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Liposomal Heparin-Spraygel in Comparison with Subcutaneous Low Molecular Weight Heparin in Patients with Superficial Venous Thrombosis. A Randomized, Controlled, Open Multicentre Study

R. Katzenschlager¹, A. Ugurluoglu², E. Minar³, M. Hirschl¹

Abstract: *Purpose:* Superficial vein thrombosis (SVT), which can be managed sufficiently with compressive bandage and locally applied or systemic nonsteroidal antiphlogistics, is generally considered as being relatively harmless. However, the SVT can spread into the deep vein system necessitating other more aggressive surgical and/or systemic treatment. In this randomised, controlled, open, multicentre, comparative study, the efficacy and tolerability of a new galenic formulation of liposomal heparin-spraygel was compared with subcutaneously administered low molecular weight heparin.

Methods: 42 patients (31 female, 11 male), diagnosed with superficial vein thrombosis confirmed by duplex sonography, were entered. All patients got a compressive therapy and were permitted to use paracetamol (1000 mg per day) as pain rescue medication. The treatment results were assessed after seven or fourteen days of therapy. The primary end points were reduction of pain (VAS, VRS), erythema (planimetry) and swelling (ordinal scale). At each visit the length of thrombus (mm) was measured by duplex sonography.

Results: None of the 42 patients developed a deep vein thrombosis. The results of the pain evaluation (VAS evaluation) showed a comparable pain reduction in both

groups. The consumption of rescue medication was also comparable. Erythema and thrombus size showed a continuous decrease in both groups without any significant difference.

Conclusion: The topical application of liposomal heparin-spraygel in combination with compressive therapy showed a comparable efficacy profile to the subcutaneously applied low molecular weight heparin in the treatment of superficial vein thrombosis.

Kurzfassung: Liposomales Heparin-Spraygel im Vergleich zu subkutanem niedermolekularem Heparin bei Patienten mit oberflächlicher Venenthrombose. Eine randomisierte, kontrollierte, offene Multicenter-Studie. Ziel: Die oberflächliche Venenthrombose (superficial vein thrombosis, SVT), die durch Kompressionsbehandlung sowie lokal angewandte oder systemische nichtsteroidale Antiphlogistika hinreichend behandelt werden kann, wird generell als relativ harmlos eingestuft. Allerdings kann eine SVT auch tiefer gehen, was eine aggressivere chirurgische und/oder systemische Behandlung nötig macht. In der vorliegenden randomisierten, kontrollierten, offenen, multizentrischen Vergleichsstudie wurden Wirkung und Toleranz des neuen galenischen

liposomalen Heparin-Spraygels mit subkutan verabreichtem niedermolekularem Heparin verglichen.

Methodik: 42 Patienten (31 Frauen, 11 Männer) mit diagnostizierter SVT, mittels Duplex-Sonographie bestätigt, wurden eingeschlossen. Alle Patienten erhielten eine Kompressionstherapie, darüber hinaus war es ihnen erlaubt, Paracetamol (1000 mg/Tag) als Schmerzmittel einzunehmen. Die Behandlungsergebnisse wurden nach 7 oder 14 Tagen überprüft. Die primären Endpunkte umfaßten Schmerzreduktion (VAS, VRS), Erythema (Planimetrie) und Schwellung (ordinale Skala). Bei jeder Visite wurde die Länge des Thrombus (mm) mittels Duplex-Sonographie gemessen.

Ergebnisse: Keiner der 42 Patienten entwickelte eine tiefe Venenthrombose. Das Ergebnis der Schmerzevaluierung (VAS-Evaluation) zeigte eine vergleichbare Schmerzreduktion in beiden Gruppen. Der Medikamentenkonsum war ebenfalls vergleichbar. Erythema und Thrombengröße zeigten einen kontinuierlichen Anstieg in beiden Gruppen, ohne signifikante Unterschiede.

