

ORIGINAL RESEARCH**Comparison of the safety & efficacy of topical penetrating solution and gel form of Heparin in the management of post infusion superficial thrombophlebitis****Sudha kumaradhas¹, Umesh Muthuvel², Henin Mohan³**¹Assistant Professor, Arunai medical College and hospital, Thiruvannamalai, Tanilnadu, India.²Assistant Professor, Arunai Cedral College and Hospital, Tiruvannamalai, Tamil Nadu, India.³Assistant Professor, Tagore Medical College and hospital Chennai, India.**ABSTRACT**

Background: To compare the safety & Efficacy of topical Quick penetrating solution of Heparin 1000 IU/ml to Heparin gel 200 IU/g in the management of post infusion superficial thrombophlebitis. **Method:** 100 Patients aged 18-60 years having grade 2-4 superficial thrombophlebitis based on phlebitis scale were randomized to receive either Heparin QPS 1000 IU/ml or Heparin gel 200 IU/g. It was applied over the phlebitis lesion 3 TDS×7days. Length of venous lesion graded as per “Standards for Infusion Therapy” phlebitic scale & Local symptoms graded on 4 point severity scale. Change in venous lesion and local symptoms were assessed on day 3 and complete healing on day 7. Global assessment by patient done at the end of study. **Results:** 3rd day change in the length of venous lesion with Heparin QPS(16.44±8.54) to heparin gel(21.26±11.25), (P=0.0177) Change in local symptoms, fall in tenderness(p=0.0065) & raised local temperature(p=0.0029) with QPS. Complete healing on day 7 was found to be 90% compared to 58% with heparin QPS to gel(P<0.001) Also significant fall in percentage of patients with grade 2&3 were reported in those treated with QPS to gel(p=0.017) Most of the patients graded Heparin QPS excellent(p<0.0001). **Conclusions:** Heparin QPS was found to be more effective in the treatment of post infusion superficial thrombophlebitis expressed by complete healing of the venous lesion as compared to heparin gel. Significant reduction in length of venous lesion from baseline, with fall in percentage of patients with grade 2&3, fall in local symptom scores on day 3. Significant proportion of patients completed healing on day 7.

Keywords: Heparin QPS Heparin GEL Thrombophlebitis**Corresponding Author:** Dr. Sudha kumaradhas, Assistant Professor, Arunai medical College and hospital, Thiruvannamalai, Tanilnadu, India.**INTRODUCTION**

Superficial thrombophlebitis is a common complication of continuous intra-venous infusion. It is a pathological condition characterized by presence of thrombus in the lumen of a superficial vein, followed by inflammatory reaction of its wall and adjacent tissues. It presents with a palpable, hot, painful and hyperemic cord through a superficial vein.

This thrombosis has variable amplitude, reaching from small tributaries until large extension of saphenous trunks in the lower limbs. In more severe cases, it can be extended to the deep venous system (DVS), it can also cause pulmonary embolism, and there are indications of an association with recurrent episodes of venous thromboembolism.

The association of superficial thrombophlebitis with deep venous thrombosis (DVT) according to publications ranges between 6-44% of affected subjects. The goals of treatment of superficial thrombophlebitis are to reduce pain and other symptoms and to prevent complications.

Effective treatment of superficial thrombophlebitis 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 for the prevention and treatment of local symptoms associated with peripheral vascular disorders including infusion induced superficial venous thrombophlebitis.

Topical formulation allows heparin to penetrate through the skin at the site of application, with a lack of systemic exposure at clinically relevant doses, hence reducing the risk of adverse bleeding effects.

Several line of clinical evidences suggest that higher concentration of topical heparin 1000 IU/g gel may be more effective than other topical preparations of heparin in treating superficial thrombophlebitis, possibly because of the relatively high heparin levels in this formulation and is generally well tolerated.

In India, topical heparin gel of lower strength (200 IU/g) is available and most commonly used in management of superficial thrombophlebitis. A newer novel topical Quick Penetrating Solution(QPS) of heparin sodium 1000 IU/ml, which contains non aqueous and non-volatile solvents with added permeability enhancers to increase penetration of the heparin across the skin is now available. Increased penetration of heparin may improve efficacy compared to conventional heparin gel.

