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Original Research Article

A prospective randomized comparative study to evaluate the safety and efficacy of topical quick penetrating solution (QPS) of Heparin (1000 IU/ml) versus Heparin gel (200 IU/ml) in prevention of intravenous cannula related thrombophlebitis in post operative onco surgical intensive care unit (ICU) patients

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ABSTRACT

Background: Intravenous cannulation usage is a vital component for the patient admitted at hospitals and is known to cause thrombophlebitis in upto 70% of patients so this study is needed to evaluate profile of topical quick penetrating solution of Heparin and compare it with Heparin gel in prevention of thrombophlebitis in post operative onco-surgery patients admitted in intensive care unit (ICU) in terms of safety and effectiveness.

Aims and Objective: To evaluate the safety and efficacy of topical quick penetrating solution of Heparin and compare it with Heparin gel in prevention of thrombophlebitis in post operative onco-surgery patients admitted in intensive care unit (ICU).

Materials and 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 72 hours indoor period were enrolled. Patients were randomized in Group A (Heparin Topical solution) vs Group B (Heparin gel). Investigational product was applied on skin around dressing covering intravenous cannulation site approximately every 8 hours for the treatment period of 72 hours. Patients were evaluated for incidences of infusion phlebitis, first signs of phlebitis and treatment emergent application site reactions and were statistically analysed 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 “heparin gel group” than in “Topical Heparin Group” (17 vs 7 patients, p=0.0192). Incidences of first sign of phlebitis grade 1 was found to be higher in “heparin gel group” than in “Topical Heparin Group” (24 vs 10 patients, p=0.003123). Mean time to develop Grade I and Grade II phlebitis was comparable and no adverse effects were reported in either group.

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

1. Introduction

Intravenous cannulation usage is essential and a vital component of care taken for the patient admitted at

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hospitals. Cannulation of peripheral vein hence is a known routine course of action performed at hospitals in ICUs and wards, for enabling the prompt & precise delivery of medicines.[1] Despite the benefits, insertion of an intravenous cannula may lead to unwanted side-effects that may negatively affect patient outcomes. One of the most frequent complications is phlebitis, which is seen to be mechanical, chemical or bacterial in nature. Phlebitis is a common local issue seen associated with peripheral intravenous therapy. In hospitalized patients, the incidence of phlebitis among those receiving IV therapy ranges from 5% to 70%.[2]

Phlebitis can be painful and causes permanent damage to the veins that are cannulated, necessitating numerous painful venipunctures, at increased costs and potentially leading to a longer hospital stay. Symptoms of phlebitis include pain, swelling, and redness (often appearing as a red-streak along the vein that is cannulated). Severe cases show formation of thrombus (thrombophlebitis) and "cording" of cannulated vein. Phlebitis is classified into three main types: mechanical, chemical, and infectious. The use of certain medications/solutions, for example: blood and blood-products, antibiotics, fluids containing glucose or fast rates of infusion, lead to the development of "chemical" phlebitis. Prolonged cannulation, placing the cannula in flexed areas, using a catheter with a gauge larger than the vein, or catheters secured poorly leads to the development of "mechanical" phlebitis. Poor hand hygiene, incorrect aseptic practices, not checking equipment before use, and failing to detect early signs and symptoms of phlebitis can contribute to the development of "bacterial" phlebitis.[3]

Reducing the risk of development of phlebitis for the patient and promptly identifying as well as treating the condition when it arises can enhance outcomes for patients and help lower their expenses. Various methods to prevent phlebitis include removing the intravenous catheter and placing a new one at a different site, using warm moist compresses on the affected area, administering analgesics, and applying local anticoagulants. Research indicates that adding medications like heparin can help decrease the frequency of development of 'phlebitis'.[4]

Complex mixture of "straight-chain mucopolysaccharides" make up the structure of Heparin, which helps reduce superficial thrombophlebitis. It works through its anti-inflammatory properties and by preventing coagulation, rather than dissolving existing clots. Therefore, initiating topical heparin prophylactically, starting from the first day of intravenous cannula insertion, can more effectively prevent or delay the onset of thrombophlebitis.[5]

Topical heparin formulations provide effective skin penetration at the application site while minimizing systemic exposure and reducing the risk of bleeding effects which maybe adverse for the patient. Heparin gel [Thrombophobe gel 200 IU/ml] is one such topical therapy. Recently, a new topical formulation of Heparin has been introduced which is called "Topical Quick Penetrating Solution [QPS] of Heparin (1000 IU/ml)".[6] This solution includes solvents which are non-aqueous and non-volatile and has surplus catalysts for permeability which help in improving heparin absorption through the skin, potentially offering greater efficacy than the traditional heparin-gel. Here, our study targets comparison of the efficacy of topical heparin QPS solution with that of heparin-gel for preventing development of superficial-thrombophlebitis.[6]

2. Materials and Methods

The study has been carried out at the Anesthesiology department of Shri Bhikhibai Kanjibhai Shah Medical Institute and Research Hospital, Piparia, Waghodia, Gujarat, with ethical-approval procured from the Sumandeep Vidyapeeth Institutional Ethics committee (SVIEC/ON/Medi/SRP/Sep/23/14).

