https://doi.org/10.31925/farmacia.2022.5.17 **ORIGINAL ARTICLE**

THE EFFICACY OF TOPICAL HEPARIN PREPARATIONS FOR THE MANAGEMENT OF PAIN AND SUPERFICIAL VASCULAR DISORDERS IN ORTHOPAEDIC SURGERY AND MUSCULOSKELETAL TRAUMA

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Abstract

Superficial symptoms (oedema, inflammation, hematoma) following musculoskeletal trauma or orthopaedic interventions are more difficult to resolve when the prescription includes heparin and nonsteroidal anti-inflammatory drugs only for systemic administration. That is why treatment prescription often includes also preparations with heparin for topical administration, available on the market in various concentrations and combinations. The present study aimed to evaluate comparatively and in clinical conditions the efficacy and safety of three topical preparations with heparin: a gel with heparin 1000 IU/g, a gel with heparin 500 IU/g and penetration enhancers (dexpanthenol and allantoin) and a gel with 500 IU/g heparin in combination with diclofenac 10 mg/g and a penetration enhancer (dexpanthenol). The study group consisted of 199 patients treated in the Orthopaedics and Traumatology department for musculoskeletal injuries or with orthopaedic surgeries assigned in 3 groups corresponding to each topical preparation studied. At inclusion and then after 3, 7 and 14 days of treatment, the following parameters were evaluated: spontaneous pain, pain on active movement, pain on passive movement (using a VAS scale 0 - 10), hematoma area (cm^2) and inflamed area (cm^2). The results show that the heparin gel 500 IU/g in combination with diclofenac 10 mg/g and a penetration enhancer (dexpanthenol) was the most effective in relieving the investigated symptoms, since it reported the largest differences in improvement from baseline even after 7 days of treatment. The highest difference from baseline was obtained for hematoma area and for inflamed area. All three topical preparations were well tolerated. The conclusion of the study is that topical administration of the combination of heparin and diclofenac together with penetration enhancers controls better and faster post-traumatic or post-surgical superficial symptoms, and the addition of this type of preparation in the post-traumatic treatment regimen brings a definite benefit for patient.

Rezumat

Simptomele superficiale (edem, inflamație, hematom) consecutive traumatismelor musculoscheletice sau intervențiilor ortopedice se remit mai greu atunci cand prescripția medicală include heparină și antiinflamatoare nesteroidiene doar pentru administrare sistemică. Studiul de față și-a propus să evalueze comparativ și în condiții clinice eficacitatea și siguranța a trei preparate topice cu heparină: un gel cu heparină 1000 UI/g, un gel cu heparină 500 UI/g și promotori de absorbție (dexpantenol și alantoină) și un gel cu heparină 500 UI/g în combinație cu diclofenac 10 mg/g și promotor de absorbție (dexpantenol). Lotul de studiu a fost alcătuit din 199 de pacienți tratați în clinica de Ortopedie și Traumatologie pentru traumatisme musculoscheletice sau cu intervenții chirugicale ortopedice alocați în 3 grupe corespunzătoare fiecărui preparat topic studiat. La includere și apoi după 3, 7 și 14 zile de tratament au fost evaluați următorii parametri: durerea spontană, durerea la mișcare activă, durerea la mișcare pasivă (cu ajutorul unei scale VAS 0 - 10), aria hematomului (cm^2) și aria zonei inflamate (cm^2). Rezultatele au arătat că gelul cu heparină 500 UI/g în combinație cu diclofenac 10 mg/g și promotor de absorbție (dexpantenol) a fost cel mai eficient în ameliorarea simptomelor urmărite, acesta înregistrând diferențele cele mai mari față de inițial începând cu raportarea de la 7 zile. Diferența cea mai mare față de inițial a fost obținută pentru aria hematomului și aria zonei inflamate. Concluzia studiului este aceea că administrarea topică a combinației heparină și diclofenac împreună cu promotori de absorbție controlează mai bine și mai repede simptomele superficiale post-traumatice sau post-chirurgicale, iar adăugarea acestui tip de preparat în schema terapeutică post-traumatică aduce un beneficiu cert pentru pacient.