QPS of Heparin sodium 1000 IU/ml in the form of spray is more effective than available Heparin gel and equally safe in management of superficial thrombophlebitis.

The study was conducted to compare the safety and efficacy of topical Quick penetrating solution of Heparin 1000 IU/ml versus Heparin gel 200 IU/g in the management of post infusion superficial thrombophlebitis.

AIMS & OBJECTIVES

To compare safety and efficacy of Heparin QPS with Heparin gel.

To compare the change in the length of venous lesion on day 3.

To compare the proportion of patients with complete healing on day 7.

To compare the change in local symptoms from baseline on day 3.

To compare the change in the grade of venous lesion on day 3.

To compare the patient's global assessment

MATERIALS AND METHODS

100 Patients of either sex aged 18-60 years having grade 2(early)-4(medium or advanced stage) of superficial thrombophlebitis based on phlebitis scale were divided in two groups.

- Group Q Heparin QPS group:n=50 with phlebitis grade 2-4
- Group G Heparin GEL group:n=50 with phlebitis grade 2-4

A. INCLUSION CRITERIA:

- Patients of either sex of phlebitis grade 2-4
- Age between 18-60 years
- Body weight between 50-80kg

B. EXCLUSION CRITERIA:

- Patients of phlebitis scale <2 & >5
- Age less <18 years and >60 years
- Body weight <50 kgs and >80 kgs
- Pregnant patients

- Personal /family history of adverse drug reactions or patients who is allergic or hypersensitive to heparin
- Patients with skin disease
- Patient with decreased number of platelet count or other bleeding disorders

All patients were randomized to receive either Heparin QPS or Heparin gel. Heparin QPS 1000 IU/ml (manufactured by Troikaa Pharmaceuticals Ltd, Ahmedabad, India) or Heparin gel containing Heparin Sodium Gel 200 IU/g (Thrombophob gel, Zydus Cadila India). The study medications were applied to cover the phlebitis lesion TDS for 7 consecutive days. Length of venous lesion in millimeter was measured using a pre calibrated stainless steel and grade of the lesion was noted using phlebitis scale, before the start of the study and on day 3 after initiation of treatment. Also the grade of the lesion using Phlebitis Scale as per “Standards for Infusion Therapy” by Royal College of Nursing IV Therapy Forum, July 2003 was noted at baseline and on day 3 after initiation of treatment. In this phlebitis scale was assessed on a 5 grade scale.

scales defining severity of PVC-related thrombophlebitis:

Grades	INS(2006)
0	No symptoms
1	Erythema at the site with or without pain
2	Pain at access site with erythema and/or edema
3	streak formation ,Palpable venous cord ,Pain at access site with erythema and/or edema
4	Streak Formation, Palpable venous cord >1inch in length Purulent drainage

Phlebitis scale:

- Grade 0-no sign of phlebitis
- Grade 1-possibly the first sign of phlebitis
- Grade 2-early sign of phlebitis
- Grade 3- medium stage of phlebitis
- Grade 4-advanced stage of phlebitis or stage of thrombophlebitis
- Grade 5- advanced stage of thrombophlebitis

On the basis of this scale, change in the grade of lesion was noted on day 3, 7 and proportion of patients with complete healing was noted on day 7.

Local symptoms like pain, tenderness, redness, raised local temperature, and venous induration were assessed on 4 point severity scale (0-none,1-light, 2-moderate,3-severe) at baseline and on day 3.

Heparin QPS is a novel formulation of topical heparin provides significantly enhanced penetration of heparin sodium through the skin resulting in faster resolution of superficial thrombophlebitis, as compared to conventional topical heparin creams or ointments

Heparin QPS is a clear colorless solution available in a glass bottle each ml delivers approximately 34-40 drops. 6-8 drops should be applied 3 TDS on the area of the affected skin with thrombophlebitis and its surroundings. Solution should be applied gently with a finger over the affected area. Patient should be advised to avoid washing treated area or come in contact with clothes or other subjects for 20-30 minutes after application.

