ORIGINAL ARTICLE

Escin/diethylammonium salicylate/heparin combination gels for the topical treatment of acute impact injuries: a randomised, double blind, placebo controlled, multicentre study

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Objectives: To investigate the clinical efficacy and safety of escin-containing gels in the topical treatment of blunt impact injuries.

Methods: Competitors in soccer, handball, or karate competitions were enrolled within two hours of sustaining a strain, sprain, or contusion and treated three times with the trial gel within a period of eight hours. Patients were randomised to three parallel groups consisting of two active treatment gels, containing escin (1% or 2%), 5% diethylammonium salicylate, and 5000 IU heparin, or placebo gel. Tenderness produced by pressure was measured at 0 (baseline), 1, 2, 3, 4, 6, and 24 hours after enrolment (within two hours of the injury). Tenderness was defined as the amount of pressure (measured by a calibrated caliper at the centre of the injury) that first produced a pain reaction as reported by the patient.

Results: A total of 158 patients were enrolled; 156 were evaluated in the intention to treat analysis. The primary efficacy variable was the area under the curve for tenderness over a six hour period. The gel preparations containing 1% and 2% escin were significantly more effective (a priori ordered hypotheses testing controlling the multiple $\alpha = 5\%$ significance level) than placebo ($p_1 = 0.0001$ and $p_2 = 0.0002$ respectively). The treatment effects were 5.7 kp h/cm² (95% confidence interval (CI) 2.9 to 8.5) and 5.9 kilopond (kp) h/cm² (95% CI 2.9 to 8.8) between 1% escin and placebo and between 2% escin and placebo respectively. These results were supported by secondary efficacy variables. The time to reach the baseline contralateral tenderness value (resolution of pain) at the injured site was shorter in the treatment groups than in the placebo group ($p < 0.0001$). Both active gel preparations produced more rapid pain relief than the placebo gel. No relevant differences were detected between the two active gels. The safety and tolerability of the escin-containing gels were excellent.

Conclusions: Escin/diethylammonium salicylate/heparin combination gel preparations are effective and safe for the treatment of blunt impact injuries.

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Sports injuries require rapid and optimal treatment. The classical primary treatment with cold compresses is often supported by topical application of a variety of anti-inflammatory and antioedematous drug combinations.

An effective topical treatment should relieve acute pain and reduce swelling in the injured area to restore normal movement. Moreover, it should be safe, well tolerated, easy to use, and accessible.

Often all these requirements cannot be satisfactorily met by a single active principle. Therefore combinations of substances with different modes of action are widely used. However, the clinical efficacy of topical gel preparations has not been satisfactorily demonstrated in randomised, placebo controlled, clinical trials.¹

The gel preparations investigated in this trial contained the active ingredients escin (1% and 2%), 5% diethylammonium salicylate (DEAS), and 5000 IU heparin. For simplicity, these two active treatment groups will be referred to as "escin 1%" and "escin 2%".

Escin is a triterpene glucoside isolated from the seeds of the horse chestnut (*Aesculus hippocastanum*). It probably acts by inhibiting exudation and oedema and increasing vascular permeability.²⁻³ Shear stress to the endothelium (such as a traumatic injury) results in activation of phospholipase A₂, which releases precursors of inflammatory mediators⁴ leading to adherence of neutrophils to the site.⁵ Escin inhibits the increase in phospholipase A₂ activity in hypoxic endothelial cells⁶ as well

as the adherence of leucocytes to hypoxic endothelium.^{6,7} The clinical efficacy, safety, and tolerability of different escin preparations (Reparil Gel N, Reparil Gel, Reparil Sportgel; Madaus Cologne, Germany) have been shown in placebo and active controlled, randomised, clinical trials.⁸⁻¹⁴ DEAS is a salt of salicylic acid and diethylamine. Like other well known salicylic acid derivatives, it exerts an anti-inflammatory and analgesic effect in several experimental models and reaches relevant concentrations in the muscles after topical administration.¹⁵ The safety and tolerability of DEAS have been shown in toxicological¹⁶ and clinical¹² experiments. The superior effectiveness of the combination escin/DEAS over escin or DEAS alone has been shown in patients with blunt impact injuries in a double blind, randomised, controlled, clinical trial.¹² The low concentrations of heparin used in the preparations tested may have an anticoagulant effect in the traumatised area and improve local microcirculation.¹⁷ A clinical investigation in 60 patients with four treatment groups (escin, heparin sodium, DEAS, and a combination of all three) supports the rationale of the combination used in this trial.¹⁸ The gel combination of the three active substances had good effects on tenderness reaction,

