REVIEW ARTICLE

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Topically Applied Heparins for the Treatment of Vascular Disorders

A Comprehensive Review

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Contents

Abstract

Effective treatment of peripheral vascular disorders is important not only for resolution of local symptoms but also for preventing the development of systemic conditions such as deep vein thrombosis. Topical heparins are widely used in Europe for the prevention and treatment of local symptoms associated with peripheral vascular disorders. This comprehensive review of the literature evaluated the efficacy and safety of topically applied heparins for the treatment of vascular disorders. A total of 1055 patients participated in a total of 20 studies that compared topical heparin formulations with placebo, no treatment, subcutaneous heparin or with each other in the treatment of superficial thrombophlebitis or venous insufficiency. Heparin gel 1000 IU/g (Lioton® 1000 gel, Menaven® 1000 gel) was more effective than placebo in reducing the signs and symptoms of superficial thrombophlebitis. Liposomal heparin gel 2400 IU/g (LipoHep Forte®) was as effective as subcutaneous low-molecular-weight heparin at relieving local symptoms of superficial venous thrombosis. In head-to-head studies comparing different topical heparin formulations, all preparations appeared effective but heparin gel 1000 IU/g was superior to a heparinoid mucopolysaccharide cream (Hirudoid®) in patients with vascular disorders in terms of resolving spontaneous pain, induced pain, oedema and heaviness in the limb. Another study demonstrated the superiority of heparin gel 1000 IU/g compared with a gel formulation

containing heparin 100 IU/g, aescinate and essential phospholipids (Essaven®), for symptom resolution. All treatments were generally well tolerated, with a relatively low incidence of local skin events. In summary, topical heparin preparations may be useful for relieving the signs and symptoms of vascular disorders while improving microcirculation. There is some evidence to suggest that heparin gel 1000 IU/g may be more effective than other topical preparations in treating these conditions, possibly because of the relatively high heparin levels in this formulation. This remains to be tested in well controlled, adequately powered clinical trials.

Table I. Topical heparin and heparinoid formulations

Topical heparin	Formulation	Ingredients
Lioton®	Gel	Heparin 1000 IU/g
Essaven®	Gel	Heparin 100 IU/g, aescinate 0.01 g/g, essential phospholipids 0.01/g
LipoHep Forte®	Spray gel	Liposomal heparin 2400 IU/g
Hirudoid®	Cream	Mucopolysaccharide polysulfate 3 mg/g (heparinoid)
Movelat®	Cream	Organoheparinoid 0.2%, adrenocortical extract 1%, salicylic acid 2%

Heparin is a naturally occurring anticoagulant produced by mast cells and basophils that activates antithrombin III, leading to inactivation of thrombin, factor Xa and other molecules involved in the blood-clotting cascade.[1] The anticoagulation benefits of endogenous heparin have been exploited in various commercial formulations that are administered intravenously or subcutaneously for the primary or secondary prevention of venous thromboembolism following surgery or periods of immobilization,[2] treatment of acute coronary syndrome,[3] and for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion.[4] However, while parenteral heparin formulations are highly effective at preventing the formation of blood clots and the extension of existing clots, they are also associated with increased risk of major bleeding,[5] which limits their usefulness in chronic or relatively minor conditions.

Several topical heparin and heparinoid formulations have also been developed (table I). These gels or creams allow heparin to penetrate through the skin to the microcirculation at the site of application, with a lack of systemic exposure at clinically relevant doses, hence reducing the risk of adverse bleeding effects.[6] Topical heparins are widely used in Europe for the prevention and treatment of local symptoms associated with peripheral vascular disorders such as superficial thrombophlebitis, varicose veins or venous insufficiency.[7] However, despite their widespread use, there are few published data evaluating the efficacy and safety of topical heparins.

This comprehensive review of the literature evaluates the efficacy and safety of topically applied heparins for the treatment of vascular disorders.