Primary efficacy end points were change in the length of the venous lesion on day 3, proportion of patients with complete healing on day 7,

secondary efficacy end points included change in local symptoms on day 3 and change in the grade of the lesion on day 3.

Medications considered necessary for any concomitant illness and which will not interfere with the study drugs were allowed. Global assessment by patient based on efficacy and safety of the treatment was assessed at the end of study.

Quantitative data are presented as mean \pm standard deviation, whereas categorical data are expressed as absolute number/proportion of patients. Quantitative data of both the treatments groups were analyzed by unpaired “t” test based on the distribution of data. Chi-square test was used to compare the categorical data of both the treatment groups. P value of less than 0.05 was considered as statistically significant difference between both the treatment groups. All statistical analyses were performed using software, GraphPad prism, version no. 7.

OBSERVATION AND RESULTS

The present study was conducted in 100 patients of either sex of age group 18 to 60 years, having Grade 2-4 phlebitis (early, medium or advanced stage of phlebitis) based on phlebitis scale, were enrolled and randomized to either receive HEPARIN QPS (n=50) or HEPARIN GEL (n=50)

Group Q: Topical quick penetrating solution (QPS) of Heparin 1000 IU/ml.

Group G: Topical Heparin gel 200 IU/g.

The statistical analysis was done by unpaired t-test for quantitative data and Chi-square test for qualitative data.

Significance of P value suggested as follows:

‘P’ >0.05 insignificant.

‘P’ <0.05 significant.

‘P’ < 0.001 highly significant.

TABLE 1: PHYSICAL PARAMETERS OF THE STUDY GROUP

Characteristics	Heparin QPS(n=100)	Heparin GEL(n=50)	P value	significant
Age (years)	41.92 \pm 12.77	38.52 \pm 12.09	0.1747	Not significant
Weight(kg)	63.42 \pm 6.07	64.36 \pm 5.92	0.43	Not significant
Gender				
Male	27	26	0.841	Not significant
Female	23	24		
Length of venous lesion	27.24 \pm 11.29	27.51 \pm 11.13	0.904	Not significant

