Original Article

Efficacy and safety of quick penetrating solution heparin, quick penetrating solution diclofenac, and heparin gel in the prevention of infusion-associated superficial thrombophlebitis: A randomized controlled trial

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Abstract

Background: The present study aimed to compare the efficacy, safety, and cost-effectiveness of quick penetrating solution (QPS) heparin, QPS diclofenac, and heparin gel in the prevention of superficial thrombophlebitis (ST).

Materials and Methods: This randomized controlled trial was conducted after approval from the Institutional Ethics Committee and registration to Clinical Trial Registry of India. Patients of 18–60 years age, *American Society of Anesthesiologists* I/II, and who needed venous cannulation for at least 72 h were included in the study. Patients were randomly divided into three groups receiving study drugs (heparin gel, QPS heparin, and QPS diclofenac) every 8 hourly for a period of 72 h. Venous cannulation site was graded using the Visual Infusion Phlebitis Scale. Patients developing no ST, mean time to reach ST Grade 1 and 2, prevention of ST probability, and cost-effectiveness of interventions during the study period were assessed.

Results: Out of 219 included patients, development of no ST in the study groups at 72 h of treatment were heparin gel (11%), QPS heparin (9.6%), and QPS diclofenac (2.7%). The mean time (hours) to develop any grade ST in the study arms was heparin gel (36.2 [11.9]), QPS heparin (40.0 [13.4]), and QPS diclofenac (37.0 [13.2]). The Kaplan–Meier analysis did not reveal significant differences for the prevention of any grade ST or severe ST in three treatment arms. The average cost-effectiveness ratio for preventing thrombophlebitis was 14.2 in heparin gel-, 13.2 in QPS heparin-, and 95.6 in QPS diclofenac-treated patients.

Conclusion: Based on efficacy, safety, and cost-effectiveness, heparin gel or QPS heparin can be used to prevent ST due to intravenous cannulation in surgical patients. QPS diclofenac is not a cost-effective option to prevent ST.

Keywords: Diclofenac, heparin, quick penetrating solution diclofenac, quick penetrating solution heparin, quick penetrating solution, superficial thrombophlebitis, topical heparin

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INTRODUCTION

Peripheral intravenous (IV) line cannulation is the most frequently performed procedure on all hospitalized patients.[1] An IV line may be put in place for many indications including fluid and antibiotic administration, blood transfusion, or drug administration. Infusion-associated phlebitis or superficial thrombophlebitis (ST) is the most frequent complication linked to IV cannulation.[2,3] In earlier studies, the incidence of ST varied from 5% to 70%.[4,5] Phlebitis can cause deep vein thrombosis if it persists. The association between ST and deep vein thrombosis has been found to be 6%–44% in previous studies.[4] Therefore, it is crucial to prevent ST to reduce patient discomfort and its complications.[6]

ST is characterized by the combination of thrombosis and inflammation in a superficial vein.[7] Drugs having anticoagulant and anti-inflammatory property could be effective in preventing and treating cannulation-associated ST. There have been many studies done for the effective treatment of ST using low-dose unfractionated heparin and low molecular weight heparin either topically or intravenously.[8-10] Studies have also been conducted to investigate the role of topical diclofenac in the treatment of ST.[11] It is suggested that if topical anticoagulants or anti-inflammatory agent is started prophylactically with cannula insertion, it can prevent or postpone ST more effectively.[12] Moreover, quick penetrating solution (QPS) of heparin and diclofenac are available. They assert efficient medication transport through the stratum corneum and thus suggested to be more effective.[13] Recently, few studies have been conducted for the prevention of ST and investigated the role of different preparation of topical heparin including QPS heparin, heparin gel/cream, and QPS diclofenac in its prevention.[13-15] These studies suggest trends of promising outcomes with QPS preparations in terms of prevention of ST and delaying its onset. Earlier studies conducted by Bansal *et al*.[14] compared placebo with QPS heparin in emergency surgical patients belonging to the *American Society of Anesthesiologists* (ASA) class I/II, while Akhileshwar and Singh[13] compared QPS heparin with QPS diclofenac among patients admitted to intensive care unit or surgery belonging to ASA class I/II/III. Both studies used different study populations. These studies had a high risk of bias in terms of lack of information about allocation concealment,[13,14] blinded assessment,[13,14] and prior trial registration (possibility of selective outcome reporting).[14] None of earlier studies had explored pharmacoeconomic aspect.[13,14] There is no randomized controlled trial conducted comparing QPS heparin and QPS diclofenac against common control heparin gel in a similar study population for the prevention of ST. The aim of the present study was to compare the efficacy, safety, and cost-effectiveness of QPS heparin, QPS diclofenac, and heparin gel in the prevention of ST.