1. Search Strategy

Clinical studies that evaluated the efficacy and safety of a topical heparin in vascular disorders were identified by performing a sensitive search of MEDLINE (1996 to September 2007) using the medical subject heading (MeSH) terms 'heparin' and 'administration, topical'. Searches were limited to clinical trials; however, no language restrictions were applied. Search results were refined by hand, with additional reports identified from reference lists of retrieved reports and reviews.

2. Efficacy and Safety in Vascular Disorders

2.1 Treatment of Superficial Thrombophlebitis

Inflammation and clotting inside a superficial vein is known as superficial thrombophlebitis or as varicose phlebitis when it affects a varicose vein. Signs and symptoms include the rapid development of localized pain and swelling, erythema and tenderness. The vein may often feel hard under the skin. Several studies have investigated the efficacy of topical heparin formulations in patients with superficial thrombophlebitis or varicose phlebitis.

2.1.1 Noncomparative Trials

Evaluation of heparin gel 1000 IU/g (Lioton® 1000 gel, Menaven® 1000 gel)[1] in a number of small noncomparative studies in patients with superficial thrombophlebitis has indicated that this agent is able to effectively resolve symptoms, particularly pain and oedema, without affecting systemic coagulation. Statistical analysis of changes from baseline was generally not performed in these studies.

The clinical effectiveness of heparin gel 1000 IU/g was assessed in 20 patients with recent-onset varicose phlebitis of the lower limbs.[8] The gel was applied three times daily for 15 days and then twice daily for an additional 15 days. At days 15 and 30, improvements in pain, erythema and oedema were observed compared with baseline, without any systemic or local adverse events being reported.[8] In a similar study of 30 patients with superficial thrombophlebitis, varicose phlebitis or periphlebitis, treatment with heparin gel 1000 IU/g three times daily for 18–25 days (mean 20.6) produced statistically significant improvements ($p < 0.05$ vs baseline) in spontaneous and induced pain, oedema, erythema, functional limitations, sense of heaviness, paraesthesia, induration and venous turgor.[9] In addition, erythrocyte sedimentation rate (a marker of inflammation) was reduced over time by 71.6%. However, no significant improvements in skin lesions, ulcerations or night cramps were reported. The drug was well tolerated, with no adverse events observed.[9] A comparable pattern of response was reported in 20 patients with phlebitis, periphlebitis or varices treated with heparin gel 1000 IU/g two or three times daily for 3–20 days.[10] In this study, acute improvements in oedema, erythema, induration and venous turgor were observed. While effects on night cramps and skin lesions were less evident, two patients with ulceration had a notable improvement in skin appearance. One patient withdrew from the study as a result of onset of erythema and pruritus.[10] In another study in which patients with a variety of vascular disorders, including superficial thrombophlebitis, were treated with heparin gel 1000 IU/g once a day for a maximum of 30 days, all clinical parameters except panniculitis and liponecrosis improved after 30 days.[11] After day 15, improvements in sense of heaviness, pruritus, oedema, haematoma, erythema, spontaneous and induced pain, cutaneous induration, skin lesions and functional limitations were statistically significant compared with baseline ($p < 0.01$). Improvements in paraesthesia, night cramps and venous turgor had reached statistical significance by day 30 ($p < 0.01$). Positive results were obtained in cases of acute superficial thrombophlebitis, where treatment contributed to regression of inflammation and resolution of thrombotic process. Two patients experienced topical adverse effects (erythema and excessive skin dryness).[11] In another study of 32 patients with superficial thrombophlebitis, hypodermitis (skin inflammation secondary to venous insufficiency) or complications after sclerotherapy, application of heparin gel 1000 IU/g for 4 weeks resulted in a significant improvement in induration, pain, swelling and function compared with baseline.[12] These findings were supported by the results from a larger study of 71 patients with superficial thrombophlebitis, varicose phlebitis, periphlebitis, varices or post-saphenectomy haematomas.[13] Treatment with heparin gel 1000 IU/g three times daily for 7–28 days resulted in a prompt improvement in subjective and objective signs and symptoms, with dermatitis being reported in only one patient.[13]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