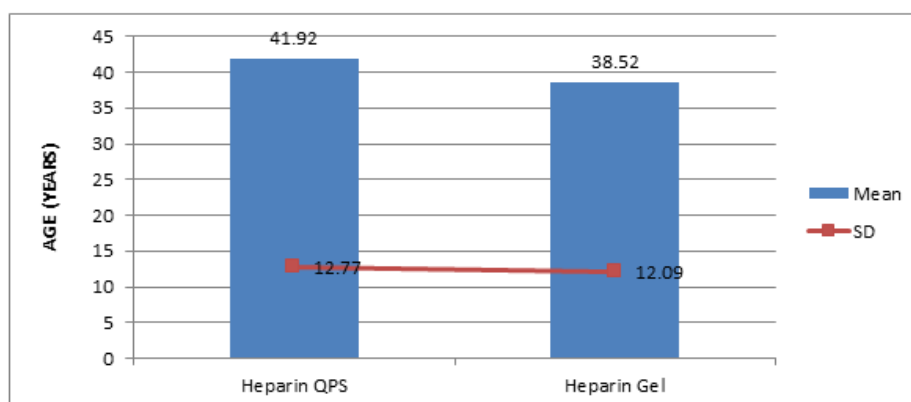


Figure 1: Chart of Age

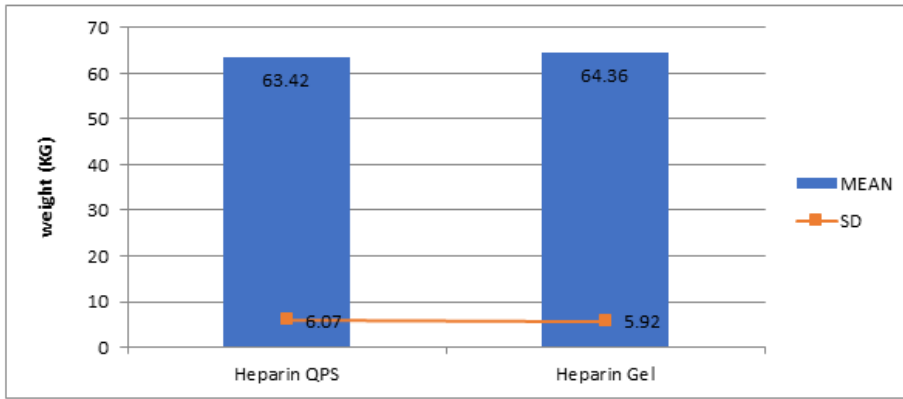


Figure 2: Chart of Weight

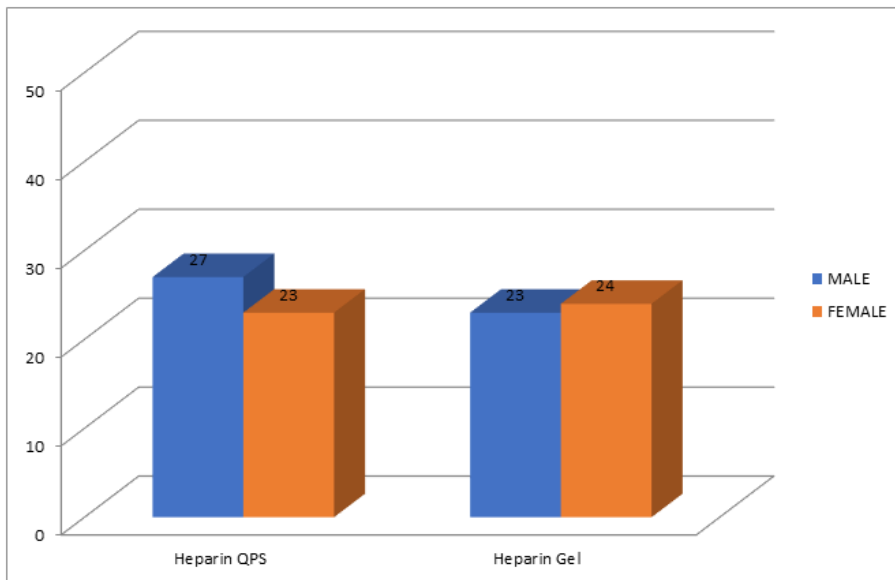


Figure 3: Chart of sex distribution

Both the groups were comparable in terms of age, weight distribution and baseline length of venous lesion and there was no significant difference between the two groups ($P > 0.05$).

PRIMARY EFFICACY END POINTS:

TABLE 2: CHANGE IN THE LENGTH OF VENOUS LESION ON DAY 3

	Heparin QPS	Heparin GEL	P value
Length of venous lesion on day 3	16.44±8.54	21.26±11.25	0.0177