Abbreviations: DEAS, diethylammonium salicylate; AUC, area under the curve; ITT, intention to treat; PP, per protocol; kp, kilopond (1 kp = 9.80665 N)

Table 1 Basic characteristics of the patients and baseline data (intention to treat)

	Escin 1% (n=54)	Escin 2% (n=51)	Placebo (n=51)
Sex			
Male, n (%)	37 (68.5)	34 (66.7)	41 (80.4)
Female, n (%)	17 (31.5)	17 (33.3)	10 (19.6)
Age (years)			
Mean (median)	29.2 (27)	31.3 (30)	30.7 (29)
SD	10.10	9.92	9.07
Q1; Q3	22; 33	24; 35	24; 37
Height (cm)			
Mean (median)	175.9 (175.5)	176.6 (176)	178.8 (179)
SD	10.27	10.45	8.21
Q1; Q3	169; 182	170; 185	173; 185
Weight (kg)			
Mean (median)	71.8 (72)	73.7 (73)	77.5 (77)
SD	12.30	13.97	10.45
Q1; Q3	63; 82	65; 83	72; 84
Tenderness injured area (kp/cm ²)			
Mean (median)	2.1 (1.9)	2.0 (1.9)	2.0 (1.7)
SD	1.12	1.00	0.93
Q1; Q3	1.4; 2.6	1.3; 2.7	1.4; 2.6
Tenderness contralateral area (kp/cm ²)			
Mean (median)	4.7 (4.7)	4.9 (5.0)	4.5 (4.3)
SD	1.45	1.65	1.48
Q1; Q3	3.5; 5.7	3.6; 6.0	3.6; 5.4
Ratio of tenderness values* (%)			
Mean (median)	44.3 (44.4)	40.2 (39.7)	43.5 (45.3)
SD	13.80	14.09	12.60
Q1; Q3	34.0; 53.3	28.3; 51.3	33.3; 51.5
VAS (cm)			
Mean (median)	2.8 (2.6)	3.3 (2.7)	3.3 (3.2)
SD	1.86	2.63	2.11
Q1; Q3	1.4; 4.1	0.9; 5.1	1.3; 4.9
Sprains†			
n (%)	4 (7.4)	7 (13.7)	7 (13.7)
Strains†			
n (%)	15 (27.8)	15 (29.4)	9 (17.6)
Contusions†			
n (%)	36 (66.7)	30 (58.8)	36 (70.6)

*Injured/contralateral; †multiple citations possible.
SD, Standard deviation; Q1, lower quartile; Q3, upper quartile.

oedema formation, and joint function, and to a lesser extent on spontaneous pain compared with each substance alone. However, the patients were enrolled in the trial according to their chronological visits to the casualty department without any random allocation.

The objective of this trial, using a double blind, randomised, controlled, group comparative design, was to determine the efficacy and safety of escin combination gels versus placebo in the treatment of acute sports impact injuries.

METHODS

The study was carried out in Germany as a randomised, placebo controlled, double blind, multicentre, phase III clinical trial with three parallel treatments in adult male or female patients. The first patient was enrolled in October 1997 after approval for the study had been obtained from an independent ethics committee, and the study was completed in February 1998. All patients had given their informed consent before enrolment. The study was performed in accordance with the Declaration of Helsinki (current version) and its amendments taking into account the recent version of the German Drug Law (AMG) and the principles of Good Clinical Practice (GCP). On inclusion in the study, each patient was assigned in chronological order to one of the treatment groups using a computer generated block randomisation list (allocation proportions 1:1:1, block size $k = 15$).

