A prospective randomized study to evaluate safety and efficacy of heparin topical solution (1000 IU/ml) compared to heparin topical gel (200 IU/g) in prevention of infusion-associated phlebitis

Vikas Saini, Tanvir Samra, Nitin Ahuja, Sameer Sethi

Abstract:
OBJECTIVES: Thrombosis and thrombophlebitis of the superficial venous system are common in hospitalized patients. Efficacy and safety of topical quick penetrating solution (QPS) of heparin were compared to heparin sodium topical gel for the prevention of infusion-associated phlebitis.

MATERIALS AND METHODS: Patients aged 18–65 years undergoing intravenous cannulation for at least 72 h were enrolled and randomized to receive 6–8 drops of topical solution of heparin (Group sodium topical solution [QPS]) or 1 g of topical gel (Group GEL) over the cannulated vein every 8 hourly for a total of 10 doses. Enrolled patients were monitored every 8 ± 1 h for phlebitis using visual infusion phlebitis scale. The primary aim was to compare the proportion of patients with Grade 0, I, and II phlebitis at the end of 72 h of treatment period.

RESULTS: Number of patients assessed for eligibility was 110; 26 excluded and 84 randomized. Analysis was done for 41 administered heparin QPS and 33 administered heparin gel as the rest were lost to follow-up. No phlebitis was reported in 32% of patients in QPS group and 9% in GEL group ($P=0.0019$). Proportion of patients with Grade I and Grade II phlebitis was 22.9% and 13.5% with QPS and 35.13% and 22.97% with gel, respectively, and the difference was statistically significant. Mean time to develop Grade I (Group QPS = 59.7 h; Group GEL = 58.46 h; $P=0.949$) and Grade II (Group QPS = 62.4 h; Group GEL = 61.17 h; $P=0.732$) phlebitis was comparable no adverse effects were reported in either group.

CONCLUSION: Heparin QPS was more effective in he prevention of infusion-associated phlebitis with similar safety profile as heparin gel.

Keywords: Heparin, quick penetrating topical solution, superficial thrombophlebitis

Introduction
The term phlebitis refers to the presence of inflammation within a vein, whereas thrombosis indicates the presence of clot within the vein. Superficial thrombophlebitis (ST) is a common inflammatory thrombotic disorder in which a thrombus develops in a vein located near the surface of the skin. A study conducted in the emergency medical and surgical units of our hospital have reported the incidence of phlebitis associated with peripheral intravenous (IV) cannula to be 29.8%.[1] However, the incidence can be as high as...
75% and although the etiology is frequently obscure, it is speculated that IV catheters cause endothelial trauma and inflammation which then leads to venous thrombosis.[2]

ST usually develops within 72 h of cannulation and factors associated with the development of ST are duration of catheterization, catheter material, catheter size, type of infusate, and catheter site infections.[3] Treatment is needed for the local symptoms and to prevent life-threatening systemic complications (deep venous thrombosis).[4] Topical application of heparin for 7 days is the standard medical therapy. Anticoagulant heparin acts predominantly by inhibiting coagulation and further progression but has a very little effect on preformed clots. Initiating prophylactic topical heparin, before thrombophlebitis sets in, that is, from Day 1 of IV cannula insertion, can be more effective in preventing or delaying thrombophlebitis.[5,6]

The evidence about the treatment and prevention of acute ST with different drug formulations is limited and of low quality in the medical, surgical, and anesthetic literature. Thus, we conducted this study with the objective to identify difference in the incidence and severity of infusion-associated phlebitis after application of heparin sodium topical solution (quick penetrating solution [QPS]) from that of heparin sodium (GEL). We have also compared the incidence of adverse reactions after application of the two drugs.