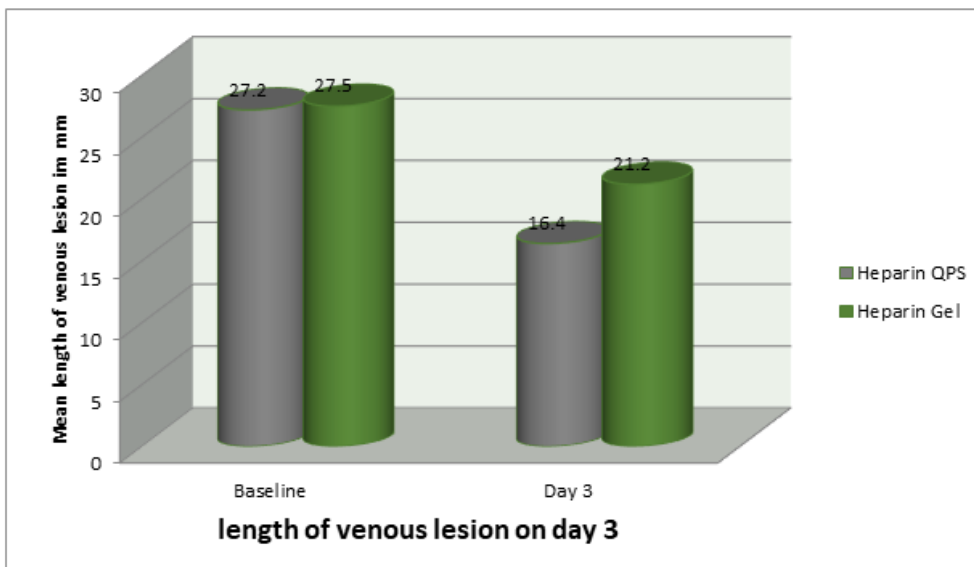


Figure 4: Change in the length of venous lesion

A significant reduction in length of venous lesion from baseline was observed in Patients treated with Heparin QPS on day 3, as compared to patients treated with heparin gel(P=0.0177).

TABLE 3: PROPORTION OF PATIENTS WITH COMPLETE HEALING ON DAY 7:

Healing	Heparin QPS	Heparin gel	P value
Yes	45(90%)	29(58%)	<0.0001
No	5(10%)	21(42%)	

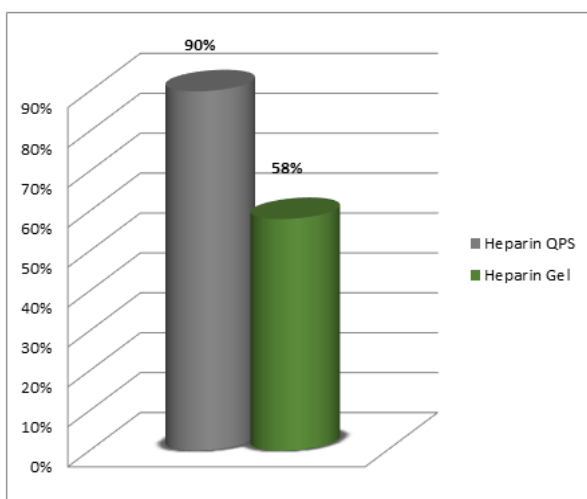


Figure 5: Proportion of Patients with Complete Healing on Day 7

In the Heparin QPS group 90% of the patients achieved complete resolution of the lesion on day 7, this was significantly higher compared to 58% of the patients treated with heparin gel(p<0.0001).

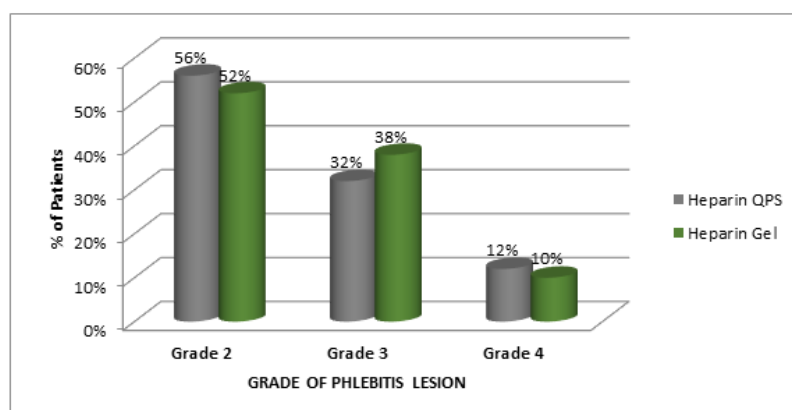
SECONDARY EFFICACY END POINTS**TABLE 4: CHANGE IN LOCAL SYMPTOMS FROM BASELINE**