In most of the studies described, heparin gel 1000 IU/g did not appear to have any effect on systemic haematological parameters (including blood or plasma viscosity, serum lipid levels, or coagulation markers).[8,10,11,13] In one study, heparin had an adverse effect on the leukocyte count, which decreased over time by 35.2%.[9] However, no other significant changes in haematological parameters were observed.[9] When measured, no clinically relevant impairment of the deep venous system was noted.[9,11]

A heparin cream has also been evaluated in a small noncomparative study in patients with superficial thrombophlebitis either induced by chemotherapy (n = 46) or of spontaneous origin (n = 2).[7] The cream was formulated by the study investigators using commercially available heparin (25 000 IU) in 25 g of an anhydrous lanolin base, and was administered for 7–10 days or until resolution of the thrombophlebitis. The majority of patients (n = 42) reported total symptom resolution within 1 week (statistical comparison with baseline not reported). It was noted that patients who did not respond to treatment had begun therapy more than 1 week after the onset of phlebitis symptoms. Prolongation of partial thromboplastin time or prothrombin time was not seen in any patient.[7]

In a small study of 15 hospitalized patients with superficial thrombophlebitis, twice-daily application of a gel formulation containing heparin 100 IU/g, aescinate and essential phospholipids (Essaven®) produced an improvement in oedema, excessive warmth, flushing and pain after 7 days of therapy, with the majority of patients having complete resolution of symptoms (statistical analysis not reported).[14] No effects on coagulation parameters were observed.

2.1.2 Comparative Trials

A number of trials have compared a topical heparin with another active treatment, placebo or no treatment (summarized in table II). These studies indicate that heparin preparations are more effective at resolving symptoms than placebo. As in the noncomparative studies discussed in the previous section, a small number of patients treated with topical heparins experienced local skin reactions.

The efficacy and tolerability of heparin gel 1000 IU/g was compared with placebo in a randomized, double-blind study of 126 patients with infusion-related superficial thrombophlebitis.[15] Heparin gel 1000 IU/g or matching placebo was applied to the lesion three times daily until clinical healing or for a maximum of 7 days. In the intention-to-treat analysis, heparin gel 1000 IU/g produced a higher incidence of healing compared with placebo (34.4% vs 21.5%, respectively; $p = 0.033$) [figure 1], resulting in a relative risk of healing in favour of heparin gel 1000 IU/g of 1.69 (95% CI 1.03, 2.78). The number needed to treat to achieve one clinical healing was six. A high rate of withdrawal was observed in the treatment groups (36.4% with heparin gel 1000 IU/g vs 37.9% with placebo), all of whom were considered as failures in the intention-to-treat analysis. The clinical course of phlebitis and investigators' global impression favoured the heparin gel 1000 IU/g group. Only one adverse event was reported: a case of mild contact urticaria in a recipient of heparin gel 1000 IU/g that was thought to be probably related to treatment.[15]

The efficacy and tolerability of a heparinoid mucopolysaccharide cream (Hirudoid®) in patients with superficial thrombophlebitis has been demonstrated in several placebo-controlled studies. In 100 patients with infusion-related superficial thrombophlebitis, 5 days' treatment with the mucopolysaccharide cream (along with firm bandaging) significantly reduced time to relief of local symptoms compared with placebo (mean 58 vs 126 hours, respectively; $p < 0.05$).[16] In this study, patients were also administered ^{125}I-fibrinogen as a means of detecting and measuring any thrombi. Those in the mucopolysaccharide cream group had a reduced percentage of radioactivity (indicating thrombus regression) compared with placebo ($p < 0.001$ on day 3). No local or systemic adverse events were reported.[16] Similar benefits of the mucopolysaccharide cream over placebo in terms of symptom resolution and thrombus regression were reported in 40 patients with postoperative infusion-related superficial thrombophlebitis ($p < 0.05$); however, in this study, one case of local allergic reaction to the muco-

