A Comparative Study of Paediatric Thermal Burns Treated with Topical Heparin and Without Heparin

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Abstract Following reports of heparin use in burn treatment, an ethics-committee-approved prospective randomized study with controls compared results obtained using traditional usual burn treatment without heparin with results in similar patients similarly treated with heparin added topically. The subjects were 100 consecutive burn patients (age <15 years) with second-degree superficial and deep burns of 5–45 % total body surface area size. Two largely similar cohort groups—a control group (C) and a heparin group (H) with 50 subjects per group—were randomly treated. The 50 control group patients received traditional routine treatment, including topical antimicrobial cream, debridement, and, when needed, skin grafts in the early postburn period. The 50 heparin group patients, without topical cream, were additionally treated, starting on day 1 postburn, with 200 IU/ml sodium aqueous heparin solution USP (heparin) dripped on the burn surfaces and inserted into the blisters two to four times a day for 1–2 days, and then only on burn surfaces for a total of 5–7 days, before skin grafting, when needed. Thereafter, control and heparin group treatment was similar. It was found that the heparin patients complained of less pain and received less pain medicine than the control patients. The heparin group needed fewer dressings and oral antibiotics than the control group. The 50 heparin group patients had 4 skin graftings (8 %), while the 50 control group patients had 10 (20 %). Five control group patients died (mortality 10 %). No heparin group patients died. The number of days in hospital for the heparin group versus control group was significantly less (overall $P<0.0001$): 58 % of heparin group patients were discharged within 10 days versus 6 % of control group

patients; 82 % of heparin group patients were out in 20 days versus 14 % of control group patients; 98 % of the heparin group versus 44 % of the control group were out in 30 days; and while 100 % of heparin group patients were discharged by day 40, 56 % of the control group required up to another 10 days. Burns in heparin group patients healed on average in 15 days (maximum period 37 days) versus an average of 25 days (maximum >48 days) in control group patients ($P<0.0006$). Procedures and costs in the heparin group were much reduced compared with the control group. Differences between the heparin and control groups are presented for the sake of comparison. It was concluded that heparin applied topically for 5–7 days improved burn treatment: it reduced pain, pain medicine, dressings, and use of antibiotics; it significantly reduced IV fluids ($P<0.04$), days in hospital ($P<0.0001$), and healing time ($P<0.0006$); and it reduced skin grafts, mortality, and costs.

Keywords Thermal burns · IIInd degree burns · Topical heparin

Introduction

Our 1200-bed Indira Gandhi Government General Hospital and Postgraduate Institute, Pondicherry, India, admits 50,000 patients per year, of whom an average of 1.5 patients per day are admitted to the burn unit. Approximately 50 % of the burn patients die because they are suicide cases with severe second- and third-degree burns covering from 60 to nearly 100 % of the total body surface area (TBSA). As survival is bleak and treatment costs prohibitively high and economically unsupportable, these dire situation patients are generally given narcotics to lessen their suffering until the burn pathology inevitably terminates in death.

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Another nearly 50 % of the patients admitted have second- and third-degree severity burns in less than 50 % total body surface area. In 3 years before this study, of the 1,344 such patients admitted, 430 died, with a mortality rate of 31.9 %. The treatment for burn patients has been onerous and difficult, and needs improvement. Measures and means that might produce new burns therapies have been explored. In this study I am concentrating on advantages of heparin therapy in children. However, we had experience of doing the study in adult population and found good results with the addition of heparin.

This study was therefore designed to evaluate whether the addition of heparin, administered only topically for a limited time and prior to any surgery, could improve burn treatment and reduce burn morbidity and mortality in our hospitalized patients [1, 2]. The ethics committee approved the study plan and the use of heparin by protocol.

