 / 50, 76 %) who received intravenous fluids was not significant. The volume of intravenous fluids infused in Nebulised group was (64 litres) compared with Topical group (36 litres) (P < 0.04, S) (Table IV). Six patients in the Topical group required skin grafting compared with 14 patients in the Nebulised (Table IV).

Hospital stay was higher in the Nebulised group than in the topical group. 14 patients (28 %) in the topical group were discharged from the hospital in 10 days or less compared with 8 patients (16 %) in the Nebulised group (P < 0.001, S). 38 out of the 50 T patients (76 %) were discharged in less than three weeks compared with 22 Nebulised group patients (32 %) (P < 0.001, S) (Table V).

The three deaths were in the 50 patients in the Nebulised group (6 %). It is essential that all three deaths were in the 25 - 35 % TBSA size. None of the Nebulised patients and none of the topical patients had a bleeding problem. So use of heparin was safe in this study. (Table VI).

The oedema, pain, and erythema were reduced in patients who received treatment with heparin. The amount of heparin required and the size of burns to produce healing were directly related. In patients treated with heparin, the revascularization of ischemic tissue was the critical feature preventing the extension of burns and resulting in a better outcome. These improvements were presumed to be due to a neoangiogenic effects of heparin.[4]

Saliba's work proved that when heparin was added in the management of burns, not only did it reduce pain, but it also limited the inflammation, caused revascularization of ischemic tissue, and enhanced tissue granulation.[1] The work of Ramakrishna showed that heparin, when used in the management of burns, had anti-inflammatory properties.[3]

Srivastava et al. comparison of standard therapy alone and with addition of heparin was done. Addition of Heparin therapy to the standard therapy use was found to be superior in terms of morbidity and mortality, wound infection rate, graft healing and uptake, and number of eschar formation.[13]

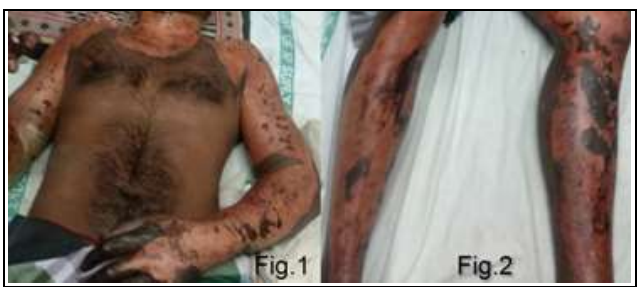

Figure 1 & 2. Patient with Scald Burns

Figure 3 & 4. Patient Treated with Topical Heparin

Venkatachalapathy et al. the study group reported a significant shorter length of hospital stay in Heparin group and also found less mortality rate and fewer skin grafts in patients treated with heparin.[10]

Reyes et al. this study reported that patients treated with heparin had better pain relief, less tissue oedema, no of fasciotomies were fewer, duration of hospital stay was significantly shorter, and revascularization of burn wound was quicker compared to patients who did not receive topical heparin therapy.[2]

Desai et al. this study examined aerosolized heparin's effect along with acetylcysteine inhalational burn injuries, the heparin group had significantly lesser reintubations and lower rates of atelectasis and lower morbidity and mortality rate compared to standard therapy group.[14]

Herndon and Traber's et al. this study strongly suggested that use of aerosolized recombinant human anti thrombin and heparin in combination could be a new therapeutic approach for management of airway in cases of smoke inhalation and cutaneous flame burn induced acute lung injury.[15]

Patients in the heparin group in this study paid less for antibiotics, had reduced infection rate, had faster healing rate, and had reduced hospital stay. IV fluids were significantly less in the T than the N group (P < 0.001). TS Venkata Chalapathi's[10] study found that requirements with IV fluids were reduced significantly. Early ambulation due to reduced pain made patients feel better. Early intake of enteral feeds led to less usage of IV fluids, fewer chances of

mucosal sloughing of the gastrointestinal tract, and reduced translocation of gut bacteria, thus reducing septic episodes. The thrombolytic effect of heparin makes the micro thrombolysis of intestinal microvasculature, and perfusion of the intestinal mucosa was improved. The chances of curling's ulcers of the gastric mucosa were less.[8] The findings were found in other studies. The revascularisation of ischaemic tissues and the improved quality and greater quantity of vascular granulation tissue were noteworthy. Using topical heparin, the areas to be skin grafted were prepared earlier to enable early surgery and better graft take. These were presumed to be a function of heparin's neoangiogenesis. With heparin, thrombus already formed due to burn insult got lysed, and microvasculature was restored. An increase in blood flow and growth factors like vascular endothelial growth factor, epidermal growth factor caused early epithelialization and neoangiogenesis. This restored blood flow to ischemic areas and early eschar separation.[10]

The benefits of relieving pain, fewer baths, antibiotics and dressings helped the treatment of topical patients more comfortable and more pleasant than that of nebulised patients. With heparin, the burn blisters, which when not removed, rarely got infected, functioned as natural skin grafts that required no further care.[7] Usually in 7 - 14 days, the new skin was evident beneath the dried thin blister when it flaked off. Heparin increased the number of smooth muscle fibroblast cells, this explained the reduced number of contractures in topical heparin compared to nebulised group.[11] The relationship between the size and severity of the burn wound and the amount of heparin dose required in therapy has been established. The correlation between burn size and the amount of heparin dose used until healing was documented and found that the patients with burn wound of less size and severity required lesser dosage of heparin.

Colour and pigmentation estimation was done at 2 months and again at 6 months, the scar outcome was favourable with the heparin group. The nebulised group had healed wound with marked hypopigmentation at six months. The healed ulcer beyond six months needed to be studied further.[12] The disadvantage of topical heparin therapy was the daily dressing of the patient with it as it was very uncomforting causing displeasure to the patient, as the soaked heparin gauze dried up and got stuck to wound and it was very painful while removing during the dressing. The time allotted and adequate sedation for each patient for a daily dressing change was more and it was very difficult to manage the patient load and it required ample amount of time and skills to manage these load by the attending surgeons.

CONCLUSIONS

1. Topical heparin has no bleeding complications and needs no monitoring by BT, CT or PTT.
2. Parameters such as scar itchiness, texture and pigmentation are more in favour of topical heparin therapy.
3. The wound infection rate is less with topical heparin group when compared to nebulised heparin.
4. Secondary procedures like skin graft, post burn contractures release were fewer in burn patients treated with topical heparin.

Limitations

Small sample size was a limitation. Longer follow-up would help in monitoring of wound healing.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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