Table II. Comparative studies in patients with superficial thrombophlebitis

Heparin	Comparator	Patients (n)	Aetiology of thrombophlebitis	Duration of treatment	Endpoints	Study design	Reference
Treatment							
Heparin gel 1000 IU/g	Placebo	126	Infusion-related	7 days	Time to healing Signs and symptoms	Double-blind Treatment allocation concealed	15
Heparinoid mucopolysaccharide cream	Placebo	100	Infusion-related	5 days	Time to local sign/ symptom relief ^{125}I-fibrinogen uptake	Double-blind Treatment allocation concealed	16
Heparinoid mucopolysaccharide cream	Placebo	40	Infusion-related	Unclear	Local sign/symptom relief ^{125}I-fibrinogen uptake	Double-blind Treatment allocation unclear	17
Heparinoid mucopolysaccharide cream	Placebo	50	Sclerotherapy in patients with varicose veins	1 or 2 weeks	Pain Signs and symptoms Investigator-assessed improvements	Double-blind One leg was exposed to mucopolysaccharide cream and the other to placebo (randomized allocation)	18
Heparinoid mucopolysaccharide cream	Placebo, piroxicam	68	Spontaneous or infusion-related	2 weeks	Thrombophlebitic status Thrombophlebitic area Pain	Single-blind for mucopolysaccharide cream Allocation concealment unclear	19
Heparin gel 1000 IU/g	Heparinoid mucopoly-saccharide cream	44	Various vascular disorders (seven patients with superficial thrombophlebitis or post-phlebitis syndrome)	4–6 weeks	Symptom score	Blinding unclear Randomization unclear	20
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	30	Various vascular disorders (six patients with superficial thrombophlebitis or post-phlebitis syndrome)	20 days	Symptom score	Blinding unclear Randomization unclear	21

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Table II. Contd

Heparin	Comparator	Patients (n)	Aetiology of thrombophlebitis	Duration of treatment	Endpoints	Study design	Reference
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	40	Various vascular disorders (32 with superficial thrombophlebitis or post-phlebitis syndrome)	Mean 57.5 days	Improvement or no improvement	Blinding unclear Randomization unclear	22
Liposomal heparin spray gel 2400 IU/g	Enoxaparin sodium	46	Superficial venous thrombosis	14 days	Symptom score Duplex ultrasound	Open-label Randomized	23
Prevention							
Heparin ointment	Untreated controls, fluocinolone acetonide	110	Prevention of infusion-related thrombophlebitis	Duration of infusion	Incidence of superficial thrombophlebitis	No blinding Unclear if treatment was randomized	24
Organoheparinoid 0.2%, adrenocortical extract, salicylic acid (Movelat®)	Placebo	97	Prevention of infusion-related thrombophlebitis	Duration of infusion	Incidence of superficial thrombophlebitis. Time to development of superficial thrombophlebitis	Blinding unclear Concealment of treatment allocation unclear	25

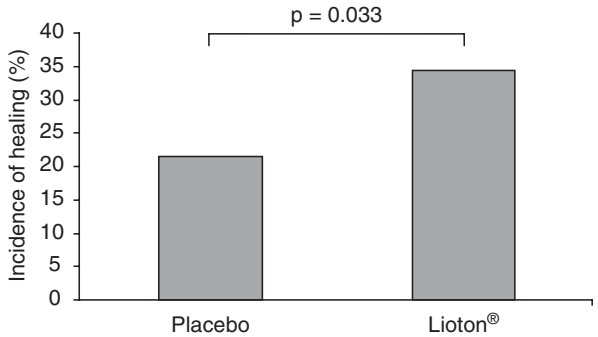

Fig. 1. Incidence of healing (%) in patients with infusion-related superficial thrombophlebitis following treatment with placebo or heparin gel 1000 IU/g (Lioton®).[15] Percentages were calculated from intention-to-treat data.

polysaccharide cream was also reported.[17] The mucopolysaccharide cream was also investigated in 50 patients with varicose veins undergoing sclerotherapy.[18] In this randomized, double-blind study, each patient received mucopolysaccharide cream on one leg and placebo on the other twice daily for 1 or 2 weeks. Legs exposed to the mucopolysaccharide cream were rated as showing greater levels of investigator-assessed 'intense improvement' than those exposed to placebo ($p = 0.002$), although no significant differences in pain, haematoma, oedema or other symptoms were reported. No adverse events were reported with either treatment.[18]