Keywords: diclofenac, heparin, pain, hematoma, topical

Introduction

Pain, oedema and hematoma are common symptoms during posttraumatic or post-interventional recovery period in orthopaedic. Their pharmacological approach includes systemic analgesics or anti-inflammatory drugs for pain relief and local inflammation control. These symptoms are often associated with the use of low molecular weight heparin for thromboembolic complications prophylaxis, an essential component of trauma treatment in orthopaedic pathology. However, topical heparin preparations are also frequently added because they have shown many

beneficial effects in clinical practice [1-3]. The use of topical heparin is not yet standardized and its efficacy is often questionable because of contradictory reported information related to heparin absorption. Although some authors did not find any significant anticoagulant effect of topical heparin [4], several other papers indicate that heparin penetrates the skin barrier especially if it is aided by penetration enhancers [5]. These contradictory findings can be explained by the fact that topical heparin preparations are marketed in a wide range of heparin concentrations, from 250 IU/g to 1000 IU/g and over, but without differentiating the indications or the administration regimens. Moreover, the efficacy of these preparations was investigated mostly versus placebo, not compared to each other. Only incidental comparison results of different heparin concentrations in topical application were reported, but in very small groups of patients [6]. The aim of this study was to evaluate comparatively the efficacy and safety of three topical preparations with heparin in different concentrations or combination, in addition to the systemic treatment administered post-interventional in the Department of Orthopaedics and Traumatology. To the best of our knowledge, this is the first study that investigates comparatively the efficacy and safety of topical heparin preparations available on the market in clinical terms.

Materials and Methods

Study population

The study was conducted in Department of Orthopaedics and Traumatology from Emergency Clinical Hospital Oradea, Romania, between January 2019 and May 2020. The patients included were selected among the patients admitted for musculoskeletal trauma (contusions, sprains, fractures) or who underwent orthopaedics-traumatology surgery, without interfering in physician's decision for prescription (non-interventional trial). That is why the approval of the ethics commission of the clinic was not necessary. The study group was formed using the following inclusion criteria: patient over 18 years for whom the post-traumatic treatment prescription includes also one of the three topical heparin preparations available in the hospital pharmacy: a sodium heparin 1000 IU/g gel (group L), a sodium heparin 500 UI/g, dexpanthenol 2.5 mg/g, allantoin 2.5 mg/g gel (group H) and a sodium heparin 500 UI/g, sodium diclofenac 10 mg/g gel that contains also dexpanthenol (group A). The patients under 18 years, needing antibiotics or corticosteroids, or the patients with other topical preparation in their prescription were excluded. Thus, a group of 199 patients was formed who were assigned according to the prescription for topical administration in one of the 3 groups.

Evaluation criteria and outcomes

The initial evaluation, before treatment, included the assessment of spontaneous pain, pain on active movement and pain on passive movement using a visual analogue scale from 0 to 10 [7] and the assessment of hematoma area and inflamed/oedematous area by measuring two diameters (cm). Baseline characteristics of the included patients are presented in Table I and Table II.

Table I

Baseline characteristics of the patients included in the three groups

Group	Diagnosis	Sex	Age (mean, range)
Group A (n = 102)	Surgical intervention 56.86% Musculoskeletal trauma (contusion, strain) 43.14%	45.09% M 54.90% F	60.10 (21-94)
Group H (n = 49)	Surgical intervention 63.26 % Musculoskeletal trauma (contusion, strain) 36.73 %	32.65 % M 67.34% F	64.06 (20-81)
Group L (n = 48)	Surgical intervention 58.33 % Musculoskeletal trauma (contusion, strain) 41.66 %	33.33% M 66.66% F	60.25 (22-89)

Table II

Baseline values of the investigated parameters in the three groups (average score ± SD)

Clinical parameters	Group A gel (n = 102)	Group H (n = 49)	Group L (n = 48)	p*
Spontaneous pain (VAS)	6.16 ± 1.39 (range 3 - 10)	7.26 ± 1.68 (range 3-10)	6.33 ± 0.83 (range 5 - 8)	< 0.05, NS
Pain on active movement (VAS)	6.89 ± 1.54 (range 2 - 10)	7.46 ± 1.25 (range 4-10)	7.18 ± 0.78 (range 6 - 9)	= 0.04, NS
Pain on passive movement (VAS)	6.64 ± 1.43 (range 3 - 10)	7.0 ± 1.33 (range 4 ± 10)	6.62 ± 1.00 (range 5 - 9)	= 0.255, NS
Hematoma area (cm^2) (%)	17.59 ± 9.84 (range 7 - 70)	20.65 ± 15.51 (range 5 - 100)	17.27 ± 5.41 (range 5 - 39)	= 0.2, NS
Inflamed area (cm^2) (%)	31.87 ± 13.77 (range 10 - 85)	32.10 ± 28.00 (range 10 - 200)	37.45 ± 10.94 (range 10 - 80)	= 0.18 NS

*p intergroup, NS=statistical non-significance

Treatment efficacy was evaluated following the same parameters in the next visits at 3 days, 7 days and 14 days from the beginning of the treatment. Also adverse effects due to topical treatment were investigated.

Statistical analysis

Descriptive statistics were used for demographic data. ANOVA, z-test three samples for mean were used to compare values between baseline and subsequent visits (intragroup analysis) and between treatment groups at subsequent visits (intergroup analysis) for a confidence interval of 95%.