Method

Subjects: Selection, Characteristics, and Distribution

During 6 months between September 2009 and February 2010, 226 patients were admitted to our burn unit. The subjects in this study were the first consecutive 100 patients, younger than 15 years, whose superficial and deep second-degree severity burns were below 50 % total body surface area size (range 5–45 %). Fifty of these selected patients were designated to be the control group (C). Control group patients received the traditional routine treatment without the addition of heparin. Control group treatment included pain medications, intravenous resuscitation fluids, oral antibiotics, topical antimicrobial sulfur-based cream, water baths, debridement, tissue-releasing incisions, blood transfusions, and skin grafts. The other 50 randomly selected patients were assigned to the heparin-treated group (H). Heparin group patients received the same treatment but without the use of topical antimicrobial creams, so that sodium aqueous heparin solution USP from a bovine intestinal mucosa source (heparin) could topically be applied for the first 5–7 days of treatment, and before skin grafting (nonrandomized study).

Contraindications

Patients with liver disease, renal disorders, a blood coagulating diathesis, an allergy to heparin, an active peptic ulcer, a thrombocytopenia, or active or potential bleeding due to trauma were excluded from the study. None of the 100 subjects had a contraindication.

Procedures

The initial evaluation and procedures on admission to the burn unit were the same in all 100 patients. Urgent life-threatening respiratory and/or cardiac emergency were managed first. Vital signs were measured and charted. Intravenous catheters were inserted, blood for laboratory tests was drawn, and intravenous resuscitation fluids were started. Total body surface area and the severity of the burn areas were determined by clinical assessment. No biopsies for histological determination of burn depth were performed. Patients with burns of more than 40 % total body surface area had a urinary catheter inserted to observe and measure urine in the collecting bag. Personal and family medical histories were recorded. A physical examination was carried out. Bathing or cleaning of contaminated or dirty burns was performed if needed, but not routinely. Fluid intake and output volumes were charted and evaluated, as also laboratory tests. The initial routine laboratory tests were urinalysis; complete blood count and platelet count; blood urea nitrogen and creatinine; and bleeding and clotting time, prothrombin time, and partial thromboplastin time. Also, patients received an injection of tetanus toxoid.

Pain Medicine

Pain medication was administered when needed. A parenteral injection of pentozocine and promethazine was used to relieve pain in the first 2–3 days, after which oral nonsteroid anti-inflammatory drugs were used.

Antibiotics

Penicillins were administered orally as the primary antibiotics for all patients, and in some patients, a third-generation cephalosporin, oral cefixime sodium, was added. Amikacin and metrogyl injections were used when indicated. In control group patients, an antimicrobial sulfur-based cream was applied topically after water-with-antimicrobial baths and debridement of necrotic tissue had been performed. In the heparin group, water baths were not routine, and no topical sulfur-based creams were applied, because heparin was being administered topically.

Heparin Administration

About 20.8 ml of 5,000 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 (heparin) [2–6]. Standard intravenous tubing was connected to the bottle and a small gauge (#28 or 30) needle was attached. This 200 IU/ml heparin solution, in an

Fig. 1 Child treated with topical heparin

intravenous set-up, was administered only topically, dripped on the burn surfaces, and inserted into the burn blisters. This heparin was administered topically three or four times on postburn day 1. The total day 1 topically administered dose was 100,000 IU (1 lakh, in India) of heparin per 15 % of burn surface size (i.e., the dose advocated in the heparin-in-burns protocol in use in burns centers in 13 other countries. Burn surfaces were treated with heparin first [7–9]. Approximately 50 % or more of the heparin estimated to be needed on day 1 was initially dripped on the burn surfaces repeatedly in the first 10–15 min of heparin treatment, until the patient reported that the burn pain had relieved and the initial burn erythema, if present, had blanched. Then the burn blisters were treated. A hypodermic needle on a syringe filled with 200 IU/ml heparin was introduced into a blister and a small hole was made, out of which the blister fluid spontaneously drained by gravity [10]. Then heparin was inserted through the needle into the blister. The blister was slowly rinsed with heparin three or four times, and then the needle was withdrawn, leaving a residual volume of heparin within the blister.

