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) (Lipohep 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,[1-3] immobilization,[4] pregnancy and puerperium, oral contraceptives use, and genetic and thrombophilic conditions[5,6] 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), unfractioned 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,[1-3,5,7] 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 compar

performed at 4 academic hospitals located Poland and Czech Republic, from October 2 2000 to May 16, 2002. The trial compared the (ficacy and safety of 7 or 14 days' treatment wi 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 symptoma superficial vein thrombosis confirmed by dupl ultrasound. The 1 week follow-up served to ide tify relapses. The study protocol was approved l Ethical Committees in each of the participati centers. The committees were informed abo 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 parti ipate in the study, when the following inclusic criteria were met: clinical diagnosis of superfici venous thrombosis confirmed by duplex ultr sound, onset of the disease (first symptoms) a pearing not earlier than 72 hours before inclusio

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 adequat contraception had to be further assured (at ir vestigators' discretion)
- Hospitalization or bed confinement
- Deep venous thrombosis, septic thrombophlebitis
- Open wound at application site
- Malignancy
- Congenital coagulopathy, history of heparin-induced thrombocytopenia, oral anticoagulan therapy, previous heparin or antiinflammator topical or systemic treatment (within 7 days (inclusion)
- Significant renal or hepatic function impairment
- Allergy to paracetamol

Paracetamol up to 1,000 mg per day and con pression therapy were permitted and documen ed. Concomitant disease medication was permi ted in unchanged doses throughout the trial, pr

Interventions

Lipohep 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 p tient (5-point scale)

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

- Documentation of adverse events, with par ular reference to DVT
- Evaluation of tolerance by patient and inve gator (targeted questionnaire, 4-point scale very good, good, moderate, no change or d terioration)

Safety secondary outcome measures were the following:

- Laboratory tests performed at the beginnin and at the end of study—red blood count (RBC), leukocyte count (LBC), platelets, al nine transaminase (ALT), aspartate transan nase (AST), gammaglutamyltranspeptidase (GGTP), fibrinogen, activated partial throm plastin time (aPTT), creatinine.

Patient randomization was performed accor to a prespecified randomization list. Each pati having fulfilled inclusion and exclusion crit and having signed informed consent, was allo

Figure 1. Pain, efficacy, and tolerance rating scale.

Pain scoring	10 cm VAS scale 0 no pain 1 mild 2 moderate 3 severe 4 extremely painful	
Rating of efficacy by investigator and patient	investigator 1 very good 2 good 3 moderate 4 no change 5 deterioration	patient 1 no complaints 2 important improvement 3 slight improvement 4 no change 5 deterioration
Rating of tolerance by investigator and patient	investigator and patient 1 very good 2 good 3 moderate 4 no change 5 deterioration	

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 grou On day 7 treatment was completed for 10 p tients from the heparin spraygel group, and fo from the heparin sc group; the remaining p tients completed therapy on day 14. No protoc violations were reported.

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

There were no significant differences b tween the 2 treatment groups concerning smo ing habits, alcohol consumption, working leisure activities, or concomitant diseases. Stu subjects in heparin spraygel and heparin groups did not differ significantly by prior thro bosis, phlebitis, or pulmonary embolism, or history of prior surgery.

Efficacy Outcomes

Pain comparison between groups, as assessed visual analogue scale (VAS) is presented in Figu 3 (intention-to-treat basis). In both groups sign icant pain decrease was observed on each poi evaluation. There were no statistically significa differences between LHSG and LMWH, neither baseline pain assessment, nor at day 7, day 1 nor at follow-up visit.

Figure 2. Participants' flow chart.

