Original Article

COMPARATIVE STUDY OF CONVENTIONAL AND TOPICAL HEPARIN TREATMENTS FOR BURNS ANALGESIA

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ABSTRACT

Objective. This prospective, randomized, open-label study controlled by active comparator aimed at assessing analgesic efficacy and overall tolerability of a burn treatment based on topic administration of unfractionated heparin.

Methods. Fifty eight male or female patients were randomly selected for conventional treatment (C group) or topical heparin treatment (TH group). Ages of patients enrolled ranged from 18 to 55 years. They had 2nd and 3rd degree burns on 10% to 30% of the body surface (BS) caused by fire or scald, no history of hemorrhagic diatheses, no hypersensitivity to heparin and less than 10% of the BS burned to 3rd degree. C group had frequent balneotherapy for injuries debridement and received silver sulfadiazine dressings. TH group had the first debridement and their burnt areas were left exposed to receive 4200 IU of unfractionated heparin topically for each 1% of burned BS, three times daily. Analgesic efficacy was evaluated in the 38 patients who completed the study according to the demand of analgesic medications and response to the pain Visual Analog Scale (VAS). Tolerability was evaluated from the files of all 58 randomized patients by the comparative incidence of adverse reactions.

Results. The TH group demanded less analgesic medications (11.83 ± 9.38 per patient against 33.35 ± 20.63 for the group C, $p<0.01$), reported less pain in the VAS, had less fever and more bleeding than C group. There was no difference in the incidence of local infection, septicemia and safety exams.

Conclusion. The TH scheme presented higher analgesic effectiveness than C scheme without important tolerability problems.

Key words: Burns. Heparin. Analgesia.

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Introduction

Current treatment for 2nd and 3rd degree burns is complex, uncomfortable for the patient and expensive for the health systems[1, 2, 3]. In Brazil, the overall mortality due to burns is estimated in 5% to 8.4%[4, 5] but can be as high as 55% for burns in more than 30% of body surface[6]. The burn sequels affect life quality and produce longstanding emotional and social impacts in the patients. The development of new treatment resources could modify this picture.

Heparin has been used to treat burns for decades[7], but due to the lack of well controlled clinical trials this indication is little disseminated. Its action on the burn probably derives from its anti-inflammatory and angiogenic properties that do not depend on its´ well-known anticoagulant action[8, 9]. The anti-inflammatory action results from deactivation of pro-inflammatory cytokines such as TNF-alpha[10], selectins secreted by leukocytes such as CD11b[11,12] integrins such as ICAM-1[13] and attenuation of complement activation[14]. Angiogenic effect derives from the interaction with vascular endothelium growth factor (VEGF)[15, 16] and with fibroblasts' growth factors (FGFs)[17, 18].

Animals submitted to experimental thermal burns and treated with heparin had a faster resolution of their wounds[19, 20]. Various unpublished clinical studies conducted with heparin in burns were presented in medical symposiums and congresses and are accessible only as abstracts[21]. Altogether, around 230 patients with 2nd and 3rd degree burns covering between 15% and 80% of body surface have been treated with heparin either topic, systemic, or both. These studies indicate that heparin offers a good treatment system for burns, in which wounds are left exposed, diminishing the need for balneotherapy, surgical

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debridement, and dressing changes.

This study was aimed at confirming this information in the context of a clinical trial with standardized methodology and in conformity with good clinical practices. Two treatment systems for burns were compared for their analgesic effects and tolerability: the conventional and the based on topical heparin..

Casuistic

Fifty-eight male and female patients with ages from 18 to 55 years were enrolled. They were victims of 2nd degree burns in 10%-30% of the body surface caused by fire or scald and seen in up to 48 hours after the accident. Exclusion criteria were: 3rd degree burns in area superior to 10% of body surface, chemical or electrical burns, presence of associated lesions that enhanced morbidity, personal or family background of hemorrhagic diatheses or heparin intolerance, active bleeding, skin alterations prior to burn, gestation, safety exams at inclusion: TTPA, creatinin, Na, K and SGOT values outside normality range; hemoglobin < 10 mg/dl, platelets $< 150{,}000$/ml and glycated hemoglobin > 8.5 %.

Efficacy analysis was based on data of 38 patients who concluded the study and fulfilled all the procedures specified in the protocol (per protocol population). Tolerability analysis was based on data of all the 58 randomized patients (intend to treat population).

Methods

This study was conducted in three centers specialized in burns treatment in Brazil, in conformity with all applicable ethical regulations. The eligible patients were submitted to wound cleaning and dead tissues removal under analgesia, sedation, or anesthesia, and anti-tetanus inoculation.