According to the trial protocol, patients aged between 18 and 60 years suffering from fresh sports impact injuries (sprains, sprains, and contusions) were enrolled. The injuries occurred during soccer, karate, or handball competitions. One of the investigators was present at these events and could

therefore recruit the patients on the spot. The time between injury and treatment had to be less than two hours. The tenderness reaction of the contralateral uninjured site had to be more than 150% of the value of the injured area. Pregnant women were excluded, as well as patients who had known allergies to escin, salicylates, heparin, or excipients of the gel. In addition, patients with skin disorders or open wounds in the area to be treated, injuries of the eye or mucosa, or injuries requiring admittance to hospital were excluded. Patients were instructed not to use any other preparations or dressings to treat the trauma. In particular, use of non-steroidal anti-inflammatory drugs, analgesics, or psychotropic agents was not allowed. Patients who had consumed more alcohol than usual on the evening before enrolment were excluded. Cooling of the wound before treatment was permitted.

The three gel preparations were indistinguishable in size, colour, weight, and odour, and none produced a burning sensation on intact skin. Additional ingredients in the three preparations were aqua purificata, buffer, lavender and neroli oil, carbopol, ethanol, and isopropanol. In the placebo preparation, the active substances escin, DEAS, and heparin were replaced by "filling" material, which made the preparations indistinguishable from each other. The drugs being studied were placed in white coloured aluminium tubes with a label according to German Drug Law. They were packaged according to the randomisation list, which was not known to the investigators and the study personnel.

The history of the injury was recorded, and a questionnaire designed to elicit the medical history, including concomitant diseases and drug history, was filled out. The tenderness reaction at the injury and contralateral sites was measured with a tonometer, and the intensity of the spontaneous pain

Table 2 Tenderness values (kp/cm²) and area under the curve (AUC) over six hours (kp h/cm²) (intention to treat)

Time (hours)		Escin 1% (n=54)	Escin 2% (n=51)	Placebo (n=51)
0	Mean (median)	2.1 (1.9)	2.0 (1.9)	2.0 (1.7)
	SD	1.12	1.00	0.93
	Q1; Q3	1.4; 2.6	1.3; 2.7	1.4; 2.6
1	Mean (median)	3.0 (2.8)	3.0 (2.9)	2.5 (2.2)
	SD	1.25	1.31	1.12
	Q1; Q3	2.1; 3.7	2.0; 4.0	1.8; 3.0
2		n=53	n=49	n=49
	Mean (median)	3.9 (3.9)	3.7 (3.6)	2.8 (2.5)
	SD	1.30	1.32	1.17
3		n=53	n=49	
	Mean (median)	4.2 (3.9)	4.2 (4.0)	3.0 (2.6)
	SD	1.38	1.55	1.24
4		n=53	n=50	
	Mean (median)	4.3 (4.0)	4.3 (4.2)	3.1 (2.9)
	SD	1.41	1.54	1.31
6		n=53		n=50
	Mean (median)	4.4 (4.1)	4.5 (4.5)	3.3 (3.0)
	SD	1.50	1.53	1.30
24		n=52	n=50	n=50
	Mean (median)	4.4 (4.2)	4.7 (4.7)	3.6 (3.5)
	SD	1.40	1.55	1.31
AUC over 6 h	Mean (median)	22.9 (21.9)	23.1 (22.8)	17.2 (15.8)
	SD	7.64	8.15	6.91
	Q1; Q3	18.1; 27.7	17.8; 29.0	12.1; 20.3
AUC over 24 h	Mean (median)	102.6 (95.7)	105.1 (105.0)	79.0 (72.0)
	SD	33.39	35.76	30.02
	Q1; Q3	77.5; 127.6	80.8; 128.5	58.7; 95.9
Confirmatory test results (a priori ordered hypotheses) for the AUC over 6 h				
Priority	Comparison	p Value	Mean treatment effect (kp h/cm ²)	95% confidence interval (kp h/cm ²)
1st	Escin 1% v placebo	0.0001	+5.70	+2.88 to +8.52
2nd	Escin 2% v placebo	0.0002	+5.86	+2.89 to +8.83
3rd	Escin 1% v 2%	0.9186	-0.16	-3.22 to +2.90

recorded. About 5 g (walnut size) of gel was applied by the investigator about five minutes after the first measurement of tenderness. Further gel was given to the patient for self application at four and eight hours after enrolment.

Tonometric measurements were performed using a calibrated caliper (Amitec Europe, Wuppertal, Germany; range 0–100 N; surface 1 cm²; with digital pressure recording). Increases in pressure during measurement were kept constant at 10 N/cm²/s. The site of measurement was marked with a water resistant marker, and measurements were repeated at the same site. The measurements were performed in such a way that the patient could not read the actual pressure exerted. A tenderness reaction was defined as the pressure that, under the above conditions, produced a painful sensation. Spontaneous pain sensation was recorded using a 10 cm visual analogue scale.¹⁹ For every evaluation point, a new scale was used and the patient was not able to compare it with the former one.