Schlußfolgerung: Die topische Anwendung von liposomalem Heparin-Spraygel mit Kompressionstherapie zeigte in der Behandlung oberflächlicher Venenthrombosen eine vergleichbare Wirkung zum subkutan verabreichten niedermolekularen Heparin. **J Kardiologie 2003; 10: 375-8.**

■ Introduction

For a long time, superficial vein thrombosis (SVT) was considered as a relatively harmless disease, which could be managed sufficiently with compression therapy and local or systemic nonsteroidal antiphlogistics [1, 2]. However, the SVT can spread into the deep vein system and then merely classic therapy is not sufficient. According to recently published literature, the incidence of this complication ranges between 5.6 and 44 % [3-7]. Therefore, the importance of the systemic treatment of SVT with low molecular weight heparin in addition to compression therapy has increased. This is mainly due to the antithrombotic and antiphlogistic actions of heparin. In this clinical study efficacy and tolerability of heparin in a new galenic form was investigated for topical application in superficial vein thrombosis in comparison with subcutaneous low molecular weight heparin.

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■ Materials and Methods

Study Design

The present study was designed as a randomised, controlled, open, multicentre comparative pilot study with 2 parallel groups of patients affected by SVT: One group of patients was treated with a topical application of liposomal heparin-spraygel (Lipohep[®] 2400 I.U./g Spraygel, CSC Pharmaceuticals Handels GmbH, Austria) and standard elastic compressive stocking, the other group was treated with subcutaneous injections of low molecular weight heparin (Enoxaparin, Lovenox[®] 40 mg, Gerot Pharmazeutika, Vienna, Austria) and compressive bandage. Ethical approval was obtained before starting the study.

Patient Selection – Study Eligibility Criteria

Male and female patients aged between 17 and 69 years diagnosed with SVT by duplex sonographic examination and with complaints and symptoms having begun not longer than 72 hours before referral to the clinic, were eligible to enter the trial. Pregnant or nursing women were not included. Other exclusion criteria were: long confinement to bed for any reason, deep vein thrombosis (DVT), septic thrombophlebitis, skin disease or open wounds at the site of medication appli-

cation, malignant tumour, congenital coagulopathy, severe impairment of liver and kidney functions, anamnesis of heparin induced thrombocytopenia, known allergy to heparin or paracetamol, parenteral application of heparin or systemic treatment with nonsteroidal antiinflammatory or anticoagulants within seven days before entering (Tab. 1).

Treatments

Liposomal heparin-spraygel group

Patients in this group were treated with liposomal heparin-spraygel. One spray puff delivers 0.19 g of spraygel which corresponds to 458 IU of sodium heparin. The medication was sprayed three times per day (morning, noon, evening) onto the skin covering the superficial thrombus region (4 spray puffs at each application). The liquid was spread gently with fingertips over the skin surface. The surface was exposed to air in order to dry before dressing with elastic stocking. Maximal treatment duration was 14 days. Paracetamol (Mexalen® 500 mg, Merckle GmbH, Blaubeuren, Germany) as rescue medication against pain was allowed at a daily dose of 1000 mg during the first week of treatment. The intake of paracetamol was recorded in the patient's diary.

Low molecular weight heparin group (Enoxaparin)

Patients in this group were treated with subcutaneous injections of low molecular weight heparin preparation (Lovenox® 40 mg, Gerot Pharmazeutika, Vienna, Austria). Each injection delivered 4000 anti Factor Xa units. Maximal treatment duration was 14 days. Patients were wearing elastic stockings and were allowed to use the same type and dosage of rescue medication as those of the liposomal heparin-spraygel treatment group. Treatments were administered in an open randomised way (topical vs. subcutaneous application). A double dummy design was not appropriate for this phase II study. As no formal hypothesis was tested, the application of placebo injections was considered as being unethical. All necessary medication for the treatment of chronic diseases already in regular use by the patient were allowed, except if interfering with the study conduct.