MATERIALS AND METHODS

Study design

This single-site, parallel, 3-arm, 1:1:1 allocation ration, randomized, open-labeled controlled trial was conducted at All India Institute of Medical Sciences, Gorakhpur. The study protocol was approved by the Institutional Human Ethics Committee. Informed consent was obtained from all enrolled patients or legally authorized representatives. The clinical trial was registered with Clinical Trial Registry of India (CTRI/2022/04/041915).

Study participants

The patients who fulfilled the selection criteria and admitted to surgical wards between May 2022 and May 2023 were assessed for eligibility. Patients were included if they were newly admitted for any surgical intervention, between the ages of 18 and 60, in ASA classes I or II, and needed venous cannulation for at least 72 h. Patients were excluded if they were unwilling to participate, had preexisting phlebitis at any other cannulation site, or had a history of hypersensitivity to heparin or coagulation disorders. Patients who were unconscious or comatose, had signs of systemic infection and bacteremia, pregnant and lactating females, and receiving irritant IV drugs or anticoagulants were also excluded from the study.

Randomization and blinding

All included patients were randomized to treatment arms (heparin gel, QPS heparin, and QPS diclofenac) through computer-generated simple randomization (1:1:1 ratio). Using sealed, opaque envelopes, the allocation was concealed. The three study medications were available in different formulations, making blinding challenging for the study team's nursing staff involved in medication administration and patients who were aware of the treatment allocation after the informed consent. Trained nursing staff who were not part of the investigator team assessed the patients for the development of thrombophlebitis. Treatment codes were not revealed to the outcome assessors and data entry team, who were blinded to the intervention.

Study procedures

After cleaning the site of cannulation (dorsum of either hand) with a surgical spirit swab, an 18-G cannula (B Braun Vasofix) was inserted under aseptic precaution. The nursing staff applied drug as per randomization code along the

length of the cannula before securing the cannula with waterproof dressing (Tegaderm IV dressing) and that time was marked as "0" h. The nursing staff kept constant for the study purpose.

Patients in group TH received heparin gel 1 g (200 IU/g - Thrombophob gel, Zydus Lifesciences Ltd., India), group QH patients received QPS heparin 6–8 drops (1000 IU/Ml - Phlebotroy QPS, Troikaa Pharmaceuticals Ltd., India), and group QD patients received QPS diclofenac 10 sprays (4 mg/spray-Dynapar QPS, Troikaa Pharmaceuticals Ltd., India) every 8 hourly for a period of 72 h. A trained nurse assessor who was not aware of the treatment group evaluated the same location for phlebitis at 8, 16, 24, 32, 40, 48, 56, 64, and 72 h using the Visual Infusion Phlebitis Scale. The following data were recorded: demography, medications (past and current), local symptoms of ST (pain, tenderness, redness, local temperature, and venous induration), grades of phlebitis, its onset time, and adverse drug events. The ST was graded using the Visual Infusion Phlebitis Scale [Table 1].[16,17]

