

An Open-label, Single-arm, Single-center, Clinical Study to Evaluate Safety and Efficacy of Heparin Sodium Topical Solution (1,000 IU/mL) in Prevention of Infusion-associated Superficial Thrombophlebitis

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ABSTRACT

Intravenous (IV) cannulation, to administer drugs, fluids, blood products and nutritional solutions, constitutes one of the most commonly carried out invasive procedures of hospital-based management. However, the use of IV cannula is often associated with the development of superficial thrombophlebitis. Topical heparin application at the site of cannulation is frequently done to prevent thrombophlebitis. Initiating prophylactic topical heparin, before thrombophlebitis sets in, i.e., from Day 1 of IV cannula insertion, can be more effective in preventing or delaying thrombophlebitis. The present study was undertaken to investigate the safety and efficacy of topical heparin sodium solution 1,000 IU/mL (Thrombotroy QPS, Troikaa Pharmaceuticals Limited) in preventing infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein. Treatment with investigational product, heparin sodium topical solution (1,000 IU/mL) in a dose of 6 to 8 drops was applied on the skin over the cannulated vein immediately on cannulation and then applied approximately every 8 hours for the treatment period of 48 hours (total 7 doses). It was seen that topical heparin sodium solution (1,000 IU/mL) was safe and effective in preventing and/or delaying infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein three times a day over a period of 48 hours after cannulation.

Keywords: Intravenous cannulation, topical heparin solution, infusion-associated superficial thrombophlebitis

Intravenous (IV) cannulation is an essential component of medical practice in the current times. It assists in the administration of drugs, fluids, blood products and nutritional solutions and constitutes one of the most commonly carried out invasive procedures in hospital-based management. However, maintaining a single indwelling IV cannula for long duration is associated with the development of superficial thrombophlebitis.^{1,2} In a study by Saini et al, conducted in an Indian tertiary care hospital, phlebitis associated with peripheral IV cannula was experienced by 29.8% of patients.²

Superficial thrombophlebitis is managed with topical heparin application for 7 days. Heparin prevents coagulation rather than lysing a formed clot. Initiating

prophylactic topical heparin, before thrombophlebitis sets in, i.e., from Day 1 of IV cannula insertion, can be more effective in preventing or delaying thrombophlebitis.¹

Bhandari et al evaluated effects of topical anticoagulant ointment on post-infusion thrombophlebitis in 169 (84 test, 85 control) pediatric patients. Topical anticoagulant ointment decreased the incidence of thrombophlebitis if the duration of infusion was ≤ 12 hours and where the polythene cannula and latex rubber tubing set were used for infusion.³

Further, existing clinical evidence suggests that improving penetration of topical products can provide higher concentration and hence effectively manage superficial thrombophlebitis.

Based on these findings, a study was designed to determine the efficacy and safety of a topical Quick Penetrating Solution of heparin sodium 1,000 IU/mL (Thrombotroy QPS, Troikaa Pharmaceuticals Limited) in preventing infusion-associated superficial thrombophlebitis.

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OBJECTIVES

The aim of the present study was to investigate the safety and efficacy of topical heparin sodium solution 1,000 IU/mL (Thrombotroy QPS, Troikaa Pharmaceuticals Limited) in preventing infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein three times a day over a period of 48 hours after cannulation. The endpoints assessed included:

- Occurrence of infusion-associated superficial thrombophlebitis
- Delay in the development of infusion-associated superficial thrombophlebitis
- Occurrence of application site reactions.

DESIGN AND METHODOLOGY

An open-label, single-arm clinical study was designed that enrolled 50 patients undergoing IV cannulation, planned to remain *in situ* for at least 48 hours indoor period. The investigational product was applied on the skin over the cannulated vein site every 8 hours for the treatment period of 48 hours (total 7 doses). Patients were monitored every 8 ± 1 hours from the time of cannulation for infusion phlebitis grade as per visual infusion phlebitis scale (Table 1)⁴ and application site reaction, if any. Patients with infusion phlebitis Grade II or above as per visual infusion phlebitis scale were to be discontinued from the study.