Materials and Methods

The study was approved by the Institutional Ethics Committee (NK/2475/study/2851) and written informed consent was obtained from all the study participants. The trial was registered with Clinical Trials CTRI/2017/08/009499. This was a prospective, randomized, open-label, active-controlled, parallel group, clinical study conducted at PGIMER, Chandigarh. Patients of either gender aged 18–65 years, belonging to the American Society of Anesthesiologists (ASA) Class I/II, and undergoing IV cannulation in the preoperative surgical wards for at least 72 h were enrolled and randomized in either of the following two groups:

- **QPS Group**: Heparin QPS (Phlebotroy QPS; 1000 IU/ml; manufactured by Troikaa Pharmaceuticals Ltd.)
- **GEL Group**: Heparin Sodium Topical Gel (Thrombophob; 200 IU/g; manufactured by ZyduaCadila).

The following patients were excluded during recruitment: preexisting phlebitis at any other cannulation site, unconscious or comatose patients, history of hypersensitivity reaction to heparin or heparin-induced thrombocytopenia, signs of systemic infection, bacteremia, planned administration of anticoagulants or nonsteroidal anti-inflammatory drugs locally (in the cannula or over surrounding area), and patients receiving irritant IV drugs.

All patients enrolled in this study were cannulated on back of the hand with 18-G cannula of the same manufacturer. Treatment with either of the investigational product was started immediately on cannulation at approximately every 8-h interval for the treatment period of 72 h (total 10 doses). Dosage for QPS group was 6–8 drops of topical solution and dosage for gel was approximately 1 g of topical gel applied on the skin over the cannulated vein around the plaster supporting the IV cannula, in the direction of venous flow.

Enrolled patients were periodically monitored by an evaluator every 8 ± 1 h from cannulation for infusion phlebitis and graded as per the Visual Infusion Phlebitis Scale [Annexure I]. Any patient with infusion phlebitis Grade II or above was discontinued from the study.

**Primary efficacy endpoints**

Both treatment groups were compared for the following:

1. Proportion of patients with no phlebitis (Grade 0) at the end of 72 h of treatment period
2. Proportion of patients who developed first signs of infusion phlebitis (Grade I and II) during the 72 h of the treatment period.

**Secondary efficacy endpoints**

Both treatment groups were compared for the following:

Mean time to reach infusion phlebitis Grade I and II in hours, based on the time point when patient was first found to have phlebitis Grade I or II. Only the proportion of patients who developed Grade I and II phlebitis were considered for the evaluation of mean time to develop Grade I and II phlebitis.

**Recording and reporting of adverse events**

The following information was recorded for each adverse effect (AE) individually:

- Date of onset/reporting (if available)
- Date of resolution (if available)
- Severity (mild, moderate, or severe)
- Treatment, if any provided for the AE
- Outcome of adverse event (resolved, resolved with squeal, ongoing, unknown, or fatal)
- Categorization of AE; expected or unexpected
- Severity of AE. Labeled as serious if AE results in death, hospitalization/prolongation of hospitalization, congenital malformation, permanent disability, or incapacity.
Serious unexpected AEs were to be reported by the investigating doctor immediately to the pharmaceutical company marketing the product.

**Statistical analysis**

We hypothesized that incidence of infusion-associated phlebitis over 72 h of the treatment period in the test group (QPS) will be lesser (approximately half) compared to incidence of phlebitis in comparator group (GEL) owing to the higher strength and more penetration of test product. Keeping the power of the study as 90% with an effect size 0.8, at least 33 participants in test group and 33 participants in comparator group were required. Sample size was calculated using the statistical software G*Power 3.1.9.2.

All primary efficacy end-points were evaluated statistically by applying nonparametric, two-tailed, and Fischer exact test using the software StatSoft 11.0 (Statistica, Tulsa, Oklahoma, USA). The secondary parameters were statistically evaluated by applying Mann–Whitney U-test using the above software. Statistical significance was considered at \( P < 0.05 \) for both end-point comparisons.

**Results**

A number of patients assessed for eligibility were 110, but 26 were excluded in view of preexisting phlebitis (24) and signs of systemic bacteremia. \([2]\) The remaining 84 were equally randomized in the two groups. The analysis was done for 41 administered heparin QPS and 33 administered heparin gel as the rest were lost to follow-up [Figure 1].