Results and Discussion

Parameters values recorded in visits from 3, 7 and 14 days are presented in Tables III, IV and V. The evolution of the parameters values from baseline to day 14 is illustrated in Figures 1 - 5.

No adverse effects due to topical treatment applied were reported in any of the three groups.

Orthopaedic surgical or traumatic injuries are often accompanied with impressive superficial symptoms that include vascular disorders (ecchymoses and subdermal hematomas), oedema and pain, as a common result of a physical trauma. Topical applications are frequently used to treat subdermal hematomas and consequent symptoms, and include anti-inflammatory and antioedematous treatments like heparin and/or other mucopolysaccharide gels and creams [8]. The present study confirmed that topical heparin is able to control these superficial symptoms. The 3 days visit results (Table III) were significantly different from baseline in all three groups as result of natural course of healing and of systemic and topical medication.

Table III

Differences from baseline for visit 1 (3 days)

Clinical parameters	Group A (n = 102)	Group H (n = 49)	Group L (n = 48)	p*
Spontaneous pain (VAS) (%)	-15.833	- 15.11	-16.32	= 0.84, NS
Pain on active movement (VAS) (%)	-16.26	-15.20	- 17.58	= 0.45, NS
Pain on passive movement (VAS) (%)	-19.03	-17.70	-17.48	= 0.57, NS
Hematoma area (cm^2) (%)	-19.78	-19.49	-17.09	= 0.44, NS
Inflamed area (cm^2) (%)	-18.482	-18.20	-14.60	= 0.03, S

*p intergroup, NS=statistical non-significance, S=statistical significance

Table IV

Differences from baseline for visit 2 (7 days)

Clinical parameters	Group A (n = 102)	Group H (n = 49)	Group L (n = 48)	p*
Spontaneous pain (VAS) (%)	-46.88	-35.55	-42.71	< 0.05, S
Pain on active movement (VAS) (%)	-44.44	-34.52	-40.09	= 0.45, NS
Pain on passive movement (VAS) (%)	-46.41	-37.74	-43.72	< 0.05, S
Hematoma area (cm^2) (%)	-51.41	-41.26	-40.91	< 0.05, S
Inflamed area (cm^2) (%)	-43.25	-39.72	-35.35	< 0.05, S

*p intergroup, NS=statistical non-significance, S=statistical significance

Table V

Differences from baseline for visit 3 (14 days)

Clinical parameters	Group A (n = 102)	Group H (n = 49)	Group L (n = 48)	p*
Spontaneous pain (VAS) (%)	-79.42	-58.71	-74.73	< 0.05, S
Pain on active movement (VAS) (%)	-72.42	-57.88	-67.32	< 0.05, S
Pain on passive movement (VAS) (%)	-78.11	-60.25	-72.34	< 0.05, S
Hematoma area (cm^2) (%)	-97.24	-66.43	-68.90	< 0.05, S
Inflamed area (cm^2) (%)	-74.95	-66.63	-59.83	< 0.05, S

