Original Article

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Role of Topical Heparin in Treatment of Burn at Tertiary Care Hospital in Western Rajasthan

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Abstract

Background: Heparin is a multifaceted compound with uses not only as an anticoagulant, but also as an anti-inflammatory, anti-allergenic, anti-histaminic, anti-serotonin, anti-proteolytic and neoangiogenic agent. The aim of the study was to study the effect of topical heparin in the management of burns in terms of morbidity, mortality & safety. **Subjects and Methods:** A hospital based RCT with total duration of 16 months from June, 2018 to September, 2019 with 100 patients (age between 15-45 years, burns from 20-60%, with less than 48 hours duration), randomly enrolled into 2 groups, after initial resuscitative measures, 50 cases receiving Topical Heparin treatment, 50 controls receiving conventional treatment (1% silver sulphadiazine) with i.v. antibiotics, after explaining the study objectives and taking informed written consent. Data analysis was performed using Epi Info software. **Results:** Patients treated with topical heparin experienced statistically significant ($p<0.05$) improved pain relief, rapid healing, lesser complications and reduced duration of hospital stays. **Conclusion:** The current study demonstrates that topical heparin can improve clinical outcomes in the treatment of burn injury.

Keywords: Burns, Topical Heparin, Efficacy

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Introduction

The history of treatment of burns is over 3500 years old. First evidence was found in cave paintings of Neanderthal man. In India with a population of over 1 billion, 70 -80 thousand burn admissions occur annually.[1] Also commonest age group afflicted being the productive age group pose a problem to society being the income generating group. Significant breakthrough took place in the advanced countries in terms of reducing mortality and controlling morbidity. This necessitates the development of newer methods of management within our means to reach the common end point of reducing morbidity and mortality.[2]

In this regard, heparin has been introduced because of its research proven role in burn wound management.[3] Multiple mechanisms explain the role of heparin in burns when used topically. Firstly, heparin may work partially because of anti-inflammatory activity. The effects may directly or indirectly mediate on many factors producing inflammation.[4] The mechanism of action may also include influencing monocyte, T-cell and neutrophil activity, nitric oxide production, chemokine and cytokine activity, complement activity, platelet activation and aggregation, and smooth muscle cell proliferation.[5] Second, heparin can restore blood flow in a shorter time and revascularize ischemic tissue, through enhanced vascular growth.[6] Possible mechanisms of this action are the inhibition of selectin-mediated cell-cell interactions, heparinase inhibition, binding of proangiogenic growth factors and stimulation of tissue factor pathway inhibitor release.[7] Third, wound healing is affected by enzymes such as elastase, cathepsin G, and proteinases, which degrade the extracellular matrix, growth factors and further recruit neutrophils to the wound area. Heparin and related molecules could inhibit the function of these cells through electrostatic interactions and enhance the healing.[8,9]

This study was conducted to study the role of topical heparin in the management of burns and to validate its efficacy and safety in Tertiary care hospital in western Rajasthan.

Subjects and Methods

After obtaining approval from the Institutional Ethical Committee, the study was conducted in Department of Surgery, S. P. Medical College and associated group of hospitals, Bikaner.

It is a hospital-based randomized control trial with total duration of 16 months from June, 2018 to September, 2019. Study groups are the patients admitted in our hospital burn ward with age group between 15-45 years & having burns ranging from 20-60%, with less than 48 hours duration. Patients with bleeding diathesis, pregnant ladies, coagulation disorders and allergic to heparin were excluded from study group.

Heparin Administration Method

20.8 ml of 5000 IU/ml (International Units per ml) of heparin solution was added to 500 ml of physiological normal saline solution in an intravenous fluid bottle to make a total 520.8 ml of 200 IU/ml concentration heparin sodium solution. The dose of heparin required for topical application was calculated to be 100,000 IU/15% burn surface area (BSA) per day in 3-4 divided doses. The medication was applied to the burnt surface drop by drop with a 50 ml syringe, until the pain was relieved, repeated for 2-4 times until blanching occurred. Beginning on the 2nd day, heparin was applied twice a day, using a diminishing quantity for 1 week.