The investigating doctor took informed written consent from all patients before enrollment using the Patient Information Sheet and Informed Consent Form. The study was conducted as per

| | |
|---|---|
| IV site appears healthy | 0 |
| One of the following signs is evident: Slight pain near IV site or slight redness near IV site | 1 |
| Two of the following signs are evident: Pain at IV site, erythema, swelling | 2 |
| All of the following signs are found: Pain along path of cannula, erythema, induration | 3 |
| All of the following signs are evident and are extensive: Pain along path of cannula, erythema, induration, palpable venous cord | 4 |
| All of the following signs are evident and are extensive: Pain along path of cannula, erythema, induration, palpable venous cord, pyrexia | 5 |

the requirement of Indian Good Clinical Practice (GCP) guidelines. Study period was a maximum of 3 days:

- Screening, enrollment and start of treatment (Day 1, cannulation)
- Monitoring for efficacy and safety (every 8 ± 1 hours from the time of cannulation)
- End of treatment (Day 3).

Treatment with investigational product was initiated immediately on cannulation and was applied approximately every 8 hours for the treatment period of 48 hours (total 7 doses). The investigator documented the observations on the case report forms (CRF). Concomitant medication taken for concomitant disease was also recorded in the CRF. The following medications were not permitted during the study treatment:

- Anticoagulants locally (in the cannula) or systemically
- Nonsteroidal anti-inflammatory drugs (NSAIDs) locally at IV site.

Inclusion Criteria

Patients meeting the following criteria were included in the study:

- Either gender, 18-65 years of age, undergoing elective surgery.
- Undergoing peripheral vein cannulation planned to remain *in situ* for at least 48 hours of indoor period.
- Willing and able to comply with study requirements (application of IP and study visit schedule, as indicated by written informed consent provided by the patient).
- If female of childbearing potential: Nonpregnant (supported by negative urine pregnancy test at screening), nonlactating and willing to maintain reliable birth control throughout the study.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Undergoing re-cannulation due to phlebitis at earlier cannulation site.
- Unconscious or comatose patients.
- History of hypersensitivity reaction to heparin or heparin-induced thrombocytopenia.
- Signs of systemic infection, bacteremia.

DRUGS

- ⊖ Planned administration of any of the following during study period:
 - Anticoagulants locally (in the cannula) or systemically
 - NSAIDs locally at IV site.
- ⊖ Having participated in any clinical trial within last 30 days at the time of screening.
- ⊖ Any disorder or condition that, in the opinion of investigator, would prohibit study participation or affect study outcome.

Efficacy and Safety Measures

Enrolled patients were periodically monitored every 8 ± 1 hours from the time of cannulation for infusion phlebitis grade as per visual infusion phlebitis scale on the following time points:

- ⊖ 0 ± 1 hours: Within 1 hour of cannulation
- ⊖ 8 ± 1 hours: Between 7 to 9 hours of cannulation
- ⊖ 16 ± 1 hours: Between 15 to 17 hours of cannulation
- ⊖ 24 ± 1 hours: Between 23 to 25 hours of cannulation
- ⊖ 32 ± 1 hours: Between 31 to 33 hours of cannulation
- ⊖ 40 ± 1 hours: Between 39 to 41 hours of cannulation
- ⊖ 48 ± 1 hours: Between 47 to 49 hours of cannulation.

The patients were periodically monitored by an evaluator every 8 ± 1 hours (as per time points mentioned above) from cannulation for any application site reaction.

The primary efficacy endpoints included:

- ⊖ Proportion of patients with infusion phlebitis (Grade II and above) during 48 hours of treatment period.
- ⊖ Mean time to reach infusion phlebitis Grade II (or above) in hours: Depending on the time point when patient is first found to have phlebitis Grade II or above, mean time to reach phlebitis Grade II will be calculated in hours. For patients not reaching Grade II by 48 hours, it will be 48 hours.

The secondary efficacy endpoints included:

- ⊖ Incidence of first signs of phlebitis (Grade I).
- ⊖ Mean time to reach infusion phlebitis Grade I (or above) in hours.

Treatment

All enrolled patients were cannulated on back of the hand with IV cannula no. 18. The investigational product was heparin sodium topical solution (1,000 IU/mL). The dosage was 6 to 8 drops applied on

the skin over the cannulated vein approximately every 8 hours for a period of 48 hours (total 7 doses).

The following information was to be recorded for each adverse effect in the adverse events (AE) form provided in the CRF:

- ⊖ 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 AE (resolved, resolved with sequelae, ongoing, unknown or fatal)
- ⊖ Is it expected or unexpected
- ⊖ Is it serious (any effect that results in death, hospitalization/prolongation of hospitalization, congenital malformation, permanent disability or incapacity) or not.

