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Evaluation of Safety and Efficacy of Quick Penetrating Heparin Solution (1000 IU/ml) in Prevention of Intravenous Cannula Related Thrombophlebitis: A Prospective, Randomized, Comparative, Parallel Group Clinical Study

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Abstract

Background and Aims: To evaluate the safety and efficacy of marketed heparin sodium topical solution (1000 *IU/ml*) compared to no heparin topical treatment group for prevention of infusion associated thrombophlebitis. *Methods:* A prospective, randomized, parallel group, comparative, single centre, clinical study. A total 100 patients undergoing intravenous cannulation that has been planned to remain in situ for at least 48 hours indoor period were enrolled. Patients were randomized in Group A (Heparin Topical solution) vs Group B (No Heparin Topical solution). Investigational product was applied on skin around dressing covering intravenous cannulation site approximately every 8 *hours* for the treatment period of 48 *hours*. Patients were evaluated for incidences of infusion phlebitis, first signs of phlebitis and treatment emergent application site reactions and were statistically analyzed for statistical significance, *p* - value below 0.05 levels was considered to be significant. *Results:* Incidences of infusion phlebitis Grade 2 was found to be higher in "no treatment group" than in "Topical Heparin Group" (20 vs 6 patients; $p = 0.00205$). Incidences of first sign of phlebitis grade was found to be higher in "no treatment group" than in "Topical Heparin Group" (48 vs 25 patients; $p = 0.000$). Time to develop first sign of phlebitis was lesser in "No Treatment Group" than in Topical Heparin Group (26 *hr* vs 36 hr; $p = 0.0023$). Also, none of the patient in the Heparin Group develop the thrombophlebitis (Grade IV- advance stage of phlebitis). *Conclusions:* Topical solution of Heparin Sodium 1000 *IU/ml* was found to be effective and safe in preventing infusion related phlebitis.

Keywords: Heparin Topical solution; Superficial thrombophlebitis; Infusion associated thrombophlebitis.

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Introduction

The use of intravenous cannulation is an integral and has become an indespensible part of patient care in hospitals. Peripheral Venous Cannulation (PVC) is a common procedure carried out in hospital to allow rapid and accurate administration of medication.[1] However, the placement of an intravenous cannula can have undesirable effects that can have an adverse impact on the clinical outcome of patients, the most common of which is phlebitis (mechanical, chemical and bacterial) is a common local complication of peripheral intravenous therapy administered through a

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peripheral venous cannula. Among hospitalized patients, 5% to 70% of patients receiving IV therapy develop phlebitis.[2]

Phlebitis is painful, can permanently damage affected veins, requires additional venipunctures at added cost, and can result in an extended hospital stay. Phlebitis symptoms include pain, edema, and erythema (which usually appears as a red streak along the vein), and in severe instances, thrombus formation and "cording" of the vein. There are three different types of phlebitis including mechanical, chemical and infectious. Chemical phlebitis is caused by irrigating medication or solutions such as antibiotics, blood products, glucose containing fluids and rapid infusion rates. Mechanical phlebitis is results from long periods of cannulation, cannula in flexed areas, catheter gauges larger than the vein lumen and poorly secured catheters. Bacterial phlebitis results from poor hand hygiene, lack of aseptic technique, failure to check all equipment before use and failure to recognize early sign and symptoms of phlebitis.[3]

Minimizing a patient's risk of developing phlebitis and early identification and treatment of the condition when it does occur improve patient outcomes and help minimizing the costs. The different modalities for prevention of phlebitis, includes the discontinuation of intravenous catheter and restarting it in another site, applying a warm moist compression to the affected site, administration of analgesics and local application of anticoagulant. Evidence suggests that the addition of drugs such as heparin can reduce the incidence of phlebitis.[4]

Heparin which is a non-uniform mixture of straight chain mucopolysaccharides reduces the superficial thrombophlebitis. It acts by its anti-inflammatory actions and by preventing coagulation rather than lysing a formed clot. So, if topical heparin is started prophylactically even before thrombophlebitis sets in, *i.e*. from *day 1* of intravenous cannula insertion it can prevent or postpone thrombophlebitis more effectively.[5]

In our study, the efficacy and safety of Heparin Sodium Topical solution (*1000 IU/ml*) compared to No Heparin Topical Treatment Group in preventing infusion associated phlebitis was evaluated.

