Liposomal Heparin Spray: A New Formula in Adjunctive Treatment of Superficial Venous Thrombosis

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The objective of this study was to assess the efficacy and safety of liposomal heparin spray—a new formula of topical heparin delivery. This was a randomized, multicenter, controlled open clinical trial with 2 parallel groups. Forty-six outpatients with clinical signs of superficial venous thrombosis (SVT) were treated with either topical liposomal heparin spraygel (LHSG) (Liposhorte Forte Spraygel, 4 puffs of 458 IU tid (n = 22) or with low-molecular-weight heparin (LMWH) (Clexane 40 mg once a day (n = 24), administered subcutaneously (sc)). Main outcome measures were efficacy parameters (improvement of local symptoms—pain control and planimetric evaluation of erythema size, duplex Doppler assessment of thrombus regression) and safety parameters (documentation of adverse events, with particular reference to deep vein thrombosis (DVT) by duplex sonography, and patients’ and investigators’ assessment of drug tolerance). Patients’ and investigators’ subjective assessment of efficacy of treatment and change in basic biochemical parameters were defined as secondary outcome measures. Statistical analysis was performed with use of Wilcoxon test, Mann-Whitney U-test and Chi-square test. Regression of SVT-related symptoms, including pain, erythema, and thrombus presence, was shown as comparable in LHSG and LMWH groups. These results were corroborated by efficacy assessment by investigators and patients. Three cases of deep venous thrombosis in heparin spraygel and 1 in heparin sc group were reported. No significant adverse reactions were observed in the spraygel group, but 1 serious allergic reaction was observed in the LMWH group. Tolerance of new formula heparin was assessed as good. Heparin spraygel—a new topical mode of heparin application, seems a promising method of heparin delivery. This initial study has demonstrated comparable efficacy and safety of LHSG and LMWH in local treatment of SVT. These findings should be confirmed by further extensive study that will reach appropriate statistical power to support such conclusion, for despite heparin treatment, significant risk of DVT was demonstrated in both groups.

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Introduction

There is increasing evidence that superficial venous thrombosis (SVT), known also as thrombophlebitis, can lead to deep venous thrombosis (DVT). Thrombophlebitis of proximal long and short saphenous vein, 1,2 immobilization, 3 pregnancy and puerperium, oral contraceptives use, and genetic and thrombophilic conditions 4-6 are considered to be risk factors.

The traditional treatment of SVT encompasses compression, ambulation, and nonsteroidal antiinflammatory agents, applied topically or systemically. In cases of increased DVT risk, there is a rationale for anticoagulant treatment. The choice of medication varies from antiplatelet drugs (aspirin), unfractionated heparin, low-molecular-weight heparins (LMWHs) subcutaneously, to oral anticoagulants (acenocoumarol, warfarin). 7 Although LMWHs seem to be particularly convenient and thus advocated as adjunctive therapy, in cases of increased risk, 8-10,23 there is still not much evidence of its effectiveness in SVT therapy. The rationales for heparin use are neutralization and inhibition of thrombin generation and prevention of pulmonary emboli, by preventing extension of thrombus into the deep system. There are opinions that the latter target of treatment could be achieved also by local application of heparin—usually by gel formula, 8 which seems to be more convenient than subcutaneous injections. 9

Liposome-encapsulated heparin has been proven to have better penetration in skin 10 and prolonged anticoagulant effect owing to gradual release of heparin from liposomes. 11 Liposome formulations of heparin have been studied, 12-14 both with regard to skin penetration and to physicochemical properties. A phase I study of a group of 64 healthy volunteers confirmed more effective absorption in comparison to gel formula, and good local tolerance of liposomal gel. 15

This study was designed to assess the efficacy and safety of liposomal heparin spraygel in the treatment of superficial venous thrombosis.