RESULTS

Out of the enrolled patients, 11 were beyond the age limit mentioned in study design. Hence, data from those patients were not included in statistical analysis.

Efficacy

Three out of 39 evaluated patients experienced Grade II phlebitis during the study period. As per the study plan, patients with phlebitis Grade II or above were discontinued from the study. It took a mean time of 46.36 hours to reach Grade II phlebitis after application of heparin sodium topical solution (1,000 IU/mL) every 8 hours. The proportion of patients with Grade II phlebitis is depicted in Figure 1.

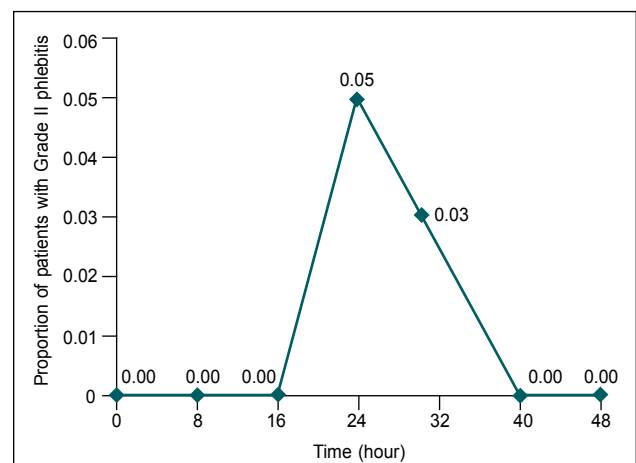


Figure 1. Proportion of patients with Grade II phlebitis.

All of the 39 patients experienced Grade I and/or Grade II phlebitis at some point of time during the study period. It took a mean time of 43.49 hours to reach the Grade I phlebitis after application of heparin sodium topical solution (1,000 IU/mL) every 8 hours. Figure 2 depicts the proportion of patients with Grade I phlebitis.

Safety

There was no site specific reaction observed for any patient during the study period.

Pain

All of the 39 patients experienced pain at some point of time during the study period. Pain intensity was 'slight' at each incidence. The incidences of pain were observed to be in correlation with phlebitis. The proportion of patients with slight pain is depicted in Figure 3.

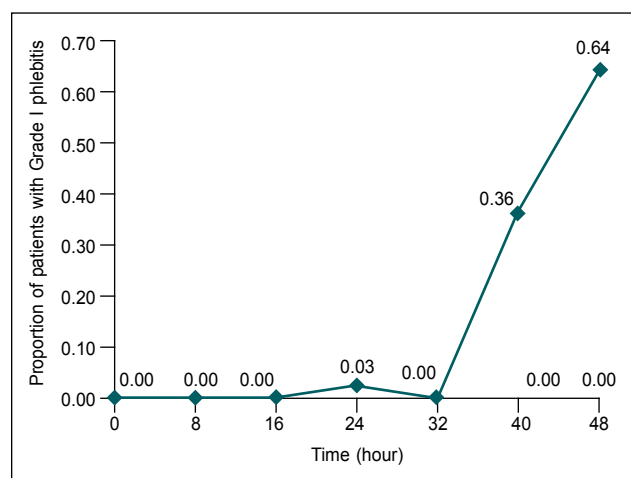


Figure 2. Proportion of patients with Grade I phlebitis.

Erythema

Three patients out of 39 experienced erythema during the study period. The incidences of erythema were observed in correlation with Grade II phlebitis. The proportion of patients with erythema is depicted in Figure 4.

Induration

Three patients out of 39 experienced swelling during the study period. The incidences of swelling were observed in correlation with Grade II phlebitis. The proportion of patients with induration is shown in Figure 5.

Palpable Venous Chord and Pyrexia

Palpable venous chord and pyrexia were not observed in any patient at any time point during study period.