Outcomes

The primary outcome of this study was to compare proportion of patients developing no ST (Grade 0) and first signs of infusion thrombophlebitis (Grade 1 and 2) at the end of 72 h of treatment period. The other outcomes were to compare mean time to reach infusion thrombophlebitis Grade 1 and 2 and prevention of thrombophlebitis probability during the 72 h of the treatment period. Number needed to treat (NNT) for the prevention of ST (Grade 0) and first signs of infusion thrombophlebitis (Grade 1 and 2) at the end of 72 h were calculated in three treatment arms. The pharmacoeconomic aspect was also explored in terms of comparing the cost-effectiveness of three treatment arms for the prevention of thrombophlebitis (any grade and severe) and the mean time to develop thrombophlebitis (any grade and severe). The cost-effectiveness grid was also illustrated to plot comparative cost (lower, same, and high) and effectiveness (lower, same, and high) outcomes. The cost (₹) of medications in December 2023 (https://www.mims.com/India) was used for the cost outcomes.

Statistical analysis

According to the previous studies, the prevalence of ST ranged from 5% to 70%.[4,5] We anticipated 50% of incidence of ST in the absence of any interventions. Null hypothesis (p[H0]) of clinically significant reduction of 15% was expected in each group. The alternative hypothesis (p[H1]) of 15% reduction in heparin gel, 20% in QPS diclofenac, and 30% reduction in QPS heparin was considered to calculate the sample size.[13,15] The other parameters considered were α error – 5% and power – 80%. The estimated sample size with G*power software (3.1.9.7) was 199. With the addition of 10% dropout rate, the estimated total sample size was 219.

The data were analyzed using Statistical Package for MedCalc® Statistical Software version 22.007 (MedCalc Software Ltd, Ostend, Belgium). The normality of continuous data was assessed by the Kolmogorov–Smirnov test. They were compared using unpaired *t*-test. The categorical data were compared using the Chi-square

Table 1: Visual infusion phlebitis scale

Grade	Appearance of cannulation site	Stage and action required
0	Appears healthy	No signs of phlebitis
I	One of the following is evident Slight pain near IV site or Slight redness near IV site	Possibly first signs of phlebitis
II	Two of the following are evident Pain at IV site Erythema around site Swelling	Discontinue the patient and recannulate at other site
III	All of the following signs are evident Pain along path of cannula Erythma around site Induration	Medium stage of phlebitis Discontinue the patient and recannulate at other site as well as consider treatment of phlebitis
IV	All of the following signs are evident Pain along path of cannula Erythma around site Induration Palpable venous cord	Advanced stage of phlebitis or start of thrombophlebitis Discontinue the patient and recannulate at other site as well as treat the thrombophlebitis
V	All of the following signs are evident Pain along path of cannula Erythma around site Induration Palpable venous cord Pyrexia	Advanced stage thrombophlebitis. Discontinue the patient and recannulate at other site as well as treat the thrombophlebitis

test. A Kaplan–Meier analysis was conducted to assess the prevention of any grade thrombophlebitis or severe thrombophlebitis (Grade 2 or above) in each group. $P < 0.05$ was considered statistically significant.

RESULTS

Out of 247 patients screened, 219 eligible patients were recruited between May 2022 and May 2023. The reasons for ineligibility were patients receiving irritant IV drugs (n = 18), anticoagulants (n = 7), and declined to participate (n = 3) [Figure 1].

Patients' baseline characteristics are given in Table 2. There was no difference in mean age of years in patients receiving heparin gel (37.6 ± 11.2), QPS heparin (34.2 ± 10.0), and QPS diclofenac (36.5 ± 10.6). All three treatment groups had comparable gender, body mass index, and ASA scores [Table 2].

Proportion of patients developing no ST (Grade 0) within 72 h of IV treatment was 11% in heparin gel, 9.6% in QPS heparin, and 2.7% in QPS diclofenac group [Table 3]. Development of any type of thrombophlebitis (Grade 1/2 or above) was 89% in heparin gel, 90.4% in QPS heparin group, and 97.2% in QPS diclofenac. The incidence of Grade 0 and any type of thrombophlebitis (Grade 1/2 or above) was higher in QPS diclofenac-treated patients, but the difference was not significant [Table 3].