After signing the Informed Consent, the patients received a number indicating their inclusion order in the Center. Each number corresponded to a randomization group previously established by a raffle. This raffle was done in blocks of four patients, assuring that among patients' numbers 1 to 4, two would be located to conventional treatment and two to topical heparin treatment. The same applied to patients 5 to 8 and so on.

Patients randomized to conventional treatment (C group) received balneotherapy and silver sulfadiazine dressings changed under analgesia within a periodicity established by each center as authorized by the protocol.

Patients randomized to topical heparin (TH group) had their wounds left exposed and received 4,200 UI of heparin for each 1% of affected body surface three times daily until the crusts appeared. The study used a spray with 10,000 UI of unfractionated heparin per mL. Each spray releases 0.14 mL of the product, corresponding to 1,400 UI of heparin.

The patients of the TH group were not submitted to balneotherapy, but received daily hygiene care in bed. After a few days, some patients in this group started taking hygienic showers with minimum assistance with no need for special analgesia.

All patients received analgesia promptly administered by demand to all patients enrolled generally made by morphine (0.05 mg/kg) associated to dipyrone (7 mg/kg) intravenously; 750 mg of paracetamol was given orally in case of fever without pain and 5,000 UI of heparin was given subcutaneously two times daily during the hospitalization period for thromboembolism prophylaxis.

Other medications, hemoderivatives and procedures were provided to all patients whenever needed. All patients were monitored for laboratory alterations more frequently associated to the use of heparin: TTPA increase, thrombocytopenia, hepatotoxicity, and hypercalcemia.

The primary endpoint was heparin's analgesic efficacy evaluated in the per protocol population by the analgesics´ demand and response to the pain Visual Analog Scale[22,23].The analgesics´ demand corresponded to the number of solicitations made by the patient in each hospitalization day. Paracetamol used for fever only was not included in this tabulation. VAS was applied in the morning, after bed hygiene, at night and immediately before each administration of the analgesics demanded.

The secondary endpoint was heparin tolerability evaluated in all the patients randomized (intend to treat population). The incidence of adverse events and the evolution of safety exams were compared.

Results

The TH group demanded fewer analgesics than C group in all hospitalization days. This difference was statistically significant in most days and in the sum of the solicitations of each patient during the hospitalization time (Table 1).

The VAS response was assessed based on the daily average of responses given by each patient (three routine measurements and occasional measurements before analgesics administration). The TH group presented lower values than C group in all hospitalization days. This difference was statistically significant in several treatment days (Table 2). Analysis of VAS responses given only in the morning, at night or after hygiene did not provide different information than that shown by daily average. VAS answered at the time of analgesics solicitation showed values generally between four and six and also did not differ between the groups.

The adverse events incidence was similar in the two groups. In TH group 26 patients presented at least one adverse event (81.3% of 32 patients) against 21 patients in C Group (80.8% of 26 patients) (Chi square $p=0.7716$; not significant).

Table 3 shows that the TH group presented less fever and more bleeding than the C group. The groups did not differ in TTPA evolution, platelets counting, SGOT and K (except for K in the sixth hospitalization day). There was also no difference in hemoderivatives consumption between the two groups.

When administered to the 2nd degree burnt areas, heparin led to the appearance of small bleeding spots associated to exudates of serum-hematic appearance. From the second hospitalization day on, the patients in group TH evolved with thick crusts of serum-hematic appearance on the burnt area. The crusts came out spontaneously between the seventh and tenth days. Although this was not objectively tabulated, the authors' subjective impression is that the quality of the restored skin was not worse and may have been even better in TH group than in C group.

In two situations there was need of special medical intervention for crusts' rupture: when they presented fluctuation, for secretions drainage and when they were formed over articular surfaces, because they reduced the patient's mobility and broke