**Proportion of patients with no phlebitis at the end of 72 h period**

Proportion of patients who developed no phlebitis was significantly higher (24 patients out of 41) in Group QPS (32.4%) as compared to Group GEL (7 patients out of 33) (9.4%) \( (P = 0.0019) \). About 17 patients in Group QPS and 26 patients in Group GEL developed signs of phlebitis during the entire study duration [Table 1].

**Proportion of patients with ST (Grade I and II)**

Lesser proportion of patients were found to develop early signs of Grade I infusion-related phlebitis in Group QPS (22.9%) as compared to Group GEL (35%); \( P = 0.0019 \) [Table 2]. The proportion of patients who developed and progressed to Grade II infusion-related phlebitis in Group QPS was 13.5%, which was significantly lesser than the proportion of patients who developed Grade II phlebitis in Group GEL, 22.9%; \( P = 0.0279 \) [Table 2].

Figure 2 shows Grade III phlebitis in a patient with heparin gel and Figure 3 shows Grade II phlebitis in a patient using heparin QPS.

Mean time to develop Grade I (QPS group = 59.7 h; GEL group = 58.46 h; \( P = 0.949 \), Mann–Whitney U-test) and Grade II (QPS group = 62.4 h; GEL group = 61.17 h; \( P = 0.732 \), Mann–Whitney U-test) phlebitis was comparable and nonsignificant in both the treatment groups.
No AEs were reported in either group.

**Discussion**

In our study, topical administration of heparin QPS was more effective than gel for prevention of infusion-associated phlebitis. Both the treatments showed comparable delay in progression and development of infusion-related phlebitis and none reported any adverse event.

Previous literature reports an overall incidence rate of thrombophlebitis of 50% with 61% developing Grade 1 phlebitis and 39% developing Grade 2 phlebitis when no prophylaxis is administered.[7] The proportion of patients with Grade I and Grade II phlebitis was 22.9% and 13.5% with QPS and 35.13% and 22.97% with gel, respectively, in our study and is less than the above-mentioned figures and thus highlights the efficacy of the drugs administered.

Various formulations of heparin have been marketed and tested for prevention and treatment of ST. Heparin-spraygel (Viatromb 2.400 IU/g heparin spraygel) has been used for the prevention of local complications of IV cannulation.[8] Heparin QPS has been reported to be more effective than the gel for treatment of superficial phlebitis.[9] It contains 1000 IU/ml of heparin, unlike other conventional products which contain only up to 200 IU/g. The QPS technology of drug delivery enhances the clinical efficacy of the drug by ensuring greater penetration. Thrice a day application of heparin for a maximum of 7 days or till healing of lesions has also been used for treatment in the previous studies, but in our study, we used thrice a day application for a treatment period of 72 h only.[8] Concomitant use of heparin infusion (5000 U) before and during the administration of antineoplastic agents for a duration of 12 h lowers the incidence of phlebitis in patients with ovarian cancers, but topical applications are definitely more easier to administer.[10]

Previous studies have reported that use of infusion pumps, insertion of catheters in the veins around the elbow, antibiotics with low pH, and hyper/hypo-osmolality increase the incidence of ST, but the use of the smallest size catheter for the largest size vein decrease the incidence.[11,12] The use of IV sets with 0.22-micron IVEX-HP filters is effective in reducing the incidence of microparticulate-induced phlebitis.[13] In our study, we have not used any infusion pumps or filters and excluded patients receiving irritant IV drugs.

Limitation of our study is that we did not include a control group, and thus, the incidence of thrombophlebitis without any medical management has not been recorded.