The primary efficacy variable was the area under the curve (AUC), where the ordinate was the pressure that produced the first tenderness reaction, and the abscissa was the time after treatment (restricted to the first six hours after the first treatment).

Secondary efficacy variables were the AUC of the tenderness values over the whole study period (24 hours), the extent of spontaneous pain on a 10 cm visual analogue scale, the swelling of the injured area measured (if possible) by a calibrated tape, the time taken to reach the contralateral (healthy) baseline value of tenderness (time to resolution of pain), and a global efficacy assessment by the patients and investigators using a four point score (excellent, good, moderate, and poor).

Safety was evaluated on the basis of adverse events. In addition, patients and investigators assessed the tolerability of the gel under double blind conditions using a four point scale (excellent, good, moderate, and poor) at the end of the study.

Statistical analysis

The AUC for tenderness over six hours after the start of treatment was determined as a summary measure for each patient using the cumulative trapezoidal rule.²⁰ Three hierarchical two sided null hypotheses were stipulated in the protocol as follows: 1st, AUC (escin 1%) = AUC (placebo); 2nd, AUC (escin 2%) = AUC (placebo); 3rd, AUC (escin 1%) = AUC (escin 2%). The first hypothesis was to be tested ($\alpha = 5\%$). If this hypothesis was rejected, the second hypothesis was to be

Figure 1 Tenderness reaction (kp/cm²). Values are means (SEM). Intention to treat analysis.

Figure 2 Pain reaction (visual analogue scale). Values are means (SEM). Intention to treat analysis.

tested ($\alpha = 5\%$); otherwise the procedure stopped. If the second hypothesis was rejected, the third hypothesis was tested ($\alpha = 5\%$); otherwise the procedure stopped. This multiple testing procedure controls the multiple α level of 5%.²¹ The treatment effect was calculated as the mean difference between two of the treatment groups. In addition, two sided 95% confidence intervals were determined.

The time needed to reach the value of the contralateral baseline tenderness at the injured site, designated time to

resolution of pain, was also determined for each patient.²² This variable was analysed by "survival analysis methods" (Kaplan-Meier estimator, two sided log rank test).

The sample size of 50 patients per group was determined statistically (assuming a standardised difference $\Delta = 0.556$, a level of significance $\alpha = 5\%$, a power $(1-\beta) = 80\%$, and a two sided t test situation). On the basis of former studies, it was anticipated that about 20% of the patients would drop out. Therefore, it was planned to enrol up to 60 patients per treatment group. Although three treatment groups were investigated in this trial, the sample size calculation was based on a two sample t test situation because of the a priori ordered comparisons of two treatment groups. This procedure results in a slightly smaller total sample size compared with a sample size calculation using an analysis of variance approach for three treatment groups.

RESULTS

A total of 158 patients were enrolled in the clinical trial by the three investigators at different sports competitions. All patients were randomised and treated with the study medication. Two patients were enrolled twice, and data from their second participation were excluded from the intention to treat (ITT) efficacy analysis. Furthermore, a per protocol (PP) analysis was carried out, excluding eight patients with major protocol violations (tenderness reaction of uninjured contralateral site less than 150% of that of the injured site or deviations from the scheduled visits) on the basis of a blind data review. All patients were assessed with regard to safety. The results of the PP analysis did not differ from those of the ITT analysis. The results for the ITT population are given unless otherwise stated.