Table 1. Daily demands for rescue analgesics

Day	Heparin	Conventional	MW
1	1.39 ± 1.24 (18)	2.75 ± 1.12 (20)	p<0.01
2	0.78 ± 1.06 (18)	2.50 ± 1.39 (20)	p<0.01
3	1.28 ± 1.41 (18)	2.60 ± 1.46 (20)	p<0.01
4	1.00 ± 1.37 (18)	1.80 ± 1.11 (20)	p<0.05
5	1.17 ± 1.34 (18)	2.45 ± 2.32 (20)	p<0.01
6	0.83 ± 0.92 (18)	1.75 ± 1.07 (20)	p<0.05
7	0.78 ± 0.73 (18)	1.65 ± 1.18 (20)	p<0.05
8	0.89 ± 0.96 (18)	2.00 ± 1.62 (20)	p<0.05
9	0.67± 0.91 (18)	2.00 ± 1.41 (19)	p<0.01
10	0.63 ± 0.81 (16)	2.00 ± 1.37 (18)	p<0.01
11	0.67 ± 0.90 (15)	1.44 ± 1.25 (18)	ns
12	0.36 ± 0.63 (14)	2.31 ± 1.96 (16)	p<0.01
13	0.23 ± 0.60 (13)	1.94 ± 1.84 (16)	p<0.01
14	0.25 ± 0.45 (12)	1.60 ± 1.50 (15)	p<0.05
15	0.42 ± 0.90 (12)	1.78 ± 1.48 (14)	p<0.05
16	0.50 ± 0.76 (08)	1.54 ± 1.61 (13)	ns
17	0.33 ± 0.82 (06)	1.18 ± 1.08 (11)	ns
18	0.20 ± 0.45 (05)	1.22 ± 1.30 (09)	ns
19	0.67 ± 0.58 (03)	1.25 ± 1.89 (04)	ns
20	0.00 ± 0.00 (02)	1.25 ± 0.50 (04)	ns
21	0.00 ± 0.00 (02)	1.00 ± 0.82 (04)	ns
Total	11.83 ± 9.38 (20)	33.35 ± 20.63 (20)	p<0.01

The number of analgesics solicitations occurred each day is expressed in average ± standard deviation (number of patients still in the study). **MW**: statistic significance in Mann-Whitney test. **Total**: average of the sum of each patient's solicitations during confinement. **NS**: no significant statistic difference.

Table 2 Analogic Visual Scale

Day	Heparin	Conventional	MW
1	1.15 ± 1.18 (18)	2.78 ± 1.92 (20)	p<0.01
2	0.99 ± 1.12 (18)	2.05 ± 1.41 (20)	p<0.05
3	1.46 ± 1.68 (18)	2.38 ± 1.36 (20)	ns
4	0.96 ± 1.20 (18)	1.82 ± 1.50 (20)	ns
5	1.48 ± 1.76 (18)	2.35 ± 1.45 (20)	p<0.05
6	0.93 ± 0.98 (18)	1.79 ± 1.23 (20)	p<0.05
7	0.74 ± 0.81 (18)	1.59 ± 1.25 (20)	p<0.05
8	0.73 ± 0.72 (18)	1.83 ± 1.79 (20)	ns
9	1.13 ± 1.31 (18)	1.72 ± 1.57 (19)	ns
10	0.85 ± 0.96 (16)	1.98 ± 1.76 (18)	p<0.05
11	0.80 ± 1.05 (15)	1.57 ± 1.61 (18)	ns
12	0.57 ± 1.10 (14)	1.86 ± 1.80 (16)	p<0.05
13	0.35 ± 0.55 (13)	1.89 ± 1.95 (16)	p<0.01
14	0.38 ± 0.56 (12)	1.42 ± 1.54 (15)	ns
15	0.28 ± 0.70 (12)	1.88 ± 1.64 (14)	p<0.05
16	0.41 ± 0.84 (08)	1.29 ± 1.35 (13)	ns
17	0.28 ± 0.69 (06)	1.29 ± 1.44 (10)	ns
18	0.46 ± 1.03 (05)	1.36 ± 1.37 (09)	ns
19	0.00 ± 0.00 (03)	1.33 ± 1.53 (03)	ns
20	0.00 ± 0.00 (02)	1.50 ± 0.50 (03)	ns
21	0.00 ± 0.00 (02)	1.07 ± 0.12 (03)	ns

The numeric value of pain Analog Visual Scale each day is expressed in average ± standard deviation (number of patients still in the study). These data are calculated counting in the three daily routine responses (morning, shower and night) and the occasional responses obtained at analgesics solicitation of all the patients who were still in the study. **MW**: statistic significance in Mann-Whitney test. **Total**: average of the sum of each patient's solicitations during confinement. **NS**: no significant statistic difference.

slowly, causing pain and bleeding. For this reason, four patients in the TH group discontinued their participation the study.

There was one death in the TH group caused by tentorial hernia: one 39 year-old male patient, victim of a gas bottle explosion that evolved with intracranial hypertension due to cranium-encephalic traumatism. Investigators unanimously concluded that topical heparin neither produced nor contributed to the casualty.

Discussion

This studied followed two groups of patients victims of burns due to fire or scald: one treated conventionally and the other treated with topical heparin. The differences in treatment routines prevented the performance of a double blind study, reason why the researchers chose to conduct an open label study, randomized and controlled by an active comparator.