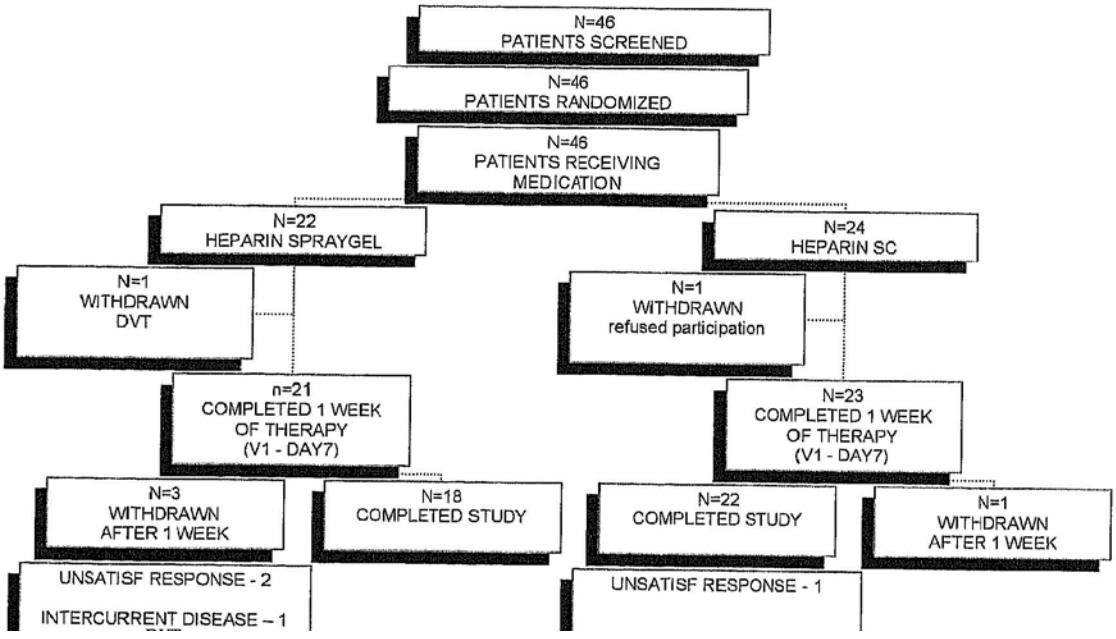


Table I. Baseline demographic and clinical parameters (intention-to-treat).

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

VTE = venous thromboembolism.

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

	Heparin Spraygel	Heparin sc
n	21	23
Baseline	21 (100%)	23 (100%)
Day 7	15 (71.43%)	17 (73.91%
Day 14	10 (47.62%)	13 (56.52%
Follow-up	11 (52.38%)	14 (60.87%

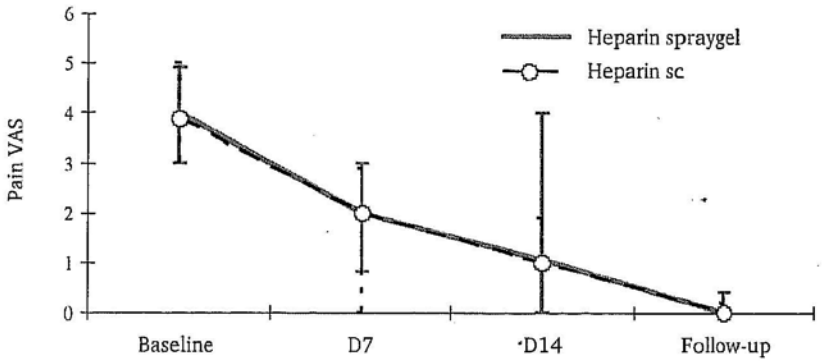


Figure 3. Median (±95% CI) pain VAS over the study, intention-to-treat basis.

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

sessments of efficacy by patients correspond those by investigators—only 2 patients in the parin spraygel group and 1 patient in the hepa sc group reported no change or deterioration. ficacy evaluation by patients was similar in th groups in all periods (day 7: p = 0.6246; day p = 0.5923; follow-up: p = 0.4620; last availa observation: p = 0.8999).