The basic characteristics of the patients and baseline values of the efficacy variables were well balanced between the treatment groups (table 1). Table 2 presents a descriptive summary of the tenderness values and the AUC over six hours. Both

Table 3 Time from injury to first tonometric measurement and to first treatment, time to resolution of pain, and global efficacy assessments by investigators and patients (intention to treat)

	Escin 1% (n=54)	Escin 2% (n=51)	Placebo (n=51)
Time from injury to first tonometric measurement (min)			
	n=53		
Mean (median)	38.3 (32.0)	36.3 (25.0)	35.7 (30.0)
SD	27.07	27.73	29.15
Q1; Q3	15.0; 53.0	15.0; 50.0	15.0; 50.0
Time from injury to first treatment (min)			
	n=53		
Mean (median)	40.4 (34.0)	37.9 (27.0)	37.7 (31.0)
SD	27.28	27.38	28.88
Q1; Q3	17.0; 54.0	17.0; 51.0	16.0; 52.0
Time to resolution of pain			
4 h	–	1 (2.0)	–
6 h	2 (3.7)	5 (9.8)	1 (2.0)
24 h	20 (37.0)	18 (35.3)	3 (5.9)
No resolution of pain*	32 (59.3)	27 (52.9)	47 (92.2)
log rank test	p<0.0001		
Global assessments of efficacy by the investigators			
Missing	1 (1.9)	–	–
Excellent	28 (51.9)	33 (64.7)	3 (5.9)
Good	18 (33.3)	13 (25.5)	12 (23.5)
Moderate	7 (13.0)	5 (9.8)	17 (33.3)
Poor	–	–	19 (37.3)
Global assessments of efficacy by the patients			
Missing	3 (5.6)	1 (2.0)	1 (2.0)
Excellent	31 (57.4)	26 (51.0)	11 (21.6)
Good	12 (22.2)	19 (37.3)	13 (25.5)
Moderate	6 (11.1)	5 (9.8)	18 (35.3)
Poor	2 (3.7)	–	8 (15.7)

Unless indicated otherwise, values are numbers of patients with percentage in parentheses.

*During the study period.

Figure 3 Kaplan-Meier survival curves for the time to resolution of pain data from table 3.

Figure 4 Ratio of tenderness values (injured/contralateral). Values are means (SEM). Intention to treat analysis.

active treatments showed a significant superiority over placebo with regard to the AUC over six hours, whereas the difference between escin 1% and escin 2% was not significant (table 2). Higher AUC values represent less pain sensitivity and therefore a better clinical outcome. Similar results were observed for the AUC over 24 hours (table 2). An appreciable superiority of the two escin preparations was already seen one hour after the start of treatment, which persisted until the end of the study (fig 1).

The average spontaneous pain measured on a visual analogue scale showed differences between the active test gels and placebo. In the escin combination groups, pain intensity was more effectively reduced than in the placebo group (fig 2).

The time needed to reach the value of the contralateral baseline tenderness at the injured site (time to resolution of pain) was also determined for each patient.²² On average, the patients treated with active gel recovered much more rapidly than the placebo treated ones (table 3 and fig 3; log rank test: two sided $p < 0.0001$). Figure 4 shows the mean ratio of injured to uninjured tenderness during the study. No differences were found between the three treatment groups with regard to swelling.

In the overall assessment of efficacy, the investigators recorded more patients with "excellent" or "good" efficacy in the treatment groups than in the placebo group (escin 1%, 85.2%; escin 2%, 90.2%; placebo, 29.4%). The patients' assessments of efficacy were comparable (table 3).

All three gels were well tolerated. No adverse events were observed in any of the 158 patients. The overall tolerability was assessed as "excellent" in nearly all cases by the investigators (escin 1%, 98.1%; escin 2%, 100.0%; placebo, 96.2%). "Excellent" or "good" tolerability was documented by more than 85% of the patients in all three treatment groups also.

DISCUSSION

Pathophysiological mechanisms of sports impact injuries are similar to those of inflammatory reactions.²³ Established treatment mainly consists of compression and cooling of the injured area and concomitant treatment with anti-inflammatory and antioedematous agents.²⁴

However, topical treatment with anti-inflammatory drugs has been a matter of medical and scientific discussion because

of the lack of pharmacokinetic data showing sufficient penetration of the skin. Furthermore, the therapeutic usefulness of the topical combinations generally used in the treatment of sport impact injuries is questionable, because the contribution of each component of the combinations has not always been confirmed.

Evaluation of the efficacy of drugs in the acute treatment of blunt soft tissue injuries is further complicated by the great variability in pain reaction.²² This is a factor of the size and localisation of the injury as well as the outside temperature, the general training status, and subjective sensitivity to pain.