The TH group presented lower VAS values in all hospitalization days. This difference reached statistic significance in most days and is of great importance due to the difficulty for demonstrating pain reduction in the presence of the effective analgesic scheme administered to all the patients for ethical reasons. Daily analgesics solicitations average was always lower in TH group. This difference was significant in most days and in the average of the each patient's solicitations sum. The association of these two parameters must be considered a clear evidence of the TH scheme's analgesic superiority, for patients in this group reported less pain while consuming less analgesic medication.

There were no important tolerability problems in the TH group in relation to C group. Around 80% of the patients in both groups presented adverse events, which is expected in cases of hospitalized burnt patients.

Individualized tabulations of each event revealed that the TH group presented more bleeding than C group. This is expected due to heparin's anticoagulant action. This occurred only at the site of administration. No bleedings were observed in sites where the medication was not administered.

Bleeding episodes were mild and occurred mainly when heparin was applied to burns associated to other injuries that occurred in the context of polytraumatisms or during the disruption of serum-hematic crusts formed on articular surfaces. Such bleedings were the reason for four patients to discontinuing their participation in the study. With the development of the study and a better comprehension of the TH system's particularities, the crusts formed on articular surfaces were disrupted early by the investigators and bleeding was reduced.

TH group presented less cases of fever than C group, and the incidence of local septicemia infection was equal in both groups. This indicates that TH system did not result in increasing the incidence of local or systemic infections, despite lesions being left uncovered.

Table 3. Frequency of adverse events

Adverse Event	Topical heparin n	%	Conventional n	%	T Fisher
Anemia	0	0%	1	3.8%	ns
Bronchospasms	0	0%	1	3.8%	ns
Coma	1	3.1%	0	0%	ns
Constipation	0	0%	1	3.8%	ns
Local pain	3	9.4%	0	0%	ns
TGP Elevated	3	9.4%	2	7.7%	ns
Fever	2	6.3%	9	34.6%	p<0.01
Photophobia	1	3.1%	0	0%	ns
Hypertention	2	6.3%	3	11.5%	ns
Hematuria	2	6.3%	0	0%	ns
Local infection	15	46.9%	14	53.8%	ns
Plaquetose Thrombocytosis	1	3.1%	1	3.8%	ns
Itching	4	12.5%	2	7.7%	ns
Bleeding	6	18.8%	0	%	p<0.05
Septicemia	9	28.1%	8	30.8%	ns
Vomiting	1	3.1%	0	0%	ns

Number and percentage of patients who presented each adverse event. In the heparin group, 32 patients were included, and in the conventional group, 26. T Fischer statistic significance in Fischer exact test. **ns**: no significant statistic difference.

All patients were monitored for laboratorial alterations more frequently associated to heparin use: TTPA increase, thrombocytopenia, hepatotoxicity, and hypercalcemia. In all these parameters the TH group was no worse than C group. These data allow for the conclusion that the population submitted to TH system did not present alterations resulting from heparin's anticoagulant activity (TTPA), neither alterations in biochemical parameters that could be attributed to the medication's action (K, SGOT, and platelets). It is possible to infer that heparin's systemic action, applied in the conditions of this study, was not clinically relevant.

Conclusion

The system for treating burns based on the topically administrated heparin presented evidence of analgesic superiority in relation to the C system without important tolerability problems, when adequately managed.

There are elements suggesting that TH scheme may be economically advantageous for the health system and more comfortable to the patient if compared to the C scheme. Studies designed specifically for evaluating these outcomes are suggested.

The authors' subjective impression is that the quality of the recently formed skin may have been higher in the TH group than in C group and also suggest studies specifically designed for evaluating this parameter.

Finally, due to characteristics of sprayed topical heparin treatment system (simplicity and comfort), its incorporation to burn treatment centers' routine may be advantageous for the patient and very interesting, in pharmacoeconomical point of view, for the health system.

The number of analgesics solicitations occurred each day is expressed in average ± standard deviation (number of patients still in the study). **MW:** statistic significance in Mann-Whitney test. **Total:** average of the sum of each patient's solicitations during confinement. **NS:** no significant statistic difference.

The numeric value of pain Analog Visual Scale each day is expressed in average ± standard deviation (number of patients still in the study). These data are calculated counting in the three daily routine responses (morning, shower and night) and the occasional responses obtained at analgesics solicitation of all the patients who were still in the study. **MW:** statistic significance in Mann-Whitney test. **Total:** average of the sum of each patient's solicitations during hospitalization. **NS:** no significant statistic difference.

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