Materials and Methods

This study was conducted at Department of Anesthesiology, Parul Sevashram Institute of Medical Science and Research Hospital, Waghodia-Gujarat ethical clearance from Parul University Institutional Ethics Committee for Human Research. The trial was registered in Clinical Trial Registry-India (CTRI) with the registration number CTRI/2017/10/010089.

The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India, and the ethical standards laid down in declaration of Helsinki 1975 as revised in 2013; and Ethical guidelines for biomedical research on human participants issued by Indian Council of Medical Research (2006), New Delhi.

This prospective, randomized, evaluator blind, parallel group, comparative safety-efficacy clinical study was conducted on 100 patients of either sex undergoing cannulation of peripheral vein that has been planned to remain in situ for at least *48 hours* of indoor period, belonging to age group of *18* to *65 years*.

All patients were explained the procedure clearly and written informed consent was obtained from each patients before their participation in the study. During screening, medical history was obtained; Physical examination and laboratory investigations were performed.

Patients with known hypersensitivity or contraindications to heparin were excluded. Patients who are on anticoagulants and required topical anti-inflammatory agent were also excluded. The women of child bearing age underwent the urine pregnancy test; the pregnant and lactating women were excluded from the study.

The patients were enrolled after verification of eligibility criteria. Enrolled patients were equally randomized using computer generated simple randomization sheet to receive either topical heparin QPS *1000 IU/ml* (Phlebotroy QPS, manufactured by Troikaa Pharmaceuticals Ltd, Ahmedabad, India) or no topical heparin.

Group A included 50 patients who received topical heparin *1000 IU/ml* and Group B included 50 patients who did not receive topical heparin.

All patients enrolled in the study were cannulated on back of the hand with intravenous cannula no. 18 supplied by same manufacturer as far as possible. For intravenous infusion through the cannula infusion set of the same manufacturer was used in all enrolled patients as far as possible. Treatment with any of the following was started immediately on cannulation. In Group A Heparin Sodium Topical QPS (*1000 IU/ml*) was applied

around intravenous cannula insertion site immediately after cannulation and thrice daily thereafter, for a period of *48 hrs* in addition to standard care for prevention of thrombophlebitis as per Hospital Protocol. 6 to 8 drops of topical solution was applied on skin over the cannulated vein approximately every *8 hours* for the treatment period of *48 hours* (total 7 doses). Group B did not receive application of any Heparin Topical solution. However, Patients received the standard care for prevention of thrombophlebitis as per Hospital Protocol.

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 every *8 hours* for *48 hours* after initiation of treatment. In this phlebitis scale, Grade 0 indicates no sign of phlebitis; Grade 1 indicates possibly the first sign of phlebitis; Grade 2 indicates early stage of phlebitis; Grade 3 indicates medium stage of phlebitis; Grade 4 indicates advance stage of phlebitis or stage of thrombophlebitis; Grade 5 indicates advanced stage of thrombophlebitis.[6]

Patient found to have infusion phlebitis Grade II or above as per visual infusion phlebitis scale, were discontinued from the study.

The Primary efficacy end point were proportion of patients found with infusion phlebitis (Grade II and above) during *48 hours* of treatment period and the mean time to reach infusion phlebitis grade in hours. The Secondary efficacy end point was the incidence of first signs of phlebitis (Grade I). The Safety endpoints evaluated for the proportion of patients with application site reaction.

Statistical Analysis for statistical significance was carried out with the help of Chi-square Test and student *t* - test. *p* - value below 0.05 levels was considered to be significant.