The heparinoid mucopolysaccharide cream has also been compared with active treatment in patients with superficial thrombophlebitis in a study that found no significant difference in efficacy between the mucopolysaccharide and topical NSAID piroxicam.[19] In this randomized, double-blind study, 68 patients with spontaneous or infusion-related superficial thrombophlebitis were treated with mucopolysaccharide cream, piroxicam gel or placebo twice daily for 14 days or until resolution of symptoms. Thrombophlebitis symptoms, size and pain improved compared with baseline in all groups, and no significant differences between treatment groups were observed. No adverse events were reported with the mucopolysaccharide cream, while one placebo recipient and one piroxicam recipient developed a reversible mild skin rash. Furthermore, one patient in each treatment group developed progres-

sive thrombophlebitis of the large saphenous vein, requiring vein stripping.[19]

Several studies have also directly compared heparin preparations in the treatment of superficial thrombophlebitis. In one study, 44 patients with different vascular diseases including superficial thrombophlebitis or post-phlebitis syndrome were treated with heparin gel 1000 IU/g or mucopolysaccharide cream, applied two or three times daily for 4–6 weeks.[20] A proportionally greater degree of improvement was observed with heparin gel 1000 IU/g compared with mucopolysaccharide cream in terms of spontaneous pain, induced pain, oedema and heaviness in the limb. Investigator and patient assessments suggested an improvement of 99% with heparin gel 1000 IU/g compared with 63% with mucopolysaccharide cream (figure 2). However, no statistical analysis was performed. No skin irritations were observed in either group and neither drug had any reported effect on systemic coagulation parameters.[20]

Potential benefits of heparin gel 1000 IU/g compared with heparin/aescinate/phospholipid gel were also reported in a comparative study in 30 patients with different vascular diseases, including superficial thrombophlebitis or post-phlebitis syndrome.[21] Both preparations significantly improved therapeutic parameters compared with baseline ($p < 0.01$). Treatment with heparin gel 1000 IU/g twice daily for 20 days produced a greater degree of improvement in terms of pain, erythema, haematoma, heaviness and oedema (all $p < 0.01$), and in functional limitations and night cramps (both $p < 0.05$), compared with the heparin/aescinate/phospholipid gel, with improvements being noted after 7 days. Safety data were not reported.[21] In another study of 40 patients with different vascular diseases, including superficial thrombophlebitis or post-phlebitis syndrome, twice-daily application of heparin gel 1000 IU/g improved symptoms of oedema, pain, erythema, haematoma and heaviness in a higher proportion of patients than heparin/aescinate/phospholipid gel; however, no statistically significant differences were observed between treatments.[22] Of note, both treatments produced reductions in erythrocyte sedimentation rate (−26.7% with heparin gel 1000 IU/g and −28.7% with heparin/aescinate/phospholipid gel); however, no coagulation parameters were modified with therapy.

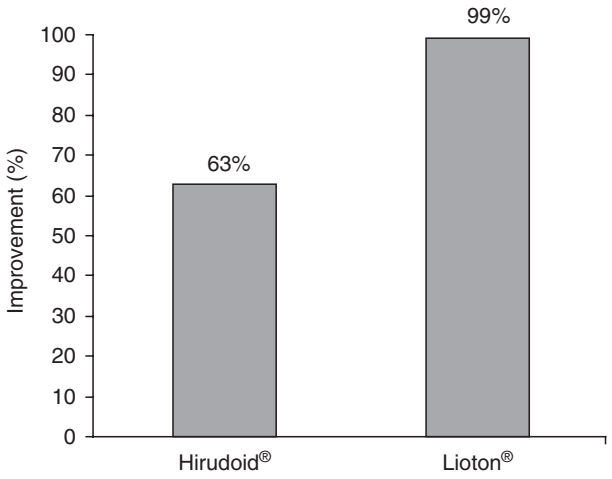

Fig. 2. Percentage of improvement in patients with different vascular diseases (including superficial thrombophlebitis or post-phlebitis syndrome) following treatment with mucopolysaccharide cream (Hirudoid®) or heparin gel 1000 IU/g (Lioton®).[20] Percentage of improvement was estimated based on investigator and patient assessments.