Table 2: Baseline characteristics of study participants

Variables	Heparin gel (n=73)	QPS heparin (n=73)	QPS diclofenac (n=73)	P
Age (years)	37.6 (11.2)	34.2 (10.0)	36.5 (10.6)	0.14
Female (%)	31 (42.5)	39 (53.4)	39 (53.4)	0.31
BMI (kg/m^2)	23.4 (3.5)	23.2 (2.9)	24.2 (3.6)	0.18
ASA grade Grade 1 (%)	73 (100)	73 (100)	72 (98.6)	0.36

Values are expressed as mean±SD or n (%). QPS: Quick penetrating solution, ASA: American Society of Anesthesiologists, BMI: Body mass index

Table 3: Comparison of development of thrombophlebitis at the end of 72 h in three treatment groups

Grade of thrombophlebitis	Heparin gel (n=73)	QPS heparin (n=73)	QPS Diclofenac (n=73)
Grade 0	8 (11.0)	7 (9.6)	2 (2.7)
Grade 1	1 (1.4)	0	2 (2.7)
Grade 2 and above	64 (87.7)	66 (90.4)	69 (94.5)

Values are expressed as n (%). QPS: Quick penetrating solution

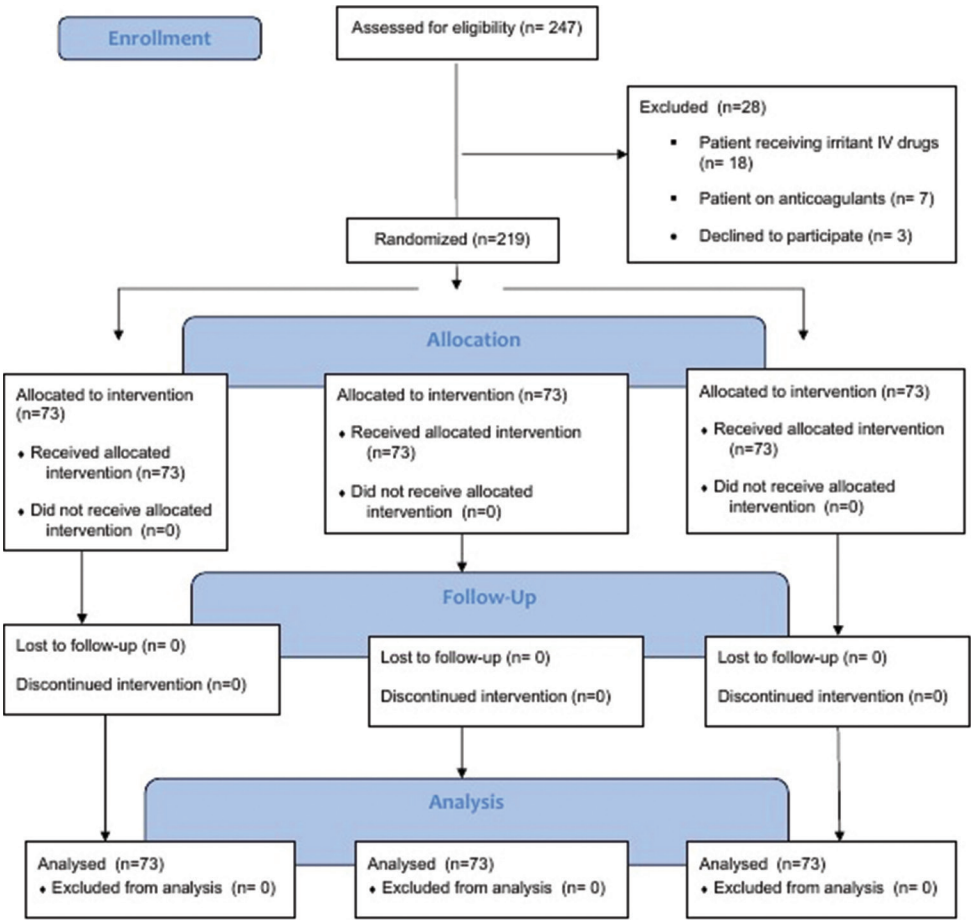

Figure 1: Consort flow diagram of patient enrolment

As shown in Figure 2, the Kaplan–Meier analysis did not reveal statistically significant differences for the prevention of any grade thrombophlebitis (long-rank test $P = 0.62$) or severe thrombophlebitis (long-rank test $P = 0.55$) at the end of 72 h in three treatment groups [Figure 2]. The mean time (hours) to develop ST of Grade 1 in heparin gel group was 36.2 (11.9) h, 40.0 (13.4) h in QPS heparin group, and 37.0 (13.2) h in QPS diclofenac group. Difference among all groups was statistically insignificant. The mean time (h) to develop ST of Grade 2 was 45.2 (15.2) h, 45.1 (15.3) h, and 45.7 (14.8) h in heparin gel, QPS heparin, and QPS diclofenac group, respectively [Table 4].

NNT for the prevention of ST (Grade 0) at the end of 72 h was 10.0 in heparin gel-, 11.0 in QPS heparin-, and 37.0 in QPS diclofenac-treated patients [Table 5].

Table 4: Mean time (h) to develop superficial thrombophlebitis in three groups

Grade of thrombophlebitis	Heparin gel	QPS heparin	QPS diclofenac	*P*
Grade 0	36.1±18.3	35.7±17.5	33.5±15.8	0.63
Grade 1	36.2±11.9	40.0±13.4	37.0±13.2	0.49
Grade 2 and above	45.2±15.2	45.1±15.3	45.7±14.8	0.97

Values are expressed as mean±SD. QPS: Quick penetrating solution, SD: Standard deviation