Results

The number of patients screened in both Group A (topical solution of heparin *1000 IU/ml*) and Group B (No treatment group) were 50 each. Out of these screened patients, 2 patients from Group A were dropped due to non-eligibility. Hence, 48 patients were enrolled in Group A and 50 patients were enrolled in Group B. Demographic data showed equal distribution of patients in both the arms in terms of age and sex, shows as in (Table 1).

Table 1: Demography of the patients

Parameter	Group A (Topical Solution of Heparin *1000 IU/ml*)	Group B (No Treatment)	*p* - value
Age in *Years*	38.29 ± 14.14	38.16 ± 14.14	0.9633*
Gender (M/ F)	29/19	31/19	0.87224**

*Data analyzed by unpaired '*t*' test

**Data analyzed by Chi-square test

Primary Efficacy Evaluation

Incidence of infusion thrombophlebitis (Grade II and above) during 48 hours of treatment period: The patients who were treated with Topical Heparin solution 1000 IU/ml had significantly lesser incidence of Grade II or above thrombophlebitis as compared to no treatment Group ($p < 0.05$), shows in (Table 2).

Table 2: Between group comparison for incidence of thrombophlebitis (Grade II or above) as determined by Visual Infusion Phlebitis Scale

Incidence of Thrombophlebitis (Grade II or above)	Yes	No	Proportion of patients with thrombophlebitis	*p* - Value
Group A (*n* = 48)	6	42	0.125	0.00205*
Group B (*n* = 50)	20	30	0.4	

Group A: Topical Heparin Solution *1000 IU/ml*

Group B: No Treatment

* Data analyzed by Chi-square test

Secondary Efficacy Evaluation

Incidence of Grade I phlebitis during *48 hours* of treatment period: The patients who were treated with Topical Heparin solution *1000 IU/ml* had significantly lesser incidence of Grade I phlebitis as compared to no treatment Group ($p < 0.05$), shows in (Table 3).

Table 3: Between group comparison for incidence of Grade I phlebitis as determined by Visual Infusion Phlebitis Scale

Incidence of Grade I Phlebitis	Yes	No	Proportion of patients	*p* - Value
Group A (n = 48)	25	23	0.521	0.00*
Group B (n = 50)	48	2	0.96	

Group A: Topical Heparin Solution 1000 *IU/ml*

Group B: No Treatment

* Data analyzed by Chi-square test

Meantime to develop infusion phlebitis (Grade I or above) in hours: The patients who were treated with topical heparin solution *1000 IU/ml* took significantly more time to develop infusion phlebitis (Grade I or above) as compared to no treatment

Group ($p < 0.05$). For patient's not reaching Grade I by *48 hours*, it was taken as *48 hours*, (Table 4).

Table 4: Between group comparison for meantime to develop infusion phlebitis (Grade I or above)

Mean ± SD Time to Develop Phlebitis (In hours)		t - value	p - value
Group A (Topical Heparin Solution 1000 IU/ml)	Group B (No Treatment)		
36.167 ± 16.41	26.24 ± 14.90	3.13	0.0022

Safety Evaluation

Incidence of treatment emergent adverse events was not reported in any groups during the treatment period.

Discussion

The topical formulation of Heparin Sodium *1000 IU/ml* was found to be effective and safe in preventing incidence of cannula related phlebitis. Topical solution of Heparin Sodium *1000 IU/ml* was found to significantly better than "No Treatment" in both the primary and secondary efficacy endpoints. The statistical analysis revealed that the patients who were treated with Topical Heparin Sodium *1000 IU/ml* has significantly lesser incidence of thrombophlebitis (Grade II or above) as determined by Visual Infusion Phlebitis scale.

Furthermore, it was also revealed that the patients who were treated with topical Heparin Sodium *1000 IU/ml* had significantly lesser incidence of phlebitis (Grade I) as compared to other Group. It has been observed that patients treated with Heparin Sodium *1000 IU/ml* took significantly greater time to develop first sign of phlebitis as compared to no treatment Group. No treatment emergent adverse event has been reported in any Groups.

Conclusion

Topical solution of Heparin Sodium *1000 IU/ml* is effective and safe in preventing cannula related phlebitis in comparison with No Treatment Group.

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