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**Table 1: Proportion of patients with no superficial thrombophlebitis at the end of the study in two groups**

| Groups/treatment | No ST (n) | ST (n) | Proportion of patients with no SVT (%) | P |
|------------------|----------|--------|----------------------------------------|---|
| QPS              | 24       | 17     | 32.432                                 | 0.0019* |
| Gel              | 7        | 26     | 9.459                                  | * |

*P<0.05 considered significant; nonparametric test Fischer exact test.

n=Number of patients; ST=Superficial thrombophlebitis, SVT=Supraventricular tachycardia, QPS=Quick penetrating solution

**Table 2: Proportion of patients with superficial thrombophlebitis (Grade I and II) at the end of the study in the two groups**

| Groups/treatment | Yes (n) | No (n) | Proportion of patients (%) | P |
|------------------|---------|--------|----------------------------|---|
| Grade I Phlebitis |         |        |                            |   |
| QPS              | 17      | 24     | 22.973                     | 0.0019* |
| Gel              | 26      | 7      | 35.135                     |   |
| Grade II Phlebitis |        |        |                            |   |
| QPS              | 10      | 31     | 13.514                     | 0.0279* |
| Gel              | 17      | 16     | 22.973                     |   |

*P<0.05 considered significant; Nonparametric test Fischer exact test.

n=Number of patients, QPS=Quick penetrating solution

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**Figure 2:** Grade III phlebitis in a patient with prophylactic topical application of heparin gel

**Figure 3:** Grade II phlebitis in a patient with prophylactic topical application of heparin quick penetrating solution
This study compares the efficacy of two different drug formulations, but the efficacy of each formulation in decreasing the incidence from the control has not been evaluated.

Various predisposing factors are known to influence the three subtypes of phlebitis, namely mechanical, chemical, and infective, and in our study, we did not collect data for the same. We do not expect any change in our results with the above-mentioned risk factors as we had randomized patients from a homogenous population; ASA 1–2 patients admitted in the hospital for a surgical procedure. It has been previously studied that age, gender, comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, and smoking do not significantly influence the incidence of ST. Limitation of the previous studies was that data were collected in the postoperative period and the pH and osmolality of IV fluids and anesthetic agents delivered were not considered, and in our study, we have overcome this limitation by recruiting patients in the preoperative period.

IV cannulation is one of the most commonly carried out invasive procedures in hospital-based management. ST is usually a benign and self-limiting disease, but it can lead to significant discomfort, pain, erythema, and swelling around a superficial vein. Local treatment has the potential to improve the painful symptoms and patient discomfort but may not prevent complications, infection or the extension of the clot into the deep vein system. Hence, prophylactic measures should be adopted to keep the incidence of ST below 5%.

**Conclusion**

Topical administration of heparin QPS is more effective than gel for prevention of infusion-associated phlebitis. Overall incidence of peripheral catheter-related thrombophlebitis was 58.1% in our setting and this is higher than the acceptable and highlights that additional measures need to be adopted to further decrease the incidence.

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**Conflicts of interest**

There are no conflicts of interest.

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## Annexure I: 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| Possibly first signs of phlebitis |
|       | Slight pain near IV site or    |                           |
|       | Slight redness near IV site    |                           |
| II    | Two of the following are evident| Early stage of phlebitis |
|       | Pain at IV site                | Discontinue the patient and recannulate at other site |
|       | Erythema around site           |                           |
|       | Swelling                       |                           |
| III   | All of the following signs are evident| Medium stage of phlebitis |
|       | Pain along path of cannula     | Discontinue the patient and recannulate at other site as well as consider treatment of phlebitis |
|       | Erythema around site           |                           |
|       | Induration                     |                           |
| IV    | All of the following signs are evident and extensive| Advanced stage of phlebitis or start of thrombophlebitis |
|       | Pain along path of cannula     | Discontinue the patient and recannulate at other site as well as treat the thrombophlebitis |
|       | Erythema around site           |                           |
|       | Induration                     |                           |
|       | Palpable venous cord           |                           |
| V     | All of the following signs are evident and extensive| Advanced stage thrombophlebitis |
|       | Pain along path of cannula     | Discontinue the patient and recannulate at other site as well as treat the thrombophlebitis |
|       | Erythema around site           |                           |
|       | Induration                     |                           |
|       | Palpable venous cord           |                           |
|       | Pyrexia                        |                           |