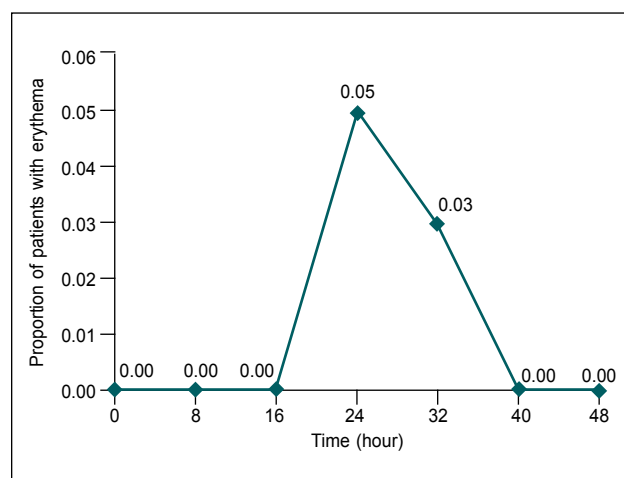


Figure 4. Proportion of patients with erythema.

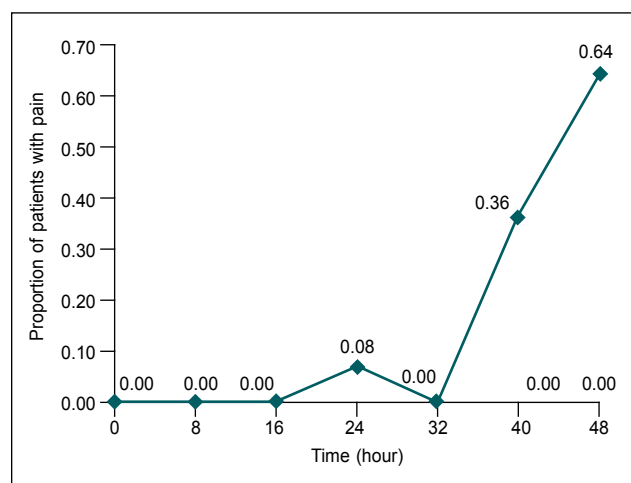


Figure 3. Proportion of patients with slight pain.

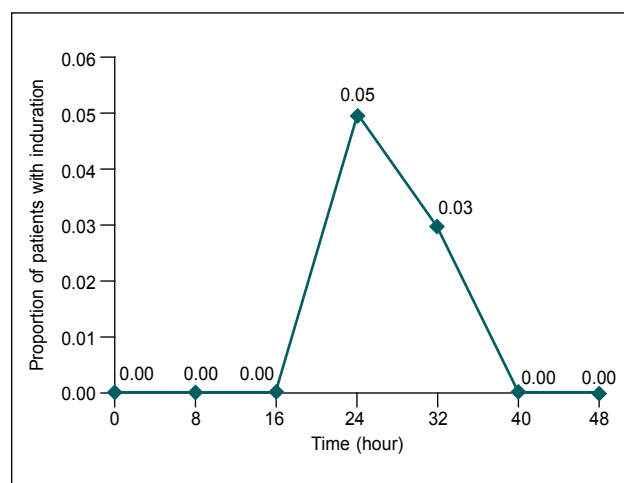


Figure 5. Proportion of patients with induration.

DISCUSSION

Intravenous cannulation, to administer drugs, fluids, blood products and nutritional solutions, is a significant part of hospital-based management. The use of IV cannula is often associated with the development of superficial thrombophlebitis. Topical heparin application at the site of cannulation is frequently done to prevent thrombophlebitis.

The present study assessed the safety and efficacy of topical heparin sodium solution (1,000 IU/mL) in preventing infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein three times a day over a period of 48 hours after cannulation. Three out of 39 evaluated patients experienced Grade II phlebitis. It took a mean time of 46.36 hours to reach Grade II phlebitis after application of heparin sodium topical solution (1,000 IU/mL) every 8 hours. Patients with phlebitis Grade II or above were discontinued from the study. All patients experienced Grade I and/or Grade II phlebitis at some point of time during the study period. It took a mean time of 43.49 hours to reach the Grade I phlebitis.

There was no site specific reaction observed for any patient during the study period. Patients experienced only slight pain at some point of time during the study period. Only 3 out of 39 patients experienced erythema during the study period. The incidences of

erythema were observed in correlation with Grade II phlebitis. Additionally, 3 out of 39 patients experienced swelling during the study period. The incidences of swelling were also observed in correlation with Grade II phlebitis. None of the patients reported palpable venous chord and pyrexia at any time point during study period.

Topical heparin sodium solution 1,000 IU/mL (Thrombotroy QPS, Troikaa Pharmaceuticals Limited) was thus found to be safe and effective in preventing and/or delaying infusion-associated superficial thrombophlebitis when applied on the skin over the cannulated vein three times a day over a period of 48 hours after cannulation.

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