The blister cover was permitted to settle onto the blister's inner surface. Blisters were not debrided or removed. After the initial treatment of blisters, the burn surfaces were then retreated with heparin at 5- to 10-minute intervals for half an hour. On day 1 the burn surfaces were retreated two or three more times using the remaining amount of the day 1 dose. In the first 24–36 h, the few blisters that refilled with burn fluid

Fig. 3 Child treated with topical heparin

were retreated a second and rarely a third time with less heparin solution. On postburn days 2–7, heparin in diminishing doses was dripped on the surface of the burns three or four times a day. During this time no surgery was performed. After day 1 or 2, revascularization of ischaemic areas and the development of granulation tissue were observed, and these signs of healing were utilized to monitor the dose of topically administered heparin [11]. Blood clotting times were also taken to monitor heparin doses. Thus, the clinical signs and laboratory values that were used to determine and monitor the dose and adequacy of heparin applied topically were relief of burn pain, blanching of burn erythema, reduced swelling and edema, decreasing burn size, drier burns, revascularization, progressive healing, and blood clotting times in the normal range and up to three times normal (see section “Discussion”).

The total amount of heparin administered to each patient varied because the nature of the burns and the condition of each patient varied. Between heparin applications, heparin patients were treated with dressings soaked with physiological normal saline. All control group patients were treated with topical applications of a sulfur-based antimicrobial cream. No sulfur-based cream was used in heparin group patients.

Serial photographs of the patients were taken (Figs. 1, 2, 3 and 4).

Fig. 2 Child treated with topical heparin

Fig. 4 Control patient without topical heparin

Table 1 Distribution of patients by age

Age distribution (yr)	Control group No. (%)	Heparin group No. (%) NS or S
<5 years	18 (36)	22 (44) NS
6–15	32 (64)	28 (56) NS

Statistical Evaluation

The study data were statistically analyzed to evaluate the differences between the control group and the heparin group. Student's *t*-test and the chi-square test derived in Epi Info-6 software were used. Values of $P \leq 0.05$ were considered to be statistically significant (S, statistically significant; NS, statistically not significant)

Results

The number of patients was the same in the control and heparin groups. Ages were not significantly different. Scalds and fire mode burns were accidental (Tables 1, 2, 3, and 4)

All 100 patients had burn pain, which was relieved by pain medicine in both control and heparin groups. Pain medicine was administered once or at most twice a day to all heparin group patients and to 30 % of control group patients. About 70 % of the control group patients and essentially no heparin group patients received pain medicine as often as three to four times a day (P not calculable) [12, 13]. In heparin group patients, the burn surface pain was relieved within 10–15 min by topical application of heparin (see section “Discussion”). In the heparin group, children stopped crying immediately after treatment. In the heparin group, patient's recurrent less intense burn surface pain was similarly relieved by another topical application of a smaller quantity of heparin solution. Burn erythema, when present, was blanched by heparin. Heparin group patients had less tissue swelling than control group patients.

All 50 control and 50 heparin group patients had superficial and deep second-degree burns in less than 50 % total body surface area (range 5–45 %).

Table 2 Distribution of patients by percentage of burns ($p < 0.01$)

Percentage of burns	Control group No. (%)	Heparin group No. (%) NS or S
5–15	9 (18)	10 (20) NS
16–25	14 (28)	15 (30) NS
26–35	14 (28)	16 (32) NS
36–50	13 (26)	09 (18) NS

Table 3 Distribution of patients by severity of burns ($p < 0.08$ NS)

Degree of burns	Control group No. (%)	Heparin group No. (%) NS or S
Superficial second	30 (60)	35 (70) NS
Deep second	20 (40)	15 (30) NS

The interval between the burn injury event and the patient's arrival at the burn unit and commencement of treatment ranged from 1 to 8 h. Twenty-eight heparin group patients (56 %) presented 5–8 h postburn, compared with 7 control group patients (14 %) ($P < 0.0001$, S). Although the time of presentation was longer or delayed in the heparin compared with the control group, mortality was lower in the heparin group than in the control group. Five control group patients died (mortality rate 10 %). No heparin group patient died.

Hospitalization period was significantly greater in the control group than in the heparin group. Twenty-nine patients (58 %) in the heparin group were discharged from hospital in 10 days or less compared with 3 patients (6 %) in the control group ($P < 0.0001$, S) [12]. Forty-one of 50 heparin group patients (82 %) were discharged in less than 3 weeks compared with 7 control group patients (14 %) ($P < 0.0001$, S). Forty-eight of 50 heparin group patients (96 %) were out of hospital in 30 days, versus 12 patients (24 %) in the control group in the same period ($P < 0.0001$, S). When all 50 heparin group patients were out of hospital, in 40 days, fewer than half the control group patients (22, or 44 %) had been discharged ($P < 0.0001$, S). The remaining 56 % of control group patients required variable additional 10 days to be discharged, with a noncalculable P value, because no heparin group patients remained in hospital.