Duplex Sonography

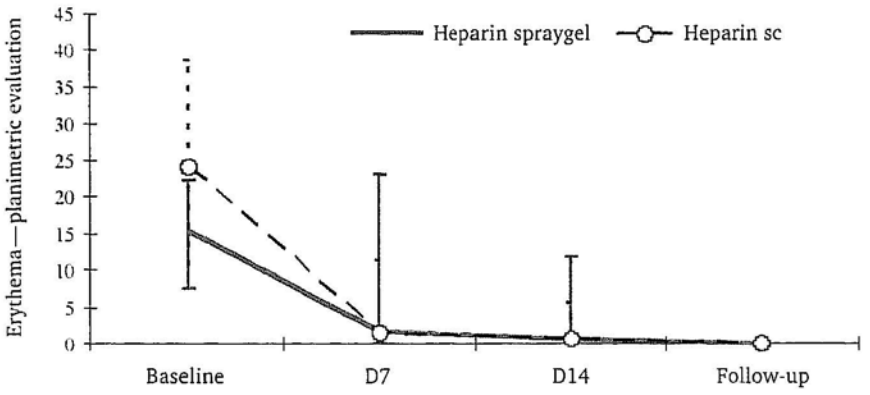


Figure 4. Median planimetric evaluation of erythema (cm^2) during study period, intention-to-treat basis.

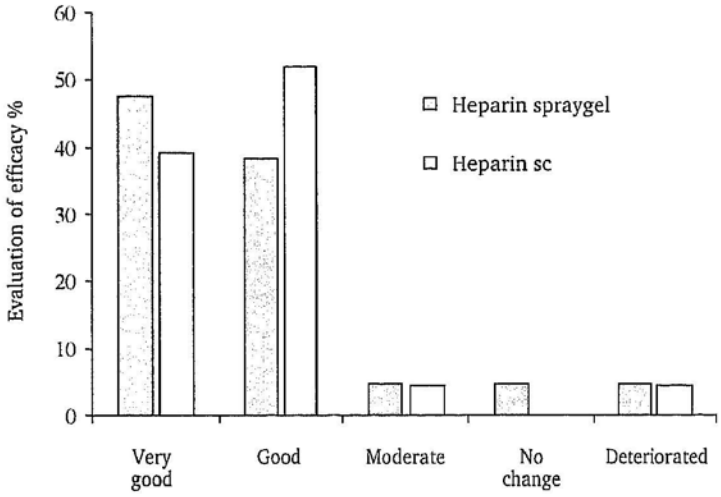
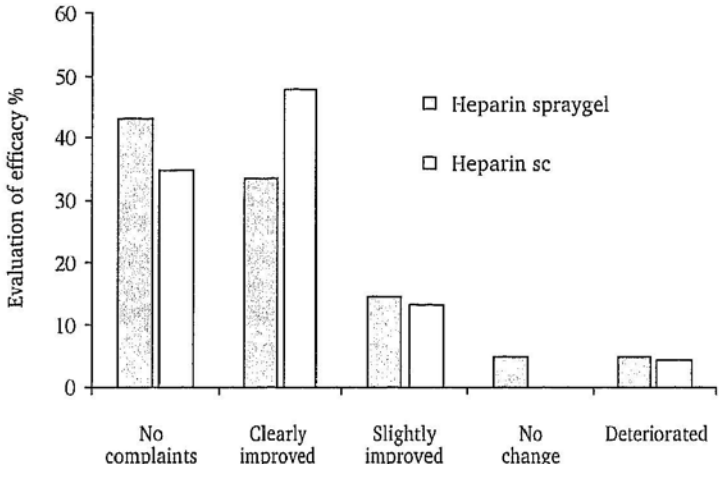


Figure 5. Evaluation of overall treatment efficacy by investigator.



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) $\times 10^3$), 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, lo swelling, erythema, and presence of thrombi.[some studies, along with relief from pain a local symptoms, local effectiveness of SVT tre ment has been measured by composite therr metry.[16] Erythema size seems to be an accepta measure, although the most objective parame 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 measu ment 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 ant flammatory drugs (NSAIDs)[7,17]; 117 patients w treated with the LMWH either as a fixed dose with dose adjusted for body weight in comp son to patients receiving the NSAID agent napr en. Following 6 days of therapy it appeared t local symptoms (heat and redness) were sign cantly improved in both LMWH groups.[17]