Blisters were rinsed with heparin solution via hypodermic syringe and were not de-roofed. Blood was drawn to test for bleeding time, clotting time, and activated partial thromboplastin time, in addition to routine blood investigations.

Relief of pain was recorded by a visual analog scale, healing of wounds, dose of heparin, complications, mortality and duration of hospital stay were reported and analyzed. This was a single blinded study that was approved by the Ethics Committee of the Institute. Written informed consent was obtained from the patients or guardians.

The Various Parameters Measured Were

- I.V. Fluid requirement (in liters)
- Severity of pain (Visual Analog Scale) and analgesic requirement (doses/day)
- Morbidity pattern (in terms of hospital stay)

Data analysis was performed using Microsoft Excel sheet and Epi Info software of WHO-CDC.

Results

100 consecutive burns patients were selected over a period of sixteen months based on inclusion and exclusion criteria. Of them, fifty were treated with topical heparin therapy (Group H) and the other fifty patients by conventional methods (Group C). After initial resuscitative measures patients were allotted to conventional therapy (1% silver sulfadiazine) to 'C' group or Heparin therapy to 'H' group. Results of both the groups were compared with various variables to know the effectiveness of topical heparin therapy.

Of these 68% were between 26-45 years and 32% between 15-25 years. There is no significant difference in age among these two groups. In both groups, there is equal distribution of males and females and study is male dominant (60% males and 40% females). There were more patients from rural areas (64%). In both groups, maximum patients associated from flame burns. Among H group, 60% of patients had 26-40% burns. Similarly among C group patients 54% of patients had 26-40% burns. In both groups approx. $3/4^{th}$ proportion were superficial burn. All the demographic parameters are not significant in the groups.

Table 1: Demographic distribution in study

Variable	Heparin Group (NH=50)	Control Group (NC=50)	P Value
Age(in years)			0.970
15-25	15 (30%)	17 (34%)	
26-35	16 (32%)	16 (32%)	
36-45	19 (38%)	17 (34%)	
SEX			0.838
Male	30 (60%)	30 (60%)	
Female	20 (40%)	20 (40%)	
Residence			0.835
Rural	32 (64%)	32 (64%)	
Urban	18 (36%)	18 (36%)	
Mode of burn			0.358
Flame Burn	39 (78%)	43 (86%)	
Electric Burn	5 (10%)	1 (2%)	
Scald Burn	6 (12%)	5 (10%)	
Acid Burn	0 (0%)	1 (2%)	
TBSA%			0.134
15-20	5 (10%)	3 (6%)	
21-25	3 (6%)	2 (4%)	
26-30	12 (24%)	4 (8%)	
31-35	5 (10%)	10 (20%)	
36-40	13 (26%)	10 (20%)	
41-45	3 (6%)	4 (8%)	
46-50	1 (2%)	8 (16%)	
51-55	1 (2%)	1 (2%)	
56-60	7 (14%)	8 (16%)	
Degree of Burn			0.644
Superficial	39 (78%)	36 (72%)	
Deep	11 (22%)	14 (28%)	

Table 2: Distribution of patients by requirements of IV fluids, Analgesic Requirement, Duration of Hospital stay, Treatment outcome and Contractures after 2 months

Variable	Heparin Group (NH=50)	Control Group (NC=50)	P Value
I.V. Fluid Requirement in 1st week			**0.001***
No. of pts. Adminis-tered	36 (72%)	45(90%)	
Amount (liters) Mean±SD	10.04±4.15	18.42±12.59	
Analgesia Requirement (times/day)			0.036*
1-2	50 (100%)	16 (32%)	
3-4	0 (0%)	34 (68%)	
DOHS (Days)			0.018*
8-14 days	34 (68%)	14 (28%)	
15-21 days	9 (18%)	23 (46%)	
22-28 days	3 (6%)	6 (12%)	
29-60 days	2 (4%)	6 (12%)	
>60 days	0 (0%)	1 (2%)	
Treatment Outcome			0.0437*
Discharged	46 (92%)	36 (72%)	
Expired	4 (8%)	14 (28%)	
Contractures after 2 months			0.001*
Yes	2 (4%)	12 (24%)	
No	44 (88%)	24 (48%)	

There is 72.00% needed IV fluid in heparin group whereas 90.00% needed IV fluid in control group. Association of both groups with amount of IV fluids found to be statistically significant (p<0.05).