A liposomal heparin spray gel (LipoHep Forte®) was compared with subcutaneous low-molecular-weight heparin in a randomized, open-label trial of 46 patients with superficial venous thrombosis.[23] Fourteen days' treatment with the liposomal heparin spray gel (four sprays of 458 IU three times daily) was as effective as subcutaneous enoxaparin sodium (40 mg once daily) in reducing local symptoms, including pain and erythema, and regressing superficial thrombi. Deep vein thrombosis was reported in three patients in the topical heparin gel group and one in the subcutaneous heparin group. Both preparations were generally well tolerated, although one serious allergic reaction was reported with subcutaneous low-molecular-weight heparin.

2.2 Prevention of Superficial Thrombophlebitis

Superficial thrombophlebitis is a frequent complication of intravenous therapy and prophylactic treatment for this condition may therefore be of benefit. Two studies were identified that evaluated use of heparin preparations for this purpose. In the

first study, 110 patients receiving postoperative intravenous fluids were treated with heparin ointment 50 IU/g or fluocinolone acetonide ointment applied every 8 hours to the skin over the vein in which the intravenous catheter was placed.[24] A third group of patients served as untreated controls. Those treated with heparin ointment or fluocinolone acetonide ointment had a lower incidence of superficial thrombophlebitis than untreated controls (5% and 2.5% vs 20%, respectively); however, this difference was statistically significant only for fluocinolone acetonide ($p < 0.05$). No infective complications were reported.[24] In the second study, 97 patients undergoing an infusion of ≥48 hours (excluding those receiving intravenous feeding or administration of uncommon drugs) were randomized to a cream containing organoheparinoid 0.2%, adrenocortical extract and salicylic acid (Movelat®) or placebo, applied three times daily to the skin over the vein in which the intravenous catheter was placed.[25] Recipients of the organoheparinoid preparation had a lower incidence of superficial thrombophlebitis than those treated with placebo (17% vs 31%, respectively; $p < 0.05$). When superficial thrombophlebitis did occur, onset was delayed in the organoheparinoid group (mean time to onset: 66.4 vs 47.4 hours in the placebo group). No infective complications were reported.

2.3 Treatment of Venous Insufficiency

Venous insufficiency is defined as impaired venous return of blood from the limbs to the heart. The condition can cause lower extremity discomfort, oedema and skin changes, and may be a consequence of deep vein thrombosis. When venous insufficiency is symptomatic, it can be known as postphlebitic or post-thrombotic syndrome.

Topical heparin preparations have been used to treat some of the symptoms of venous insufficiency. A number of noncomparative studies have evaluated heparin gel 1000 IU/g for this condition. In 110 patients with acute and chronic venous insufficiency of the lower extremities who had undergone surgical intervention, treatment with heparin gel 1000 IU/g for 7–15 days reduced oedema, postoperative haematoma and pain, although statistical comparisons versus baseline were not performed.[26] Similarly, in 107 patients with a variety of vascular disorders who had undergone surgery, heparin gel 1000 IU/g produced a notable clinical improvement over time.[27] Furthermore, in 147 patients with lower extremity varicose syndrome, treatment with heparin gel 1000 IU/g significantly improved symptoms after 14 days ($p < 0.001$).[28] Improvements were particularly noted in terms of spontaneous pain and tenderness.