Tonometric measurement and pain assessment by a visual analogue scale were the efficacy variables used in this clinical trial. Obviously both methods have their limitations because of the subjectivity of the recordings, resulting in a large range of variation and reduced sensitivity.²⁵ These drawbacks can only be partially met by standardising measurement conditions as much as possible and by using controlled, double blind, parallel group study designs with a relatively high number of patients. However, a combination of a measurement method for spontaneous and induced pain seemed to be the most suitable one to accurately reflect the clinical situation of a blunt injury. The tonometric comparison with the uninjured contralateral area takes all variables into account by providing an "internal standard" and may therefore be especially suitable for the sensitive testing of pharmacological topical treatments. The applicability of this method was confirmed in a similar study,²⁶ in which the tonometric measurement produced similar results as an independent, accepted variable (figure of eight method) in patients with ankle sprains.

Only early treatment of an injury can usefully contribute to the relief of the symptoms. Evaluation of a topical preparation for the acute treatment of blunt soft tissue injuries is certainly most informative if the application occurs within minutes of the injury. Therefore, this study was performed at the actual site of the sports events to ensure standardised and timely treatment.

This study clearly shows that both preparations are effective for the treatment of minor blunt injuries when applied under the trial conditions. Treated patients had statistically and clinically relevant significant reductions in pain scores and were free of pain significantly earlier than patients in the placebo group.

On average, patients in the treatment groups were able to continue their sports activities sooner than those in the placebo groups, a relevant result with regard to safety: pain free movement allows normal coordination reducing the risk of additional injuries.

We believe that the efficacy of the topical preparations depends largely on the time between injury and treatment. If treatment is started too late—for example, after several hours—they may have little or no benefit.

As expected from the results of other clinical trials, no significant difference was detected between the two preparations.¹⁴ Although, theoretically, a dose-effect relation could be postulated, the sample sizes of the clinical trials performed so far have probably been too small to detect the expected differences. Furthermore, it is possible that the amount of escin penetrating the skin is limited,²⁷ and doubling the concentration in the gel would not necessarily double the concentration in the subcutis, fat layer, and muscles. On the other hand, escin is a very potent agent, as shown by experiments with intravenous applications.²³ It can be assumed that a relatively low local concentration would exert maximum blockage of the damaged capillary vessels in the injured area. This concentration, however, may well be reached with a 1% escin preparation, and whether the 2% preparation produces any better clinical results needs further investigation.

Measurement of the swelling using a tape did not show any differences within and between the treatment groups. The

Take home message

Gels containing escin, diethylammonium salicylate, and heparin are effective in the early treatment of blunt impact injuries. In most patients they produce rapid pain reduction or resolution. They are very well tolerated, exert a pleasant cooling effect, and can be administered easily by the patients.

measuring technique is probably not sensitive enough to detect differences in this type of injury.

The rationale for using the combination of escin and DEAS was demonstrated in a previous double blind, randomised, clinical trial.¹² The clinical efficacy of this combination in patients with blunt impact injuries of the extremities was shown in the latter trial and in two placebo controlled, double blind, randomised clinical trials in patients with blunt injuries.^{8, 13} One trial showed that the mobility of the joint concerned improved in the treatment group.⁸ An open, uncontrolled study and several clinical investigations support the usefulness of the escin/DEAS gel preparation in patients with traumatic injuries, haematomas, phlebitis, and subjective symptoms of varicose veins.^{28–31} The role of heparin, the third active component of the gel preparation used in our study, cannot be deduced from this investigation. The scientific rationale for including it can be found in the literature,¹⁷ but it needs to be confirmed by a placebo controlled, clinical trial of the gel preparation with or without heparin.

In active controlled, double blind, randomised, clinical trials in volunteers with a standardised injection induced haematoma, an escin/DEAS combination gel was more effective than diclofenac gel⁹ and showed a trend towards being more effective than a gel containing adrenocortical extract, mucopolysaccharide polysulphuric acid ester, and salicylic acid.³²

Apart from blunt impact injuries, the escin combination gel has also been shown in clinical investigations to be effective for tendovaginitis.³³

The safety of the components of the preparations as well as the safety of the galenical composition of the gel has been extensively tested in a number of pharmacological and clinical trials.^{8–14}

The results confirm the excellent safety and tolerability profile of 1% escin/5% DEAS/5000 IU heparin gel and 2% escin/5% DEAS/5000 IU heparin. In view of their efficacy and safety, they can be recommended for the treatment of blunt impact injuries.

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