In heparin group all patients needed analgesic (injection tramadol 100mg/2ml) for 1-2 times per day. None of the case required analgesic more than 2 times a day. In control group approx. 2/3rd proportion needed analgesic for 3-4 times a day. Association of both groups with analgesic use was statistically significant (p<0.05).

In heparin group maximum 68.00% had 8-14 days hospital stay whereas no patient had hospital stay more than 60 days. In control group maximum 46.00% had 15-21 days hospital days whereas minimum 2.00% had more than 60 days of hospital stay. Association of hospital stay with both groups was found to be statistically significant (p <0.05).

Maximum 92.00% were discharged whereas 8.00% were expired in heparin group. Maximum 72.00% were discharged in control group whereas 28.00% were expired. Association of both groups with treatment outcome was statistically significant (p<0.05).

Only 4.00% in heparin group had contracture whereas 24.00% of control group had contractures. Association of presence of contractures at follow up visit after 2 months with both groups was statistically significant (p<0.05).

Table 3: Distribution of Heparin group according to their Heparin dose requirement (Lac IU)

Total Body Surface Area (%)	Heparin Group (N_H =50)	Heparin Dose(Lac IU) Mean	P value
	Frequency		
15-20	5 (10%)	3.7 ± 0.91	
21-25	3 (6%)	4.43 ± 1.16	
26-30	12 (24%)	5.18 ± 0.56	
31-35	5 (10%)	5.68 ± 1.13	
36-40	13 (26%)	7.63 ± 1.78	
41-45	3 (6%)	7.76 ± 2.12	
46-50	1 (2%)	9.8 ± 0.0	
51-55	1 (2%)	10.0 ± 0.0	
56-60	7 (14%)	10.17 ± 1.36	
Total	50	100.00 %	

Maximum 10.17±1.36 (Lac IU) heparin was consumed by 14% whereas minimum 3.7±0.91 (Lac IU) heparin was consumed by 10% of heparin group. Maximum 26.00%of heparin group had consumed 7.63±1.78 (Lac IU) heparin. Association of TBSA and Heparin consumed was found to be statistically significant (p<0.05).

Table 4: Distribution of Heparin group and Control group according to VAS scale scoring on day 1 and day 7 of treatment

VAS Scale	Heparin Group (N_H =50)		Control Group (N_C =50)	
	Day 1	Day 7	Day 1	Day 7
MEAN±S	6.87±2.46	3.15±0.92	7.95±0.95	7.71±1.58
P value	0.001**		0.360 NS	

Discussion

Burns are painful wounds. The sufferings and squeal of burn victims are disastrous. Burn sequels affect life quality and produce longstanding emotional and social impacts in the patient's life. The development of new treatment resources could modify this picture. In this study, a new treatment