Several studies of heparin gel 1000 IU/g in patients with various vascular disorders including varices and post-saphenectomy haematomas were discussed earlier (see section 2.1.1). These studies all showed that patients treated with heparin gel 1000 IU/g had improvements in signs and symptoms without effects on systemic coagulation parameters.[10,11,13]

A number of studies have compared heparin/aescinate/phospholipid gel with placebo in patients with venous insufficiency, particularly focusing on the endpoint of microcirculation (table III). Microcirculation was evaluated by measuring transcutaneous oxygen pressure (PO_2) and carbon dioxide pressure (PCO_2) in the affected area. In two randomized, double-blind studies of patients with venous hypertensive microangiopathy due to varicose veins or venous ulcers, respectively, a single application of heparin/aescinate/phospholipid gel improved microcirculation parameters compared with placebo or no treatment ($p < 0.05$).[29,30] No adverse effects were reported in either study. Similar findings were reported following 3 days' treatment with heparin/aescinate/phospholipid gel or placebo in patients with venous hypertensive microangiopathy due to venous hypertension and venous ulcers.[31] In a similar study of 30 patients with venous incompetence due to post-thrombotic changes and well defined venous hypertensive microangiopathy, 4 weeks' treatment with heparin/aescinate/phospholipid gel also improved oedema, pain and microcirculation parameters compared with placebo or no treatment ($p < 0.05$). It should be noted, however, that all patients had clean, small

Table III. Comparative studies in patients with venous insufficiency

Heparin	Comparator	Patients (n)	Aetiology of venous insufficiency	Duration of treatment	Endpoints	Study design	Reference
Heparin/aescinate/ phospholipid gel	Placebo	22	Varicose veins	Single dose	Microcirculation	Double-blind Treatment allocation concealed	29
Heparin/aescinate/ phospholipid gel	Placebo	10	Venous ulceration	Single dose	Microcirculation	Double-blind Treatment allocation concealed	30
Heparin/aescinate/ phospholipid gel	Placebo	28	Venous ulceration	3 days	Microcirculation	Double-blind Treatment allocation concealed	31
Heparin/aescinate/ phospholipid gel	Placebo	30	Venous ulceration	4 weeks	Pain and oedema Microcirculation Ulcer healing	Double-blind Treatment allocation concealed	32
Heparin/aescinate/ phospholipid gel	Placebo	30	Diabetic neuropathies	Single dose	Microcirculation	Double-blind Treatment allocation concealed	33
Heparin/aescinate/ phospholipid gel	Placebo	15	Diabetic neuropathies	4 weeks	Microcirculation	Double-blind Treatment allocation concealed	34
Heparin/aescinate/ phospholipid gel	Placebo	35	Diabetic neuropathies	2 weeks	Microcirculation	Double-blind Treatment allocation concealed	36
Heparin gel 1000 IU/g	Heparinoid mucopoly-saccharide cream	44	Various vascular disorders (31 patients with chronic venous insufficiency)	4–6 weeks	Symptom score	Blinding unclear Randomization unclear	20
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	30	Various vascular disorders (24 patients with chronic venous insufficiency)	20 days	Symptom score	Blinding unclear Randomization unclear	21
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	40	Various vascular disorders (eight patients with varicose ulcers)	Mean 57.5 days	Improvement or no improvement	Blinding unclear Randomization unclear	22

ulcers.[32] Microcirculation was also evaluated in patients with diabetic neuropathies and localized small ulcers, in whom a single application of heparin/aescinate/phospholipid gel improved microcirculation parameters compared with placebo ($p < 0.05$).[33] Likewise, in patients with diabetic neuropathies and no ulceration, 2 and 4 weeks' treatment with heparin/aescinate/phospholipid gel improved microcirculation parameters in the feet compared with placebo ($p < 0.05$).[34,35] No adverse effects were reported in any of these studies.