Patients and Methods

Study Design

A randomized, controlled, open clinical comparison performed at 4 academic hospitals located in Poland and Czech Republic, from October 2, 2000 to May 16, 2002. The trial compared the efficacy and safety of 7 or 14 days' treatment with topical liposomal heparin spraygel (LHS) (Lipohep Forte Spraygel, 4 puffs of 458 IU tid) low-molecular-weight heparin (LMWH) (Clexa 40 mg once a day) in patients with symptomatic superficial vein thrombosis confirmed by duplex ultrasound. The 1 week follow-up served to identify relapses. The study protocol was approved by Ethical Committees in each of the participating centers. The committees were informed about any unexpected events or protocol deviations.

Patient Selection

Patient selection was performed according the principles of GCP (Good Clinical Practice). Patients aged 19-70 years were eligible to participate in the study, when the following inclusion criteria were met: clinical diagnosis of superficial venous thrombosis confirmed by duplex ultrasound, onset of the disease (first symptoms) appearing not earlier than 72 hours before inclusion.

The following criteria excluded from the trial:

- Pregnancy, breast feeding or nursing, women of childbearing age were asked to perform pregnancy test before inclusion, and adequate contraception had to be further assured (at investigators' discretion).
- Hospitalization or bed confinement.
- Deep venous thrombosis, septic thrombophlebitis.
- Open wound at application site.
- Malignancy.
- Congenital coagulopathy, history of heparin-induced thrombocytopenia, oral anticoagulant therapy, previous heparin or antiinflammatory topical or systemic treatment (within 7 days of inclusion).
- Significant renal or hepatic function impairment.
- Allergy to paracetamol.

Paracetamol up to 1,000 mg per day and compression therapy were permitted and documented. Concomitant disease medication was permitted in unchanged doses throughout the trial, provided the study medication was not contraindicated.
Interventions

Lipchep Forte Spraygel (Medicom International S.r.o.) containing 2,400 IU of heparin per 1 g gel, based on ethanol, lecithin, potassium, hydrogen phosphate, sodium hydroxide, and distilled water, was applied on the affected area: 4 puffs tid, then evenly massaged and left intact for 10 minutes, until spray film was dry. In the control group enoxaparin-sodium (Clexane®, Rhone Poulenc Rohrer) 40 mg was injected subcutaneously, preferably into the abdominal area. Patients’ compliance was assured by counting and weighing remaining medication.

Primary outcome measures of efficacy included the following (Figure 1):

- Pain scoring (10 cm visual analog scale and ordinal scale 0–4; 0, no pain; 4, extremely painful)
- Erythema (ordinal scale and planimetric measurement)
- Duplex ultrasound examination performed on days 1, 7, 14, and 21 of treatment in order to exclude DVT on entry and during the study and to confirm presence of thrombus in superficial vein

Secondary outcome measure included the following:

- Assessment of efficacy by investigator and patient (5-point scale)

Evaluation of safety parameters, as primary outcome measures, included the following:

- Documentation of adverse events, with particular reference to DVT
- Evaluation of tolerance by patient and investigator (targeted questionnaire, 4-point scale: very good, good, moderate, no change or deterioration)

Safety secondary outcome measures were the following:

- Laboratory tests performed at the beginning and at the end of study—red blood count (RBC), leukocyte count (LBC), platelets, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyltransferase (GGTP), fibrinogen, activated partial thromboplastin time (aPTT), creatinine.

Patient randomization was performed according to a prespecified randomization list. Each patient having fulfilled inclusion and exclusion criteria and having signed informed consent, was alloc...
ed to a treatment group according to the next free number on the randomization list. No stratification was performed. Treatments were administered in an open way, there was no blinding (topical vs sc application).

All variables assessed were statistically evaluated in a descriptive way. Evaluations were done using Wilcoxon test, Mann-Whitney U-test, and Chi-square test.

Results

Participants’ flow sheet is shown in Figure 2. Forty-six patients were recruited from October 20, 2000 to May 16, 2002. Twenty-two patients were allocated to the heparin spraygel treatment group, and 24 to the heparin sc treatment group. One patient in heparin spraygel arm and 1 in the heparin sc arm dropped out before any post-baseline evaluation (deep vein thrombosis and refusal of participation, respectively). Following day 7 of treatment, 3 patients from heparin spraygel and 1 from heparin sc were withdrawn from the study. Overall 18 patients from the heparin spraygel group completed the study compared to 22 patients from the heparin sc group.