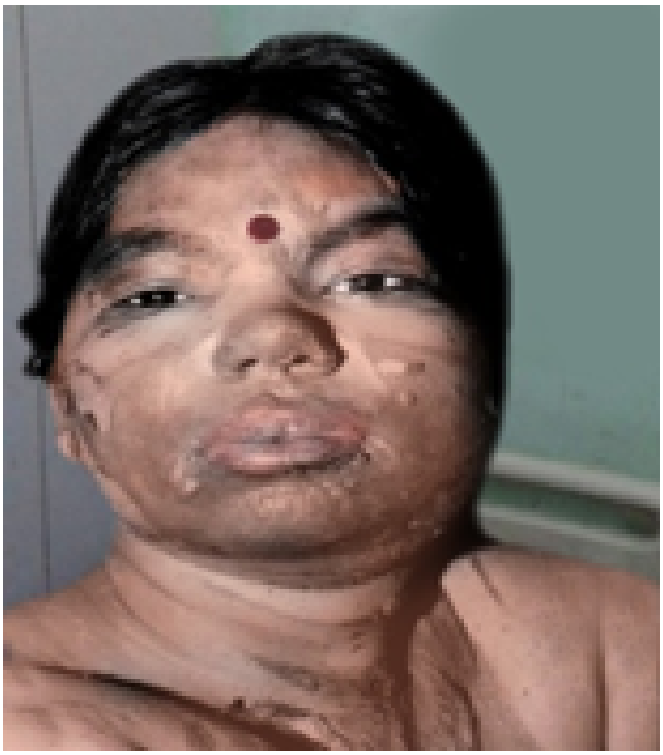

Figure 1: Photograph showing edema over face especially over left side (at the time of admission)

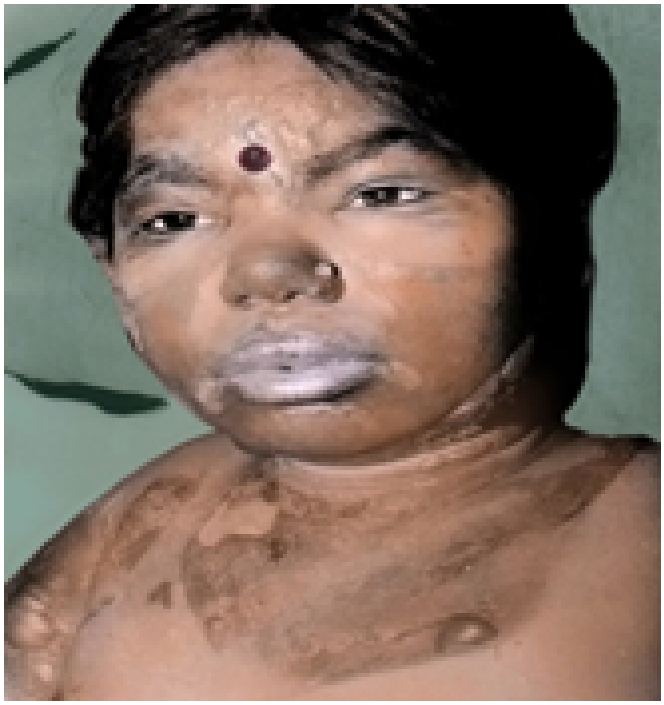

Figure 2: Photograph showing significant elimination of edema, after 3 days of topical heparin therapy

approach using topical heparin was used to assess the efficacy and safety of topical heparin therapy in burns.

The numbers, ages, gender of the patients, as also the mode of burn was comparable in both the groups which were insignificant.

In our study, average hospital stay of control group is 19.6 days while in H-group average hospital stay is 14.48 days (p=0.018). Masoud M et al, [10] found average hospital stay of 18.3 days in the C-group while patients belonging to the H-group had an average hospital stay of 12.3 days ($P < 0.05$). M. Swatantra Bharathi et al, [11] found average duration of hospital stay in C group is 34.72 days and in H group it was 21.36 days ($p< 0.001$).

In our study, there was 8% mortality in heparin group whereas 28.00% mortality was observed in control group. Association of both groups with treatment outcome was statistically significant ($p<0.05$). Venakatachalapathy TS et al, [12] observed mortality in C group (10%) but not in H group. Zayas GJ et al, [13] observed increase in survival with heparin from 11% to 60% and, therefore, the decrease in mortality from 89% to 40% were significant ($p < 0.04$).

In our study, the heparin patients complained of less pain and received less analgesia doses than the control patients (i.e.