Several comparative studies of heparin gel 1000 IU/g in patients with various vascular disorders including simple or chronic venous insufficiency or varicose ulcers were discussed earlier (see section 2.1.2). These studies showed that patients treated with heparin gel 1000 IU/g had a greater degree of improvement in signs and symptoms than those treated with mucopolysaccharide cream[20] or heparin/aescinate/phospholipid gel,[21] in particular regarding those symptoms most frequently reported by patients with this condition, including feeling of heaviness, cutaneous dyscrasias, erythema and pain due to haematoma.[22]

3. Discussion

Effective treatment of peripheral vascular disorders is important not only for resolution of local symptoms but also for preventing the development of systemic conditions such as deep vein thrombosis.[37] While it has been proposed that the local anticoagulation effects of topical heparins may produce improvements in microcirculation and vascular disorder symptoms, as well as preventing further development of disease, there is a paucity of robust data to support these suppositions.

In practice, several types of treatment for superficial thrombophlebitis have been used, including anticoagulants, NSAIDs and surgery; however, there is no consensus on the optimal treatment.[38] A systematic review of available data has suggested that currently there is most evidence for the use of low-molecular-weight heparin or NSAIDs.[38] The same systematic review found that topical treatments improved local symptoms.

The purpose of the current review was to evaluate the efficacy and safety of topical heparins in the treatment of vascular disorders, particularly superficial thrombophlebitis and venous insufficiency. Several noncomparative studies have provided a preliminary indication that topical heparins do improve symptoms of superficial thrombophlebitis or venous insufficiency, particularly pain, erythema and oedema, without affecting systemic coagulation or producing systemic adverse events.[7-14] However, few robust conclusions can be drawn from such studies, as the extent of the effect of topical heparins compared with normal healing processes is unclear.

A number of comparative trials were identified that compared topical heparin formulations with placebo or no therapy in the treatment of superficial thrombophlebitis or venous insufficiency. These studies provide a greater indication of the absolute benefits of topical heparin in patients with these conditions. Heparin gel 1000 IU/g and heparin/aescinate/phospholipid were both shown to be more effective than placebo in reducing the signs and symptoms of superficial thrombophlebitis.[15,34,35,39] Heparin/aescinate/phospholipid was also more effective than placebo in improving microcirculation parameters in patients with chronic venous insufficiency relating to varicose veins, venous ulcers or diabetic neuropathy.[29-34,37] Interestingly, while a heparinoid mucopolysaccharide cream produced greater improvements than no treatment or placebo in the signs and symptoms of superficial thrombophlebitis,[16-18] the magnitude of these improvements did not achieve statistical significance in one study.[17] Furthermore, the mucopolysaccharide cream was not as effective as an NSAID preparation.[19]

Several head-to-head studies were identified that compared different topical heparin formulations with each other. While all preparations appeared effective, heparin gel 1000 IU/g was superior to mucopolysaccharide cream in patients with vascular disorders in terms of resolving spontaneous pain, induced pain, oedema and heaviness in the limb.[20] Another study showed the superiority of heparin gel

1000 IU/g compared with heparin/aescinate/phospholipid with respect to symptom resolution.[21]

All treatments were generally well tolerated, with a relatively low incidence of local skin events, such as pruritus or erythema.

When comparing topical heparin preparations, it is important to consider what other active ingredients are included in the formulation (table I). For example, the aescinate and essential phospholipids in the heparin/aescinate/phospholipid gel may have an effect on inflammatory parameters.

It should be noted that the conclusions of this comprehensive review are primarily limited by the quality of the studies included. Many of the studies were conducted more than two decades ago, possibly limiting their current external validity given advances in clinical practice. Furthermore, studies generally included small numbers of patients and did not provide appropriate power calculations. While a number of studies evaluating heparin/aescinate/phospholipid gel were included in this review, these were mainly derived from the same journal supplement, and since it is not clear if these articles were peer reviewed, this could suggest a lack of credibility. In addition, the randomization methods used in head-to-head studies between topical heparin preparations were not clear. These studies were also all published in non-English language journals.

4. Conclusion

In summary, topical heparin preparations may be useful for relieving the signs and symptoms of peripheral venous disorders. There is some evidence that indicates that heparin gel 1000 IU/g may be more effective than other topical preparations in treating these conditions, possibly because of the relatively high heparin levels in the heparin gel 1000 IU/g formulation. This remains to be confirmed in well controlled, adequately powered clinical trials.

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