This study followed the Good Clinical Practice (GCP) guidelines established by the Central Drugs Standard Control Organization (CDSCO) under the Ministry of Health, Government of India. It also adhered to the specified standards of ethics outlined in the Declaration of Helsinki (1975, revised in 2013) and the Ethical Guidelines for Biomedical Research on Human Participants issued by the Indian Council of Medical Research (ICMR) in 2006, New Delhi.

The study was a prospective, parallel, randomised group study comparing safety profile and effectiveness of heparin formulations in preventing thrombophlebitis for 100 onco-surgery patients, aged 18 to 65 years, undergoing peripheral vein cannulation intended to remain in place for at least 72 hours during their ICU stay.

All participants were fully informed about the procedure, and written consent was obtained. The screening process included medical-history collection, physical-examinations and performing laboratory tests. Patients who had known hypersensitivity or contraindications to heparin, those on anticoagulants, or those requiring topical anti-inflammatory agents were excluded. Females from childbearing age-bracket were tested for pregnancy, and pregnant or lactating women were excluded.

Eligible patients were randomly assigned into two groups using a computer-generated simple randomization sheet. The Group-A, consisting of 50 patients, received topical heparin QPS solution of 1000 IU/ml [Phlebotroy QPS] while the Group-B, also with 50 patients, received Heparin gel 200 IU/ml [Thrombophobe gel].

All patients were cannulated with an 18-gauge intravenous cannula on the back of the hand, using equipment from the same manufacturer whenever possible. For intravenous infusions, the same manufacturer's infusion set was used. Group-A applied Heparin Topical QPS solution (1000 IU/ml) and Group-B applied heparin gel (200 IU/ml) around the site of insertion of cannula on

immediate basis post-cannulation and then three times on a daily basis for 72 hours, in addition to standard thrombophlebitis prevention care as per hospital protocol. Six to eight drops of the solution were applied every 8 hours, totalling 10 doses.

The severity of phlebitis lesion was assessed using the Phlebitis Scale from the "Standards for Infusion Therapy" at baseline and every 8 hourly for upcoming 72 hours. Grade-0 indicated no phlebitis, Grade-1 showed the possible first sign, Grade-2 showed the early stage, Grade-3 signified the medium stage, Grade 4 showed the advanced stage or thrombophlebitis, and Grade 5 showed advanced thrombophlebitis. Patients who developed Grade II or higher phlebitis score were discontinued.

Primary efficacy endpoint was the fraction of all the patients developing infusion-related phlebitis (Grade-II or higher) during the 72-hour treatment period and the mean-time taken to reach that grade. Secondary efficacy endpoint was determined by the incidence of development of first signs of phlebitis (Grade-I). Safety profile endpoint was judged by the fraction of patients developing application site adverse reactions. Complications related to Heparin administration were monitored by assessing platelet count levels daily for the ICU patients enrolled for the study till the study lasted.

Sample size calculation was based on the formula,

$$n = \mathrm{f}\left(\frac{\alpha}{2}, \beta\right) \times \frac{(p1 \times (100 - p1) + p2 \times (100 - p2)]}{(p2 - p1)^2}$$

Where p1and p2 represent the percentage of 'success' in Group A and Group B, respectively. Calculations were performed using G* Power 3.0.10 software. The primary objective was to assess the incidence of phlebitis (Grade II or higher) over a 72-hour period in patients treated with a topical heparin solution (Group A) compared to those receiving heparin gel (Group B). The significance level ($\alpha \backslash \text{alpha} \alpha$) was set at 0.05 (95% confidence), and the power of the study (β) at 80%.'success' was defined as the percentage of patients who did not develop phlebitis (Grade II or higher) within the 72-hour monitoring period. Data for this calculation were drawn from a previous study by Saini V et al.[7]

Statistical significance was determined by the Chi-square Test & Student's t-test, with a p-value below 0.05 considered significant.

3. Results

3.1. Demographic data

Fifty patients each were screened and enrolled in both: the Group-A (treated with topical QPS heparin solution 1000IU/ml) & the Group-B (treated with heparin gel 200IU/ml). The demographic data, as shown in (Table 1), indicate that the patients in both groups were equally distributed in terms of age and gender.

3.2. Primary efficacy evaluation

The occurence of phlebitis (Grade-II & above) found whilst the 72-hour treatment period was significantly lower in patients treated with the topical heparin solution (Group-A) compared to those who received Heparin gel (Group-B), as shown in (Table 2) ($p < 0.05$).

3.3. Secondary efficacy evaluation

The occurrence of development of Grade-I phlebitis (first possible signs) whilst the 72-hour treatment period was significantly lower in the group treated with topical heparin QPS solution 1000 IU/ml (Group A) compared to the group treated with heparin gel 200 IU/ml (Group B), as depicted in (Table 3) ($p < 0.05$).

