THE USE OF LIPOSOMAL HEPARIN SPRAY-GEL IN THE TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS: A MULTICENTER CLINICAL INVESTIGATION ANALYSIS

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The aim of the study was to evaluate the efficacy and safety of liposomal heparin spray-gel in the treatment of superficial thrombophlebitis.

Material and methods. The presented study is an analysis of two clinical investigations performed during the period between March 1999 and May 2002, which evaluate the efficacy and safety of liposomal heparin spray-gel (Lipohep) in the treatment of superficial thrombophlebitis, as well as a comparison with results obtained following subcutaneous enoxaparin injections. The study group comprised 88 patients, including 43 on Lipohep treatment and 45 on low molecular weight heparin.

Results. Two patients withdrew from the investigation before the control visit. After seven days, therapy was stopped in the case of 16 Lipohep patients and 18 low molecular weight heparin patients. After 14 days, therapy was stopped in 21 and 25 patients, respectively. One low molecular weight heparin and five Lipohep patients did not finish the investigation. This was connected with a lack of clinical improvement and development of side-effects. A statistically significant reduction of pain and the appearance of erythema was observed in both patient groups during the initial seven days of treatment. One patient on low molecular weight heparin was diagnosed with superficial thrombophlebitis recurrence. Ten patients developed complications, with deep venous thrombosis being most significant (two patients were treated with Lipohep and one with enoxaparin). One patient on Lipohep treatment developed superficial thrombophlebitis of the upper extremity.

Conclusions. Liposomal heparin spray-gel is safe and effective in the treatment of local superficial thrombophlebitis symptoms. The initial results considering the use of Lipohep are promising and should be confirmed in a larger group of patients.

Key words: heparin spray-gel, superficial thrombophlebitis

Superficial thrombophlebitis can lead to the development of deep venous thrombosis. According to different authors, the above-mentioned complication is observed in 5.6-44% of cases. The risk of deep venous thrombosis is increased by the following: massive superficial thrombophlebitis of the saphenous and small saphenous veins, long-lasting immobilization, pregnancy, puerperium, oral contraception, thrombophilia, and male gender (1-7). According to other sources, chronic venous insufficiency is considered to be a significant risk factor of superficial thrombophlebitis (8).

The typical treatment of thrombophlebitis consists of the administration of local or oral anti-inflammatory drugs in combination with compression therapy. In cases of increased risk, therapy should be supplemented by low molecular weight heparin (9, 10, 11). According to some authors, the local use of low molecular weight heparin in the form of a gel is connected with similar treatment results obtained after the subcutaneous administration of he-
parin, which is more convenient for the patient (12). Recently, heparin in the new form of liposomal spray-gel appeared on the market. Investigations showed that heparin administered by means of the above-mentioned method is better absorbed and its activity lasts longer, which is connected with the gradual release of liposomes (13-16).

The presented study is an analysis of two clinical investigations determining the efficacy and safety of spray-gel heparin in the treatment of thrombophlebitis, as well as the comparison of results obtained after subcutaneous administration of heparin (17, 18).

MATERIAL AND METHODS

Two multicenter, randomized, II-phase clinical investigations were undertaken on two similar patient groups with superficial thrombophlebitis, confirmed by means of ultrasonography. Initial symptoms developed no earlier than 72 hours after diagnosis. Both sexes, with ages between 18 and 70 years, were qualified for the study. Table 1 presented the exclusion criteria.

The first group of patients received Lipohep three times daily and four atomizations with 458 units of heparin each followed by a delicate skin massage. The second group of patients received low molecular weight heparin (enoxaparin 40 mg) in the form of subcutaneous injections. Additionally, all patients were subjected to compression therapy using elastic stockings individually fitted to the size of the patients’ extremity. In the case of pain, patients received paracetamol at a maximum dose of 1000 mg daily, which was noted in the study protocol. During every visit, the Lipohep bottle was weighed in order to determine the amount of drug used, as well as the number of remaining enoxaparin ampoules. Therapy lasted 7 or 14 days, until the regression of clinical symptoms. Seven days after treatment, patients showed up for the control visit, in order to exclude disease recurrence. Investigations with the use of placebo were not undertaken, as it was considered unethical.

When evaluating the efficacy of the treatment, the following were considered:

- evaluation of pain – a 10 centimeter image scale (VAS – Visual Analog Scale), and five-degree pain scale (0 – no pain, 4 – most intensive pain),
- erythema – linear calculation and determination of the surface of the field,
- duplex Doppler ultrasound examinations performed during the 1st, 7th, 14th and 21st days of the investigation, in order to exclude deep venous thrombosis and determine the size of the superficial venous system thrombus,
- evaluation of the efficacy of treatment on the basis of a five-point scale determined by the patient and investigator.