Lowering of DVT risk is perceived as 1 of endpoints of successful SVT treatment,[18] a DVT prophylaxis is 1 of the key elements of S treatment.[3] A large study of more than 560 tients with DVT has shown that the average D risk within 6 months of SVT treatment is ab 6%, regardless of the treatment method us Others[2] point out up to 11% of DVT risk in si lar 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 t way in our study. We consider DVT a dise process rather than a side effect related to S therapy. Nevertheless hospitalization follow DVT implied considering it as a primary end p of the safety assessment. Three cases of DV the heparin spraygel and 1 in the heparin sc gr underline the importance of this phenomen Despite the difference in that outcome betw 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 sap nofemoral junction is a debatable risk facto DVT,[2,3,19] adjuvant heparin treatment seems t justified. Subcutaneous form of heparin admi tration can lead, however, to noncompliance r as high as 28%.[20] From this point of view ton

Previous studies[8] 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[11] 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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REFERENCES

deep venous thrombosis complicating supe thrombophlebitis. J Vasc Surg 27:338-343, 19

2. Chengelis DL, Bendick PJ, Glover JL, et al: Pr sion of superficial venous thrombosis to deep thrombosis. J Vasc Surg 24:745-749, 1996.
3. Guex JJ: Thrombotic complications of varicose A literature review of the role of superficial ve thrombosis. Dermatol Surg 22:378-382, 1996.
4. Bounameaux H, Reber-Wasem MA: Super thrombophlebitis and deep vein thrombosis. A troversial association. Arch Intern Med 157:1 1824, 1997.
5. Martinelli I, Cattaneo M, Taioli E, et al: Genet factors for superficial vein thrombosis. Th Haemost 82:1215-1217, 1999.
6. Van der Molen HR: [Ambulatory recurring o grating phlebitis of subacute appearance (analy 30 cases)]. Phlebologie 30:65-81, 1977.
7. Kalodiki E, Nicolaides A: Superficial thrombophl and low-molecular-weight heparins. Angiolog 659-663, 2002.
8. Incandela L, De Sanctis MT, Cesarone MR, e Treatment of superficial vein thrombosis: Cli evaluation of Essaven gel—a placebo-controlle week, randomized study. Angiology 52(suppl 3): S72, 2001.
9. Belcaro G, Nicolaides AN, Geroulakos G, e Essaven Gel—review of experimental and cli data. Angiology 52(suppl 3):S1-S4, 2001.
10. Betz G, Nowbakht P, Imboden R, et al: Heparin etration into and permeation through human from aqueous and liposomal formulations in v Int J Pharmacol 228:147-159, 2001.
11. Kim TD, Kambayashi J, Sakon M, et al: Metabolis liposome-encapsulated heparin. Thromb Res 56: 376, 1989.
12. Betz G, Imboden R, Imanidis G: Interaction of some formulations with human skin in vitro. I Pharmacol 229:117-129, 2001.
13. Rades T, Gerke A, Schütze W, et al: Characteriza of a commercial liposome spray. Pharmazie 52 50, 1997.
14. Artmann CW, Fassihi A, Kroling P, et al: Vehik hängige Mikrozirkulation der haut. Verbess bioverfugbarkweit am Beispiel von heparin lip males spruhgel versus konventionelle heparin-g Zeitschrift für Allgemeinmedizin 73:242-244, 2 248, 1997.
15. Artmann CW, Kroelling P, Regenold J, et al: Lip males spruehgel. Zeitschrift für Allgemeinmed 71:655, 1995.
16. De Sanctis MT, Ceasarone MR, Incandela L, et Treatment of superficial vein thrombosis with s dardized application of Essaven gel. A placebo-c trolled, randomized study. Angiology 52(suppl S57-S62, 2001.

agement of superficial venous thrombosis with calcium nadroparin. Dosage testing and comparison with a non-steroidal anti-inflammatory agent. Ann Cardiol Angiol 43:160-166, 1994.

18. Decousus H: Treatment of superficial-vein thrombosis: A randomized double-blind comparison of low-molecular-weight heparin, non-steroidal anti-inflammatory agent and placebo (abstract). Thromb Haemost 163:1657-1663, 2003.
19. Jorgensen JO, Hanel KC, Morgan AM, et al: The incidence of deep venous thrombosis in patients with superficial thrombophlebitis of the lower limbs J Vasc Surg 18:70-73, 1993.
20. Spahn G: Compliance with self-administration of heparin injections as outpatients. Eur J Trauma 28:104-109, 2002.