Table 5: Number needed to treat for the prevention of thrombophlebitis at the end of 72 h in three treatment groups

Variables	Heparin gel (95% CI)	QPS heparin (95% CI)	QPS diclofenac (95% CI)
NNT for any grade thrombophlebitis	10.0 (5.5–26.4)	11.0 (6.1–35.3)	37.0 (−15.4–99.5)
NNT for Grade 2 and above thrombophlebitis	9.0 (5.0–20.9)	11.00 (6.1–35.3)	19.0 (9.3–386.3)

NNT: Number needed to treat, QPS: Quick penetrating solution, CI: Confidence interval

As shown in Table 6, the average cost-effectiveness ratio for the prevention of thrombophlebitis was 14.2 in heparin gel-, 13.2 in QPS heparin-, and 95.6 in QPS diclofenac-treated patients. The average cost-effectiveness ratio for mean time to develop thrombophlebitis was 4.33 in heparin gel-, 3.17 in QPS heparin-, and 6.97 in QPS diclofenac-treated patients. The cost-effectiveness grid was illustrated to demonstrate the cost-effectiveness of heparin gel and QPS heparin over QPS diclofenac [Figure 3].

DISCUSSION

We found no significant differences regarding prevention of thrombophlebitis (any grade) or severe thrombophlebitis with heparin gel, QPS heparin, or QPS diclofenac. Prophylactic treatment with heparin gel, QPS heparin, or QPS diclofenac can delay the development of thrombophlebitis. Heparin gel and QPS heparin seem cost-effective over QPS diclofenac for the prevention of thrombophlebitis.

Heparin-based topical formulations showed a trend of better outcomes at a lesser cost as compared to diclofenac topical preparation in preventing the incidence of thrombophlebitis in surgical patients. Similarly, NNT patients for the prevention of ST was maximum in QPS diclofenac (37.0) as compared to heparin gel (10.0) and QPS heparin (11.0) [Table 5]. This is in line with a previous study. Akhileshwar and Singh in a randomized controlled trial compared QPS formulation of heparin and diclofenac in preventing thrombophlebitis and found QPS heparin is more effective than QPS diclofenac for the same.[13] In this study, 23% of patients developed Grade 1 thrombophlebitis in diclofenac QPS, but no