On day 7 treatment was completed for 10 patients from the heparin spraygel group, and for 11 from the heparin sc group; the remaining patients completed therapy on day 14. No protocol violations were reported.

Baseline demographic and clinical parameter (intention to treat) are presented in Table I.

There were no significant differences between the 2 treatment groups concerning smoking habits, alcohol consumption, working leisure activities, or concomitant diseases. Subjects in heparin spraygel and heparin groups did not differ significantly by prior thrombosis, phlebitis, or pulmonary embolism, or history of prior surgery.

Efficacy Outcomes

Pain comparison between groups, as assessed visual analogue scale (VAS) is presented in Figure 3 (intention-to-treat basis). In both groups significant pain decrease was observed on each point of evaluation. There were no statistically significant differences between LHSIG and LMWH, neither at baseline pain assessment, nor at day 7, day 14, nor at follow-up visit.
**Table I.** Baseline demographic and clinical parameters (intention-to-treat).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Heparin Spraygel Group n=22</th>
<th>Heparin sc Group n=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median), years</td>
<td>51</td>
<td>54</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>17/5</td>
<td>14/10</td>
</tr>
<tr>
<td>BMI (kg/m²), median</td>
<td>25.07</td>
<td>29.41</td>
</tr>
<tr>
<td>Concomitant diseases</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Prior episodes of VTE</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Tobacco nonsmokers, %</td>
<td>86.4</td>
<td>70.1</td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.

**Table II.** Patients with present thrombus at different evaluation periods.

<table>
<thead>
<tr>
<th></th>
<th>Heparin Spraygel</th>
<th>Heparin sc</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Baseline</td>
<td>21 (100%)</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Day 7</td>
<td>15 (71.43%)</td>
<td>17 (73.91%)</td>
</tr>
<tr>
<td>Day 14</td>
<td>10 (47.62%)</td>
<td>13 (56.52%)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>11 (52.38%)</td>
<td>14 (60.87%)</td>
</tr>
</tbody>
</table>

**Figure 3.** Median (±95% CI) pain VAS over the study, intention-to-treat basis.

Planimetric evaluation of erythema is shown in Figure 4. Except from baseline (LHSG mean 15.25 cm² (95% CI 7.50–22.09), LMWH 24.00 (95% CI 10.00–38.57), there were no statistically significant differences.

Subjective assessments of efficacy of treatment in investigators' and patients' opinion are shown in Figures 5 and 6. No statistically significant difference in efficacy, neither in investigator's nor in patient's opinion were demonstrated between heparin spraygel and heparin sc group.

Assessments of efficacy by patients correspond those by investigators—only 2 patients in the parin spraygel group and 1 patient in the heps sc group reported no change or deterioration.

**Duplex Sonography**

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Figure 4. Median planimetric evaluation of erythema (cm²) during study period, intention-to-treat basis.

Figure 5. Evaluation of overall treatment efficacy by investigator.
with present thrombus at different evaluation periods.

Safety Results

Mean treatment exposure was 12.52 days (SD 2.94) in the heparin spraygel group in comparison to 13.48 days (SD 1.81) in the heparin sc group. No deaths were reported. Three adverse events were reported in each treatment group. The most common adverse event was DVT of the lower leg, recorded in 2 patients from heparin spraygel and in 1 from heparin sc group. A case of upper leg DVT was recorded in the heparin spraygel group, and the remaining 2 events in the heparin sc group were allergic reaction and elevated sedimentation rate (ESR). One adverse event in the heparin sc group (allergic reaction) was reported as serious. All adverse events reported in the heparin spraygel group were assessed as not related to the study drug. In the heparin sc group 2 events were reported as not related to the study drug, and 1 (allergic reaction) was reported as of probable relation. All patients with DVT required hospitalization and were withdrawn from further study. These patients were taking multiple concomitant medications and tended to be overweight.