Patient randomisation

The assignment of patients to the treatment was done accordingly to a randomisation list using a validated system. Each valid subject according to inclusion and exclusion criteria, having signed a written consent after being informed about the study, was assigned to the next number on the randomisation list.

Table 1: Forty-two patients (31 female, 11 male aged 21–69 years; mean age 53 years \pm 10) with superficial vein thrombosis were entered between March 1999 and August 2000. The table shows the baseline characteristics of the patients.

| | Liposomal heparin-spraygel group (Lipohep®) | Enoxaparin group (Lovenox®) |
|-----------------------|---|-----------------------------|
| Age (years) | 52.16 \pm 12.03 | 53.51 \pm 8.41 |
| Weight (kg) | 80.71 \pm 17.75 | 82.48 \pm 16.91 |
| Height (cm) | 170.1 \pm 11.17 | 167.38 \pm 9.91 |
| Smokers | 85.7 % | 57.1 % |
| Prior thromboembolism | 52.4 % | 61.9 % |

Study Conduct

Prior to the first dose of the study medication, the patient's general and current disease as well as the medical histories were taken. Duplex sonography examination of the deep and superficial veins with thrombus size (mm) measurement was performed. Sonographic examinations were carried out on both extremities in order to exclude concurrent DVT. Pain was assessed by using a standard 10 cm visual analogue scale (VAS) and 5-point verbal rating scale (VRS) (no pain, mild, moderate, severe, extremely painful). The size of erythema (planimetry) was taken by using a transparent foil. Swelling was described by using a 3-point arbitrary scale (none, mild, moderate). Venous blood sample was taken for routine clinical laboratory exams. Treatment results were first assessed after one week. In case of a complete resolution of symptoms and thrombus, patients were asked to come again after another week for a follow-up visit. If signs and symptoms persisted, the same treatment was continued for a further week. At each control visit, the same clinical and laboratory tests were performed.

Tolerance

An adverse event was defined as any reaction, side effect, intercurrent disease or unexpected event or abnormal laboratory finding that occurred during the course of clinical trial, whether or not considered therapy medication related. The adverse events were defined as mild, moderate or severe and their relationship to the trial medications was classified by both the investigator and the study monitor.

Treatment outcome

Treatment outcome was assessed after 7 days of therapy against the parameters described above: presence of thrombus, pain, erythema and swelling. Global treatment outcome assessment by patients and physician was also recorded. The use of rescue medication was measured by the number of paracetamol tablets returned by the patient. Treatment compliance (spray) was measured by weighing the bottles of medication returned by the patient at visit 2 and/or 3.

Statistical Analysis

Statistical analysis was performed taking into account the outcome of all randomised patients and treatment at least one week after baseline assessment. For continuous variables, descriptive statistics (mean, standard deviation, minimum, maximum, median and quartiles) were computerized. All parameters measured on discrete scales were analysed by using the Chi-square test and those measured on ratio or interval scales were analysed by using the Mann-Whitney-U test. Comparisons within a group (comparison to baseline) were performed by using the Wilcoxon-matched-pair test. All parameters were tested in an explorative way and not as tests of hypothesis.

Results

42 patients entered the study, 39 of them (18 in the heparin-spraygel group and 21 in the Enoxaparin group) finished the trial. No patient died or developed a deep venous thrombosis.

One patient dropped out after the baseline visit, two patients in the liposomal heparin-spraygel group discontinued the study, due to an aggravation of the superficial thrombosis, according to the protocol. In one case, the compliance could not be assessed as the patient did not return the study medication. Both were successfully treated with high dose Enoxaparin (2×60 mg and 2×80 mg for 7 days). The disposition of the patients is depicted in Table 2.

Treatment was completed by 85.7 % of patients in the liposomal heparin-spraygel- and all patients in the low molecular weight heparin group. In one patient treated with low molecular weight heparin, the SVT relapsed before the last follow-up visit.

Pain, erythema and swelling

Course of pain (mean VAS values) and erythema (surface in cm^2) are depicted in Figure 1 and Figure 2.