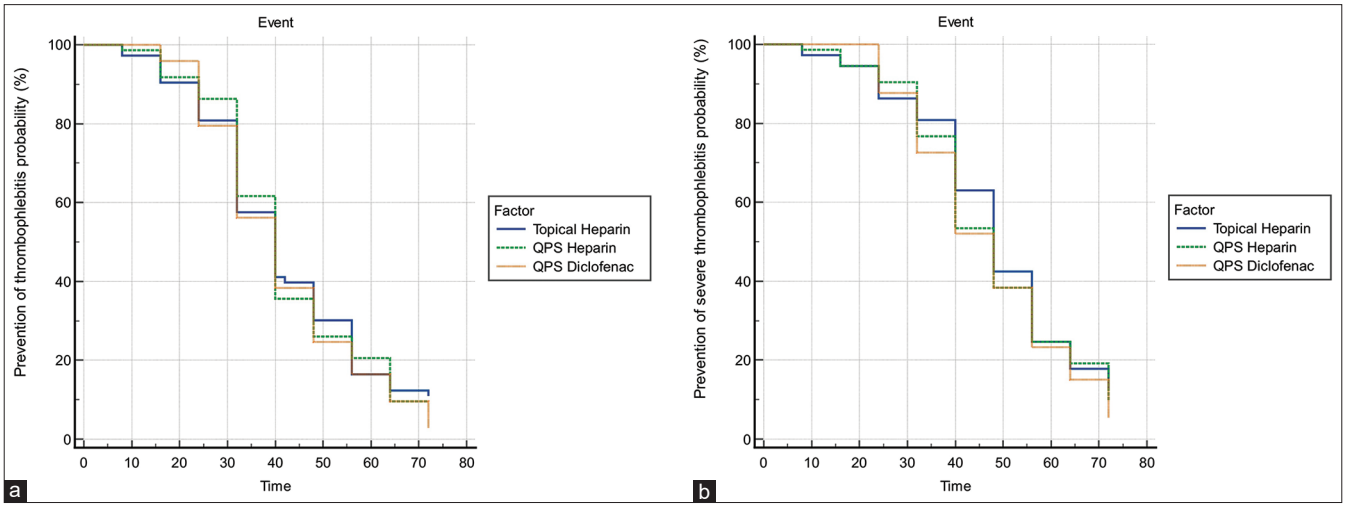

Figure 2: (a) Prevention of thrombophlebitis probability using Kaplan–Meier survival analysis at the end of 72 h in three treatment groups. (b) Prevention of severe thrombophlebitis (Grade 2 and above) probability using Kaplan–Meier survival analysis at the end of 72 h in three treatment groups. QPS: Quick penetrating solution

Table 6: Cost-effectiveness analysis of three treatment groups

Outcome	Heparin gel	QPS heparin	QPS diclofenac
Cost-consequence analysis			
Cost outcome per patient (₹)	156.0	126.8	258.0
Prevention of thrombophlebitis (%)	11.0	9.6	2.7
Prevention of severe thrombophlebitis (%)	13.3	9.6	5.5
Mean time to develop thrombophlebitis (h)	36.0	40.0	37.0
Mean time to develop severe thrombophlebitis (h)	45.2	45.1	45.7
Average cost-effectiveness ratio			
Prevention of thrombophlebitis (₹/%)	14.2	13.2	95.6
Prevention of severe thrombophlebitis (₹/%)	11.73	13.21	46.91
Mean time to develop thrombophlebitis (₹/h)	4.33	3.17	6.97
Mean time to develop severe thrombophlebitis (₹/h)	3.45	2.81	5.65

QPS: Quick penetrating solution

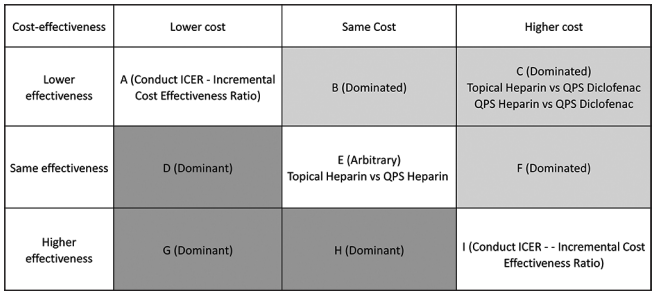

Figure 3: Cost-effectiveness grid for all three treatment pair comparisons. QPS: Quick penetrating solution

patient had developed Grade 1 thrombophlebitis in QPS heparin ($P = 0.034$)-treated patients.[13]