*p intergroup, S=statistical significance

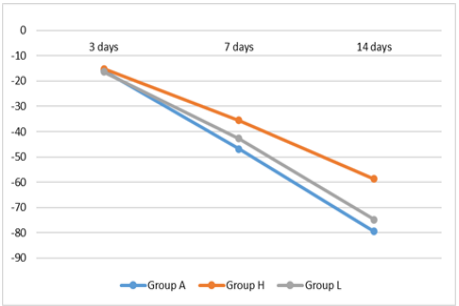

Figure 1.
Differences from baseline for spontaneous pain

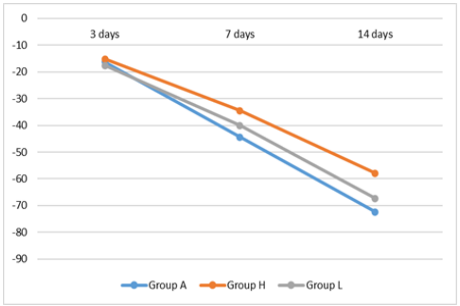

Figure 2.
Differences from baseline for active movement

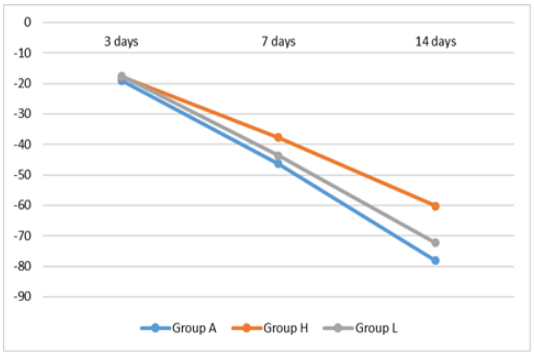

Figure 3.
Differences from baseline for passive movement

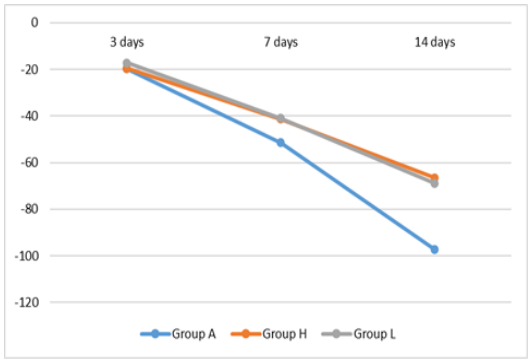

Figure 4.
Difference from baseline for superficial hematoma area

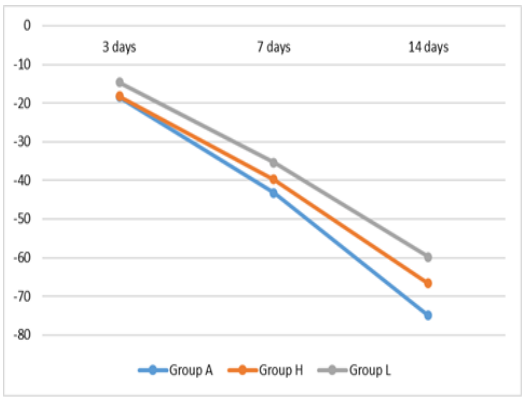

Figure 5.
Difference from baseline for inflammation/oedema area

At this point the results between the three groups were not significantly different and it was not expected to be otherwise since it is too early from the trauma/intervention. But the results from 7 days visit (Table IV) is significantly different from the previous visit. Systemic medication is still acting as in the first days, but in group A the differences from baseline are significantly higher than in other two groups. The same trend is even more evident in day 14 visit results (Table V) when the difference from baseline in group A are the highest among the three groups. This confirms from medical practice that topical heparin aided by penetration enhancers (dexpanthenol) and combined with diclofenac for an improved anti-inflammatory effect (group A) brings faster and better results in pain control and superficial vascular disorders symptoms than the same concentration of heparin only with penetration enhancers (Group H) and double concentration of heparin with no penetration enhancers and without diclofenac (group L). The analysis of each parameter's evolution explains this conclusion even better: even if group A results were better across all parameters at the end of the investigated period, the best results were reported for hematoma area (Figure 4) and inflammation/oedema area (Figure 5) where the differences from baseline were the highest. These results provide further evidence that in group A heparin local action is enhanced. For pain parameters the results were still better in group A (Figures 1, 2 and 3) *versus* group L and group H, but not as significant as in hematoma and inflammation area (Figures 4 and 5). This different evolution can be explained by the depth and the magnitude of the injuries in Orthopedic and Traumatology clinic and by the fact that topical heparin induces mostly local superficial effects because topical heparin cannot follow diclofenac in systemic flow in clinically significant concentrations in order to induce intense and profound anti-inflammatory effect [4]. The present results are in line with previous reports showing that, even if it was demonstrated that topical heparin is not able to modify coagulation parameters [9, 10], yet topical heparin demonstrated positive local microcirculation changes as increased capillary venous oxygen saturation, increased blood filing of microvessels, increased blood flow and velocity [11, 12] and enhanced fibrinolytic effect [13]. The reported effects were more prominent when topical heparin was aided by dexpanthenol as penetration enhancer [12, 14].

However, the overall results from the present study confirm also the enhanced efficacy of topical heparin combined with an anti-inflammatory agent for the treatment of local trauma injuries versus topical heparin alone, as it was already signalled. *Balasubramanian et al* reported previously the superior efficacy of topical heparin-diclofenac combination *versus* each individual component treatment in local injury models on laboratory animal, using paw oedema method in rats and formalin induced paw licking method on mice [15]. Heparin-diclofenac topical combination proved to be more efficient than diclofenac alone also in clinical conditions in the treatment of ankle sprain in adults [16]. Other reports mentioned heparin-diclofenac topical combination efficacy on acute blunt and soft tissue injuries [17] or heparin and other anti-inflammatory agent (diethylammonium salicylate) topical combination efficacy on acute blunt impact

injuries [18]. The present results support also the consistent previous reports on heparin topical use in wound healing [19], but is the first signal of topical heparin efficacy after surgical injuries. The safety was evaluated as very good since no adverse effect due to topical medication was reported even if all the investigated gels were used on injured skin area.

Conclusions

Heparin-diclofenac topical combination with penetration enhancers is more effective than topical heparin with penetration enhancers or topical heparin alone in controlling superficial vascular disorders and pain from orthopaedic trauma or surgical intervention. Multi-component composition with a lower dose of heparin brings more advantages in term of efficacy than a higher dose of heparin alone. This combination brings a real benefit even if it is administered along with systemic low molecular weight heparin and non-steroidal anti-inflammatories.

Conflict of interest

The authors declare no conflict of interest.

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