The size of erythema was reduced in both groups within the first seven days of medication ($p < 0.001$). There were no differences at any point of measurement between the groups. These two objective parameters, pain and erythema reduction, were further confirmed by the outcome of the evaluation of efficacy by investigator and patient. For both categories the ratings of efficacy were comparable.

Thrombus size

The length of the superficial vein occlusion was considered primarily as the safety parameter. Both groups showed a comparable reduction of the thrombus length (Tab. 3). In both

groups, median values reached zero at the last follow-up visit, though it has to be stated that the mean value of the thrombus length at the baseline in the heparin-spraygel group was double that of the low molecular weight heparin group. The maximum size in the liposomal heparin-spraygel group was 562 mm, while in the low molecular weight heparin group it was 200 mm respectively.

Safety and Tolerability

No deaths or serious adverse events occurred during the study. Four patients in the liposomal heparin-spraygel group and 3 patients in the low molecular weight heparin group shared adverse events. Two patients in the heparin-spraygel group experienced mild pruritus, one had mild skin exfoliation at the site of application and exanthema, the other one reported headache. In the Enoxaparin group, one patient reported pruritus, one shared a mild, transient elevation of liver enzymes and one a relapse of the SVT.

Pruritus, exfoliation and exanthema are quite frequent in patients with chronic superficial thrombophlebitis, therefore, a clear differentiation between underlying disease and local intolerance reaction is difficult. Headache was considered as a therapy unrelated adverse event.

Discussion

The classic therapy of the SVT was compression therapy and local or systemic nonsteroidal antiphlogistics. However, the SVT can spread into the deep vein system and then compression therapy alone is not sufficient. According to recently published literature, the incidence of this complication ranges between 6 and 44 % [3–7]. Therefore, the importance of the systemic treatment of SVT with low molecular weight heparin in addition to compression therapy has increased [5–7]. This is mainly due to the antithrombotic and antiphlogistic actions of heparin.

In 1995 Artmann et al. showed in 64 healthy volunteers a better skin penetration of heparin from liposomal heparin-

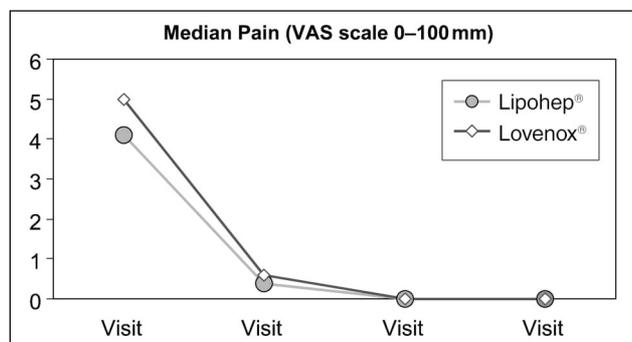


Figure 1: The mean differences of pain scores. In both groups, pain reduction between the baseline and day 7 were statistically significant ($p < 0.01$). On day 14 in both groups the median pain VAS scores were 0 in both groups of patients. The intergroup differences were negligible at any point. The pain assessed by VRS paralleled the values of pain reduction obtained by VAS. There were no differences between the groups concerning the pain rescue medication consumption.

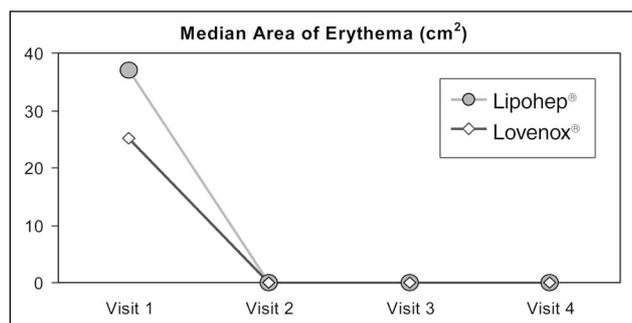


Figure 2: The size of the erythema surface (cm^2)