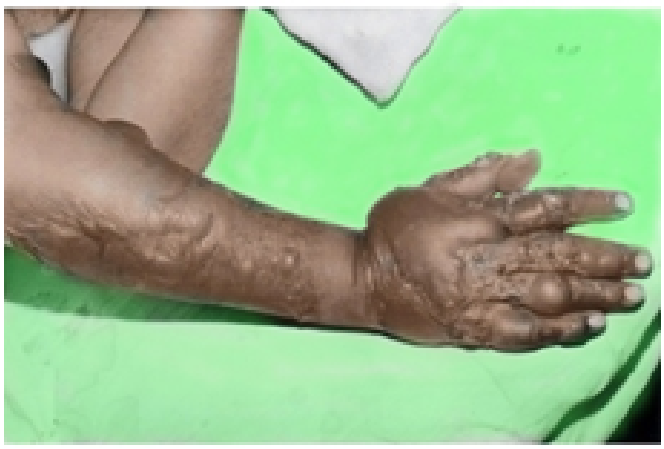

Figure 3: Photograph showing burn of right arm with edema and blisters on admission

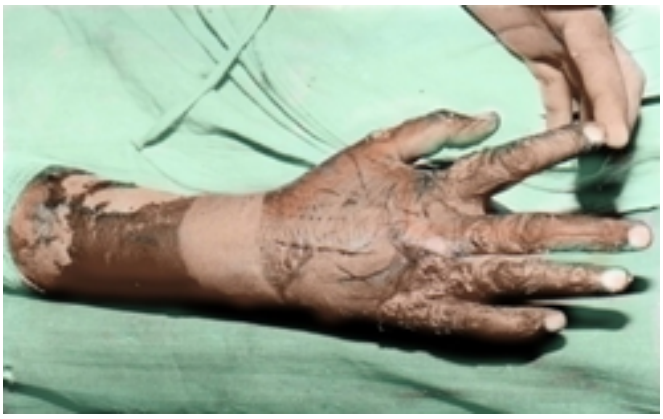

Figure 4: Photograph showing healing of burn after 7 days

6.56±4.55 in H group vs. 16.70±7.83 in C group). Association of both groups with analgesic use was statistically significant ($p<0.05$). Barretto MG et al, [14] found that group H demanded less analgesic medications (11.83 +/- 9.38 per patient against 33.35 +/- 20.63 for the C group, $p<0.01$).

Our study found that there is a significant difference in fluids infused between C-group: 20.46 liters in 45 C patients vs. 13.94 liters in 36 H patients ($p< 0.05$). Venakatachalapathy TS et al, [12] also found that significantly less intravenous fluid was infused in H: 33.5 liters in 39 H patients vs. 65 liters in 41 C patients, i.e. nearly 50% less ($p < 0.04$).

In our study, maximum 10.71 ± 1.36 (Lac IU), heparin was consumed by 14% whereas minimum 3.7± 0.91 (Lac IU) heparin was consumed by 10% of heparin group. As TBSA increased in our study, the heparin requirement of H group increased accordingly. Association of TBSA and Heparin consumed was found to be statistically significant ($p<0.05$).

In our study, heparin group had lesser prevalence of contractures (4% vs. 24%). M. Swatantra Bharathi et al, [11] found one contracture release later after discharge in C group while in H group none had any post burn contracture.

When VAS scale on day 1 and day 7 were observed in both groups of our study, the control group was observed with much higher VAS values as compared to Heparin group on day 7 (i.e.7.71±1.58 in control vs. 3.15±0.92 in heparin group) and the difference was statistically highly significant ($p<0.05$). Sobia Manzoor et al, [15] found mean pain score was also lower in the heparin group (3 ± 1 in heparin vs. 7 ± 1 in control group).

Conclusion

From our study, it was concluded that topical heparin is an effective pharmacological agent to overcome immediate post burn problems i.e. pain, hypovolemia. It decreases the duration of hospital stay, analgesic use and requirement of I.V. fluid. It decreases the morbidity in burn i.e. post burn contractures. There was less number of mortality in heparin patients.

By the results of our preliminary study, it was not being said emphatically that heparin is any panacea for patients of burns but it is definitely a good supportive measure, if added.

Longer clinical trials are needed before it can be recommended for routine use in burns.

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