With the exception of leukocyte count (heparin spraygel mean 6.03, SD 1.02, heparin sc 7.37, SD 1.91) × 10⁹/l, laboratory parameters did not differ between groups. On second evaluation at day 14, laboratory parameters did not differ between both groups. Seventeen patients from the heparin spraygel had 58 abnormal laboratory findings in total, predominantly elevated ESR (40.9% in baseline investigation vs 36.4% on day 14), followed by abnormal fibrinogen. In heparin sc group 18 patients had 58 abnormal laboratory findings (33.3% ESR, 20.8% fibrinogen, respectively).

Discussion

Treatment of SVT is targeted at restriction of local inflammatory process and at prevention of DVT. Although the complication rate in terms of DVT risk can be assessed with adequate precision, it is quite difficult to establish objective and adequate measures of efficacy of local treatment. Clinical evaluation of SVT treatment was based on an of 6 items: pain, tenderness, disability, l¢ swelling, erythema, and presence of thrombi. Some studies, along with relief from pain, local symptoms, local effectiveness of SVT treatment has been measured by composite terminology. Erythema size seems to be an acceptable measure, although the most objective parameter appears to be duplex ultrasound investigation.

The efficacy parameters in this study w comparable to those cited above: pain control VAS and categorical scale, planimetric measurement of erythema together with categorical sc measurement of thrombus presence/resolution sonography, and the assessment of efficacy by vestigator and by patient.

It has been shown that LMWH is at least efficient in SVT treatment as nonsteroidal anti inflammatory drugs (NSAIDs)7,17; 117 patients w treated with the LMWH either as a fixed dose with dose adjusted for body weight in comparison to patients receiving the NSAID agent naproxen. Following 5 days of therapy it appeared that local symptoms (heat and redness) were significantly improved in both LMWH groups.

Lowering of DVT risk is perceived as 1 of endpoints of successful SVT treatment.18, DVT prophylaxis is 1 of the key elements of treatment.3 A large study of more than 500 patients with DVT has shown that the average 1 risk within 6 months of SVT treatment is at 6%, regardless of the treatment method used. Others point out up to 11% of DVT risk in similar groups of patients. Jorgensen et al noted 2 incidence of occult DVT in SVT patients, though up to 44% of such complications sometimes observed.19

That issue has not been fully perceived in our way in our study. We consider DVT a disease process rather than a side effect related to therapy. Nevertheless hospitalization follow DVT implied considering it as a primary end point of the safety assessment. Three cases of DVT had the heparin spraygel and 1 in the heparin sc group underline the importance of this phenomena. Despite the difference in that outcome between the groups, it is not possible to draw clinically evant conclusions owing to small group size possible influence of other risk factors.

Although location of SVT in vicinity of saphenofemoral junction is a debatable risk factor it is justified. Subcutaneous form of heparin admi-
Previous studies have proved safety of Essaven gel. It is anticipated that topical delivery of liposomal spray is more effective in comparison to gel formula.

The study has shown heparin liposomal spray to be an efficient and safe formula, causing no more adverse reactions than low-molecular-weight heparin administered subcutaneously.

Although, with the exception of generalized pruritus, we have not observed local skin reactions to sc heparin injections, bruises and mild local irritation are quite common, though their clinical significance is probably limited. Local topical heparin application, particularly with prolonged release time seems to be very attractive, as it can act both locally and systemically with possibly a lower complication rate.

Conclusion

Liposomal spray heparin, applied topically, seems to be an interesting option for treatment of superficial phlebitis. This initial study has demonstrated a comparable efficacy and safety of LHSG and LMWH in local treatment of SVT. These findings should be confirmed by further extensive study that will reach appropriate statistical power to support such conclusion, as despite heparin treatment significant risk of DVT has been demonstrated in both groups. A future large clinical trial should encompass as efficacy endpoints both the limitation of local inflammatory process and lowering of DVT risk.

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