Table 2: Disposition of the patients, Lipohep® vs Lovenox® group

| | Lipohep® | | Lovenox® | | Total | |
|---------------------|-----------|-------------|-----------|-------------|-----------|--------------|
| | N | % | N | % | N | % |
| Drop outs | 1 | 4.8 | 0 | 0.0 | 1 | 2.4 |
| Completed on day 7 | 6 | 28.6 | 9 | 42.9 | 15 | 35.7 |
| Completed on day 14 | 12 | 57.1 | 12 | 57.1 | 24 | 57.1 |
| Discontinued | 2 | 9.5 | 0 | 0.0 | 2 | 4.8 |
| Total | 21 | 50.0 | 21 | 50.0 | 42 | 100.0 |

Table 3: Thrombus size, Lipohep® vs Lovenox® group

| | Lipohep® | | | | Lovenox® | | | |
|--------|-----------|--------|--------|-----------|-----------|-------|--------|-----------|
| | Base-line | Day 7 | Day 14 | Follow-up | Base-line | Day 7 | Day 14 | Follow-up |
| Mean | 94.28 | 60.52 | 11.54 | 5.25 | 44.48 | 16.53 | 12.97 | 7.18* |
| S.D. | 145.63 | 191.98 | 15.59 | 11.26 | 44.06 | 14.1 | 12.64 | 9.7 |
| Median | 32.3 | 13.0 | 8.0 | 0.0 | 29.0 | 18.4 | 14.20 | 0.0 |
| N | 21 | 19 | 12 | 17 | 21 | 21 | 12 | 21 |

* In the Lovenox® group there was one patient in whom the SVT had relapsed by the time of the follow-up visit.

spraygel versus conventional gel-formulations applied in equivalent doses [8]. The local absorption rate of the liposomal heparin-spraygel was at least 3 times higher than of the heparin gel. The good results of this study led us to initiate this clinical study comparing the efficacy and safety of liposomal heparin-spraygel to subcutaneous low molecular weight heparin (Enoxaparin) in superficial venous thrombosis for the first time.

The randomised open design of the study was considered adequate because the application of subcutaneous injections of placebo was not regarded ethical at this point of the clinical development phase. The study duration of 7 respectively 14 days (depending on therapeutic response) was sufficient for an evaluation of the efficacy and safety of this new form of heparin preparation for this indication. No deaths, no deep thrombosis or serious adverse events occurred during the study. This showed the efficacy of both therapies in comparison with another study [9]. Four patients with liposomal heparin-spraygel and three patients with low molecular weight heparin experienced mild adverse events. In two patients in the liposomal heparin-spraygel group the thrombosis aggravated. In one of these patients the compliance could not be assessed because he did not return to the study medication. Both patients were then treated with high-dose Enoxaparin, a resolution of symptoms was achieved after approximately one week. The results of VAS and VRS pain evaluations showed a comparable and continuous pain decrease in both treatment groups. This was paralleled by the observation that the consumption of pain rescue medication was equal in both groups. Reductions of the other two signs, erythema and swelling, were comparable as well. The objective parameters were confirmed by the results of the evaluation of efficacy by the investigator and the patient. The length of

thrombus measured by duplex sonography also diminished proportionally in both groups.

In conclusion, this study showed that the therapy of superficial venous thrombosis with liposomal heparin-spraygel and compression therapy is comparable with the combination low molecular weight heparin therapy and compression therapy. Yet, the therapy with liposomal heparin-spraygel is less invasive and, therefore, considerably more patient-friendly. However, as both low dose low molecular weight heparin therapy and therapy with liposomal heparin-spraygel can result in a progression in rare cases, regular clinical controls as well as sonographic controls are recommended, which has also been described by other authors [10]. As the present study is a pilot study including a small number of patients, these positive results should be confirmed by a randomised study with a higher number of patients, before applying liposomal heparin-spraygel as standard treatment of SVT routinely.

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