Local Symptoms	Heparin QPS(n=50)			Heparin GEL(n=50)			P value
	Baseline score	Day 3 score	Change in score	Baseline score	Day 3 score	Change in score	
Pain	1.64± 0.66	0.88± 0.77	0.76± 0.62	1.6± 0.69	1.04± 0.72	0.56± 0.5	0.0789
Tenderness	1.6± 0.63	0.72± 0.83	0.88± 0.32	1.62± 0.69	0.98± 0.93	0.64± 0.52	0.0065
Redness	1.26± 0.48	0.66± 0.65	0.6± 0.49	1.56± 0.7	1.14± 0.92	0.42± 0.49	0.069
Raised local Temperature	0.68± 0.84	0.28± 0.60	0.4± 0.49	0.64± 0.7	0.5± 0.67	0.14± 0.35	0.0029
Venous Induration	0.64±0.69	0.44±0.6 11	0.2± 0.40	0.62± 0.94	0.54± 0.81	0.08± 0.27	0.081

The local symptoms were comparable at baseline in both the treatment groups. There was a significant fall in tenderness (p value 0.0065) and raised local temperature (p value 0.0029) as compared to baseline in patients treated with heparin QPS.

CHANGE IN THE GRADE OF VENOUS LESION**TABLE 5: GRADE OF PHLEBITIS LESION AT BASELINE:**

Grade of phlebitis	Heparin QPS	Heparin gel	P value
Grade 2(early stage of phlebitis)	28(56%)	26(52%)	0.810
Grade 3(medium stage of phlebitis)	16(32%)	19(38%)	
Grade 4(advanced stage of phlebitis)	6(12%)	5(10%)	

**Figure 6: Grade of Phlebitis Lesion at Baseline****TABLE 6: GRADE OF PHLEBITIS ON DAY 3**

Grade of phlebitis	Heparin QPS	Heparin gel	P value
Grade 0(no sign of phlebitis)	8(16%)	5(10%)	0.017
Grade 1(possibly the first sign of phlebitis)	26(52%)	12(24%)	
Grade 2(early stage of phlebitis)	11(22%)	22(44%)	
Grade 3(medium stage of phlebitis)	4(8%)	10(20%)	
Grade 4(advanced stage of phlebitis)	1(2%)	1(2%)	

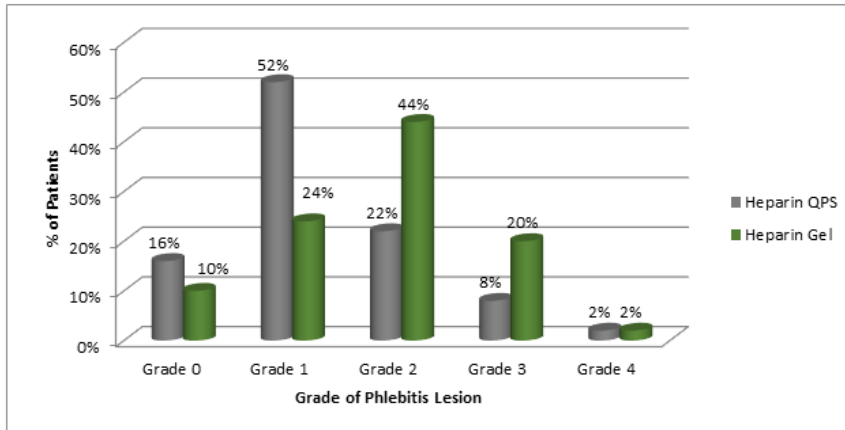


Figure 7: Grade Of Phlebitis at Day 3

Grade of venous lesion was comparable between both the treatment groups at baseline (p=0.810), however on day 3, a significant fall in percentage of patients with grade 2 & grade 3 was reported in those treated with heparin QPS as compared to heparin gel (p=0.017).

At baseline percentage of patients having phlebitis of grade 2 & 3 were 88% & 90% in Heparin QPS and Heparin GEL group respectively.

At day 3 of treatment proportion of patients in grade 2 & 3 of phlebitis were less in Heparin QPS 30% as compared to Heparin GEL group 64%.