Our findings of high incidence of thrombophlebitis in heparin gel, QPS heparin, and QPS diclofenac suggest that prophylactic use could mainly delay the development of thrombophlebitis and prophylactic agent could not completely prevent it. This is in line with the earlier study.[15]

Our findings suggest no advantage of quick penetrating technology in topical treatment with heparin or diclofenac to delay the onset or decrease the incidence of ST after cannulation. Average time to appear Grade 1 ST after cannulation was around 36–40 h in heparin gel-, QPS heparin-, and QPS diclofenac-treated patients. Average time to develop Grade 2 ST after cannulation was around 45 h in all three intervention groups in our study. The literature suggests that ST usually appears 12–36 h after cannulation.[18-20] Our findings of no difference in delay of onset of thrombophlebitis with heparin gel and QPS heparin are in line with a previous study done by Saini *et al.* In a study done by Saini *et al.*, the mean time to develop Grade 1 thrombophlebitis (QPS heparin - 59.7 h vs. heparin gel - 58.46 h; $P = 0.949$) and Grade 2 (QPS heparin - 62.4 h vs. heparin gel - 61.17 h; $P = 0.732$) was comparable and nonsignificant in QPS heparin- and heparin gel-treated patients. However, our findings regarding no difference in the incidence of thrombophlebitis with heparin gel and QPS heparin are contradictory to this study.[15] Saini *et al.* compared these two preparations of heparin in 84 patients. They observed less incidence of ST at the end of the study period in QPS heparin- than heparin gel-treated patients (32.4% vs. 9.4%; $P = 0.00019$). Furthermore, the proportion of patients who developed and progressed to Grade 2 infusion-related phlebitis was significantly lesser in QPS heparin as compared to heparin gel (13.5% vs. 22.9%; $P = 0.0279$) treated patients.[15] An earlier study has demonstrated effectiveness of both preparation of heparin either gel or QPS as compared to no intervention in the prevention of ST.[14,21,22]

The present study has compared effectiveness and cost implications of gel and QPS-based medications in 219 patients. These newer preparations such as QPS heparin and QPS diclofenac developed by adding nonaqueous and nonvolatile solvents along with added permeability enhancers increase the penetration of the drug either heparin or diclofenac across the skin resulting in to more delivery of drug at the site of action. These drugs seem to be promising in better prevention of ST due to novel technology and few earlier studies have also found the same results. Use of QPS heparin helps heparin to penetrate the skin effectively without any systemic absorption or risk of bleeding.[23] Contradictory to previous studies, the present study does not report any significant benefit of either of the QPS preparations over heparin gel.

This study has highlighted the fact that either of the heparin preparation can be used for prevention of ST with the same efficacy safety and cost-effectiveness. Preference for selection of either of heparin ointment or QPS heparin can be decided depending upon other factors. QPS solutions allow hands-free application and thus improve compliance of patients as well as nursing staff.

Use of topical heparin is a standard practice for the treatment of ST and can be considered for prevention also. Use of QPS diclofenac for the prevention of ST can be

considered in patients having contraindications of heparin use and are at high risk of developing thrombophlebitis like use of irritant drugs or chemotherapy as compared to no intervention.

This study has several limitations. This study included surgical patient cohort, so result of this study cannot be generalized for all group of patients. Confounding factors like individual body response to IV medications, frequency of stat drugs and IV infusions, and movements of hand due to dexterity of the patient could potentially affect the development of ST and thereby overall result of the study.

CONCLUSION

Based on efficacy, safety, and cost-effectiveness, either heparin gel or QPS heparin can be used to prevent ST due to IV cannulation in surgical patients. QPS diclofenac is not a cost-effective option to prevent ST.

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Data availability

Full-trial protocol and dataset are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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