When evaluating the safety of treatment, the following were considered:

- documentation of side-effects and occurrence of deep venous thrombosis,
- evaluation of the tolerance of the drug by the patient and investigator using a special questionnaire,
- laboratory results collected at the beginning and end of therapy (morphology, alanine and aspartate transaminases, GGTP, fibrinogen, APTT, creatinine).

All variables were subjected to statistical analysis using Wilcoxon’s, U Mann-Whitney’s and Chi-square tests.

RESULTS

During the period between March 1999 and May 2002, the study group was comprised of 88 patients; 43 were subjected to Lipohep treatment and 45 to subcutaneous low molecular weight heparin therapy. Both groups were comparable, considering the following parameters: age, body weight, height, smoking, history of thromboembolic episodes, and concomitant diseases. Two patients, one from each group, withdrew from the study before the control visit (the so-called drop-outs). Sixteen Lipohep and 18 low molecular weight heparin patients stopped treatment after 7 days of the investi-
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The remaining patients (21 and 25 in each group, respectively) finished treatment after 14 days. Five patients from the Lipohep group and one from the enoxaparin group did not finish the study. This was connected to a lack of clinical improvement or occurrence of complications. Table 2 presents the number of patients during different stages of the investigation.

Table 2. Patients’ participation in the trial

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<tr>
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<th>Lipohep</th>
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<td>K</td>
<td>G</td>
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<tr>
<td>Drop outs</td>
<td>1 0 1</td>
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<tr>
<td>Completed on day 7</td>
<td>6 10 16</td>
<td></td>
</tr>
<tr>
<td>Completed on day 14</td>
<td>12 9 21</td>
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</tr>
<tr>
<td>Discontinued</td>
<td>2 3 5</td>
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<td>43 45</td>
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Considering both groups, we observed a statistically significant reduction of pain measured by means of the VAS image scale during the initial seven days of treatment (fig. 1), as well as reduction of the size of the erythema (fig. 2). The subjective evaluation, considering improvement after treatment (both in case of patient and physician), showed no statistically significant differences between the investigated groups. Thrombus reduction was observed in both groups following duplex Doppler examinations, and median values reached 0 during the control examination. Only one patient on low molecular weight heparin was diagnosed with recurrence of thrombophlebitis.

Ten patients developed complications. Deep venous thrombosis was the most significant complication, and was observed in one enoxaparin and two Lipohep patients. One patient on Lipohep therapy developed deep venous thrombosis of the upper extremity. All of the above-mentioned patients required hospitalization. Six of the patients were diagnosed with an allergic reaction resulting in redening and itching of the skin and epidermal desquamation. Since these symptoms often coexist with superficial thrombophlebitis, it is difficult to unambiguously determine whether they are connected with drug intolerance in all cases.

Laboratory results showed elevated levels of fibrinogen in nearly 40% of patients. One patient on low molecular weight heparin presented with transient elevated transaminase levels. The remaining laboratory results were within normal limits. No statistically significant differences were observed between patient groups.

DISCUSSION

Recommendations concerning treatment of superficial thrombophlebitis are often divergent; the discussion concerning the issue is in full bloom. Thus far, treatment of superficial
thrombophlebitis has been limited to compression therapy and non-steroid anti-inflammatory drugs. However, the above-mentioned disease entity can lead towards the development of deep venous thrombosis and thus, compression therapy is insufficient (1-5). According to recently published data, the coexistence of deep venous thrombosis and superficial thrombophlebitis ranges between 5.6 and 44% (3, 4, 5). The investigation that compared the efficacy of naproxen and nadroparin demonstrated that low molecular weight heparin is as effective in the treatment of superficial thrombophlebitis as non-steroid anti-inflammatory drugs (19). Thus, the importance of combined treatment consisting of compression therapy and low molecular weight heparin injections, considering both its antithrombotic and anti-inflammatory activity.

In 1995, Artmann and co-authors examined 64 healthy volunteers and demonstrated that the penetration of heparin through the skin by means of the liposomal spray was threefold better, in comparison to the gel form (considering the same amount of heparin) (14). In 2001, Incadel and co-authors published initial study results concerning the use of Essaven–liposomal gel containing heparin, estimating it as effective and safe (12).

Study results with the use of Lipohep and subcutaneous low molecular weight heparin demonstrated that liposomal spray-gel heparin is safe and effective in the treatment of superficial thrombophlebitis. The above-mentioned form seems to be more attractive for the patient due to the easy applicability without the need for injections. However, one should not forget that none of the above-mentioned drugs completely protect one from deep venous thrombosis development. Although the complication is rarely observed, patients with superficial thrombophlebitis should be monitored. In case of clinical suspicion of deep venous thrombosis, ultrasound examinations should be performed. Initial results concerning Lipohep use are promising and should be confirmed on a larger group of patients.

REFERENCES

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