The overall mortality of 100 consecutive randomly selected patients in this study was a relatively low, 5 % compared with previous years. The five deaths in 50 patients were reported in the control group (10 %). It is notable that all five control group deaths were with the 35–45 % total body surface area size (see section “Discussion”). None of heparin group patients died, meaning that P and S values were not calculable.

Table 4 Cost of treatment ($p < 0.04$)

Type of treatment	Average cost of treatment per patient (rupees) Control	Cost benefit less (%) Heparin	
IV fluids	34.80	18.80	46 ($p < 0.04$ S)
Analgesics, antibiotics, others	1720	540	69 ($p < 0.04$ S)

Patients at Indira Gandhi Government General Hospital and Postgraduate Institute, including our burn unit, receive totally free treatment. In this study the average cost to the hospital for IV fluids, analgesics, antibiotics, and other items for the control group patients was [COMP: Rupee symbol]Rs1,754.8, significantly more than the average cost of Rs558.8 for heparin group patients, with a 68.2 % cost benefit ($P<0.05$, S) (Table 4). The total amount of heparin (in lakh) administered and the average cost (in rupees) of the heparin used in treating heparin group patients increased progressively with the increase in total body surface area. An amount of 1 lakh is equivalent to 100,000 IU of heparin.

None of the control or heparin group patients had a bleeding problem. Except for mortality, there were no other serious complications. Topical use of heparin was safe in this study.

Discussion

Heparin administered topically for a limited time in these burn patients clearly improved treatment. This ethics-committee-approved study was conducted in a uniformly controlled manner without any bias in the initial selection of patients and without any deviation in performance. The duration of the study was 6 months. The same physicians, nurses, and ancillary staff treated all the control and heparin group patients in the same burn unit, using the same facilities. During the test period, 226 patients were admitted to the unit. Subjects in the study were the first 100 consecutively admitted burn patients, out of 226 patients, who had the same parameters and characteristics as regards age (<15 years) and presentation of scald or fire mode burns in less than 50 % total body surface area, as in the previous 3 years 60 % of burn mortality occurred in this age group; second-degree superficial and deep burns were chosen as the degree of severity because historically survival rates were higher in this group [14–16]. The 100 patients with these parameters were prospectively randomized without bias into two similar 50-patient cohorts, the control group and a test-variable group, the heparin group.

There were benefits to physicians, nurses, and ancillary therapists with heparin use. The benefits of relieved pain, along with the fewer water baths and dressings and the nonuse of hard-to-manage antibiotic topical cream, rendered the treatment of heparin group patients easier and more pleasant than that of control group patients for these therapists. Also, the burn unit environment was notably quieter, calmer, and more pleasant.

With heparin, the burn blisters, which were not removed and rarely became infected, functioned as natural skin grafts that required no further care [17, 18]. Smooth new skin was

evident beneath the dried thin blister when it flaked off, usually in 7–14 days [19].

Clinically, without determination of quantity, there was a reduction in burn surface infections in the heparin group patients compared with the control group. One explanation may be that orally administered antibiotics were able to reach the burns from within the body via the increase in blood flow mediated by the enhanced neoangiogenic revascularization of the ischemic burns [20, 21], which was consistently evident in heparin group patients, and at earlier times in the heparin group than in the control group, as also reported in previous studies.

Conclusions

Clearly, in similarly treated equal numbers of statistically similar children patients with similar burns, the addition of heparin administered only topically in the initial week significantly reduced the amount of IV fluids ($P<0.04$), days in hospital ($P<0.0001$), and the time before healing ($P<0.0006$). Equally clearly, patients treated with heparin suffered less pain and required less pain medicine and fewer antibiotics, dressings, and procedures; costs were also lower than in the control cohorts. The lower mortality and the fewer grafts in heparin-treated patients than in non-heparin-treated patients observed in this study were not clearly found to be heparin-related. Further studies are planned.

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