At day 3, more proportion of patients of grade 0-1 were seen in Heparin QPS group 68% as compared to Heparin gel group 34%

PATIENT’S GLOBAL ASSESSMENT

TABLE 7: PATIENT’S GLOBAL ASSESSMENT

Global assesment	Heparin qps	Heparin gel	P value
Excellent	31(62%)	11(22%)	<0.0001
Good	16(32%)	14(28%)	
Fair	3(6%)	21(42%)	
Poor	0(0%)	4(8%)	

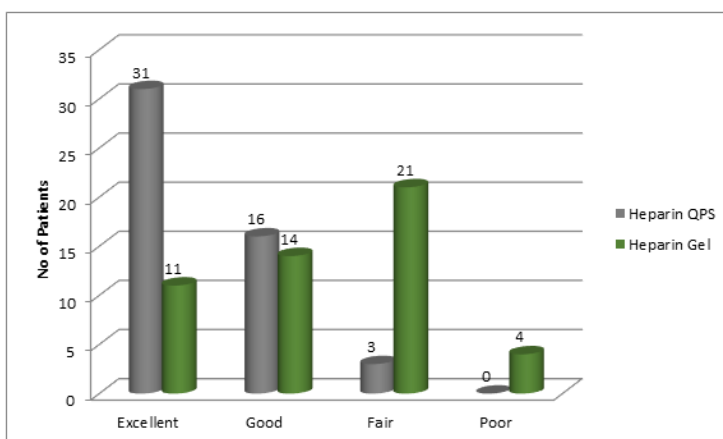


Figure 8: Patient's Global Assessment

Heparin QPS was rated Excellent to Good in most of the cases by patients (p<0.0001).

SAFETY END POINT:

No adverse events were reported and observed in either group during the study period.

DISCUSSION

Peripheral vein infusion thrombophlebitis is one of the most common complications associated with peripheral intra catheter, with the incidence of 25%-35% in hospitalized patients. Upto 75% of hospitalized patients with peripheral intravenous catheter develop infusion thrombophlebitis. Superficial thrombophlebitis leads to pain at the site of iv, erythema, swelling & induration, which cause a delay in intravenous therapy with extended hospital stay, adding up to the overall cost & discomfort. Also superficial thrombophlebitis leads to various complications like suppurative thrombophlebitis, bacteremia, DVT and pulmonary embolism.

Currently, medical therapies comprising bed rest, elastic stockings, compression bandages, NSAID and LMW heparin are used to reduce the extension of inflammation and recurrence of thrombotic events in patients experiencing SVT. Evidence based guidelines from American college of chest physicians,2008 recommended the use of oral diclofenac or topical heparin till symptoms resolved or up to 2 weeks.

NSAIDS show significant efficacy in reducing superficial thrombophlebitis, progression of inflammation and recurrence of SVT, however use of NSAIDS neither produce any change in the incidence of thrombotic events nor shorten the course of resolution of symptoms related to SVT. Randomized clinical trials have demonstrated the efficacy of topical heparin in the treatment of SVT, showing positive effect on pain and reduction in thrombus size. Topical formulation allows heparin to penetrate through the skin at the site of application, with a lack of systemic exposure at clinically relevant doses, hence reducing the risk of adverse bleeding effects.

In India, topical heparin gel of lower strength (200 IU/g) is available and most commonly used in management of superficial thrombophlebitis. A newer novel topical Quick Penetrating Solution (QPS) of heparin sodium 1000IU/ml, which contains non aqueous and non-volatile solvents with added permeability enhancers to increase penetration of the heparin across the skin, is now available. Increased penetration of heparin may improve efficacy compared to conventional heparin gel.

The study was undertaken to evaluate the safety and efficacy of topical quick penetrating solution of heparin 1000 IU/ml versus heparin gel 200 IU/g in the management of post infusion superficial thrombophlebitis. A randomized open label comparative clinical study was conducted, Patients of either sex aged 18-60 years, having early, medium and advance stage of superficial thrombophlebitis based on phlebitis scale (grade 2-4) were selected.

Total 100 Patients were enrolled and randomized to either receive heparin QPS (n=50) or heparin GEL(n=50).The study medications were applied to cover the phlebitis lesion 3 TDS for 7 consecutive days.

Primary efficacy endpoints were change in length of the venous lesion on day 3, proportion of patients with complete healing on day 7; while secondary efficacy endpoints included change in local symptoms on day 3, change in the grade of the lesion on day 3 and global assessment by patients at the end of study.

Mean age, weight, sex distribution and length of the venous lesion(Heparin QPS 27.24 ± 11.29 & Heparin GEL 27.51 ± 11.13) were comparable among both the groups($P > 0.05$). A significant reduction in length of venous lesion from baseline was observed in patients treated with Heparin QPS(16.44 ± 8.54) on day3,as compared to patients treated with Heparin gel(21.26 ± 11.25),(P value= 0.0177). The proportion of patients with complete healing on day 7 was found to be 90%, this was significantly higher compared to 58% of the patients treated with heparin gel ($P < 0.0001$).

The local symptoms were comparable at baseline in both the treatment groups, there was a significant fall in tenderness($P, 0.0065$) and raised local temperature ($P 0.0029$) as compared to baseline in patients treated with heparin QPS.

Grade of venous lesion was comparable between both the treatment groups at baseline ($p=0.810$), however on day 3, a significant fall in percentage of patients with grade 2 and grade 3 were reported in those treated with heparin QPS as compared to heparin gel ($p=0.017$).

At baseline percentage of patients having phlebitis of grade 2 and 3 were 88% and 90% in heparin QPS and Heparin GEL group respectively. At day 3 of treatment, proportion of patients in grade 2 and 3 of phlebitis were less in Heparin QPS 30% as compared to Heparin GEL group 64%. At day 3, more proportion of patients of grade 0 to 1 were seen in Heparin QPS group 68% as compared to Heparin gel group 34%. In patient's global assessment Heparin QPS was rated as excellent to good by most of the patients ($p < 0.0001$).

No complications like Allergic hypersensitivity, Bleeding diathesis and Local adverse effects like pruritus, Dermatitis, Urticaria and Skin exfoliation were found during the study.

Dr. Sanjay Kumar. H Maroo, conducted a study on Novel Topical Quick Penetrating Solution Of Heparin In management Of Superficial Thrombophlebitis. A randomized controlled study was done to compare the safety and efficacy of topical quick penetrating solution (QPS) of heparin 1000 IU/ml versus heparin gel 200 IU/g in the management of post infusion superficial thrombophlebitis. Total 202 patients of early, medium and advance stage of superficial thrombophlebitis were randomized to receive either treatment. Treatments were applied 3 times daily until healing or for a maximum of 7 days. Primary efficacy endpoints were change in length of the venous lesion, proportion of patients with complete healing; while secondary efficacy endpoints included local symptoms, change in the grade of the lesion, global assessment by patients and investigator. Mean change in length of the venous lesion from baseline was significantly higher in heparin QPS group as compared to heparin gel on day 3 ($P = 0.0144$). 90.0% patients in heparin QPS group were healed at day 7 which was significantly higher as compared to 65.7% patients in heparin gel group ($P=0.00001$). Heparin QPS was also found better in secondary efficacy endpoints. He concluded that Heparin QPS was found more effective in treatment of post infusion superficial thrombophlebitis with similar safety profile to heparin gel. In our study also we have observed there was a significant reduction in the length of venous lesion on day 3 and proportion of patients with complete resolution of venous lesion on day 7 was significantly higher in Heparin QPS as compared to Heparin GEL.

CONCLUSION

Heparin QPS was found to be more effective in the treatment of post infusion superficial thrombophlebitis expressed by complete healing of the venous lesion as compared to heparin gel.

Heparin QPS demonstrated a similar safety profile as heparin gel.

The superior efficacy of Heparin QPS over heparin gel was established by:-

Significant reduction in length of venous lesion from baseline on day 3.

Significant fall in percentage of patients with grade 2 and 3 on day 3.

Significantly higher proportion of patients with complete healing on day 7.

Significant fall in local symptom scores on day 3.

From this study, we concluded that Heparin QPS is more effective than Heparin gel in the management of post infusion thrombophlebitis because of its safety and efficacy.

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