The mean time to develop phlebitis (Grade-I or above) was slightly more by the group treated with topical heparin solution (Group-A) compared to the Heparin gel treatment group (Group-B), as shown in (Table 4) ($p < 0.05$).

4. Discussion

Superficial thrombophlebitis frequently occurs as a complication of ongoing intravenous infusions, characterized by a blood clot forming in a superficial vein lumen, which leads to inflammation of the vein's wall and nearby tissues. Phlebitis frequently occurs with IV therapy, influenced by several factors. These include chemical irritants from certain medications and physical factors such as the duration of catheterization. Inserting a peripheral venous catheter can damage the vein, and the catheter itself may act as a foreign body, prompting an inflammatory response. This inflammation increases the risk of clot formation and phlebitis. The risk of thrombophlebitis is higher with prolonged catheter use due to the extended presence of the catheter.[8]

The primary goals in managing superficial thrombophlebitis are to relieve pain and other associated symptoms, while also preventing complications. Effective treatment should focus on both local symptom relief and the reduction of systemic risks, such as DVT (deep vein thrombosis).[9] Topical heparin has been shown to be effective in achieving these objectives.[10]

In the study, phlebitis was assessed using the Visual-Infusion-Phlebitis-Scale, revealing that mild cases were the most prevalent around two third cases, while moderate to severe cases were less common and Heparin topical QPS demonstrated greater efficacy compared to Heparin-gel which is also supported by the study by Devdas et al. and Pandya et al. This increased efficacy is attributed to the advanced QPS technology, which enhances heparin's absorption through the skin.[11,12] These results support the evidence that the heparin QPS topical formulation is superior to other topical heparin preparations in preventing superficial thrombophlebitis.[10,13,14]

Table 1: Demographic characteristics of study participants

Parameter	Group A (Topical QPS Heparin solution 1000IU/ml)	Group B (Heparin gel 200IU/ml)	p - value
Age (Years)	38.29 ± 14.14	38.16 ± 14.14	0.9633*
Gender (Male/ Female)	29/24	31/22	0.87224**

Note: Data studied by unpaired 't' test.* Data studied by Chi-square test**

Table 2: Comparison of incidence of infusion-related thrombophlebitis (Grade II or above) between both Groups as assessed by visual infusion phlebitis scale

Incidence of infusion-relatedThrombophlebitis (Grade-II & above)	Seen	Not seen	Percentage of patients developing infusion-related thrombophlebitis	Chi-square	p -Value
Group A (n= 50)	7	43	14%	4.4408	0.0192*
Group B (n = 50)	17	33	34%		

Group-A: Heparin topical QPS Solution (1000 IU/ml)
Group-B: Heparin gel (200 IU/ml)
Data analyzed using Chi-square test

Table 3: Comparison of grade I phlebitis incidence between groups as assessed by visual-infusion-phlebitis-scale

Incidence of Grade-I Phlebitis	Observed	Not Observed	Percentage of patients	"Chi-square"	"p-Value"
Group A (n = 50)	10	40	25%	8.7344	0.003123*
Group B (n = 50)	24	26	48%		

Group-A: Topical QPS Heparin Solution (1000 IU/ml)
Group-B: Heparin Gel (200 IU/ml)
Data studied by Chi-square test.

Table 4: Comparison of mean time to develop infusion phlebitis (Grade I or above)

Mean +/- SD time to develop infusion-related phlebitis in hours			
Group-A	Group-B	"t-value"	"p-value"
60.167 ± 16.41	56.24 ± 14.90	2.13	0.022

Safety profile: No complications were seen in either group in the duration of study.

The length of time a catheter remains in place significantly influences the likelihood of developing thrombophlebitis, with patients who have a catheter for more than three days being at greater risk. This aligns with earlier research and underscores the duration of catheter placement as a modifiable risk factor. To mitigate this risk, it is recommended to prophylactically reposition or replace catheters at a different site. [15]

Adverse-events were reported in neither of the study drugs, indicating that the increased efficacy of the quick-penetrating solution did not compromise patient safety. The study found that the topical Heparin QPS solution (1000 IU/ml) was significantly more effective than Heparin-gel (200 IU/ml) for both primary & secondary efficacy endpoints. Statistical analysis showed that patients using the topical solution had a significantly lower incidence of Grade-II or higher thrombophlebitis, as measured by the Visual-Infusion-Phlebitis-Scale. Additionally, those treated with Topical Heparin QPS (1000 IU/ml) experienced fewer instances of mild phlebitis (Grade-I) and showed a longer time to the first signs of phlebitis in contrast to those receiving Heparin gel. No treatment-emergent complications were noted in both the groups.

5. Limitations

The application site was not monitored beyond 72 hours in patients who did not develop signs of superficial thrombophlebitis. Therefore, the precise time for phlebitis onset following catheter placement remains unclear for patients beyond the 72-hour window, for both types of heparin solutions..

6. Conclusion

Heparin sodium topical QPS solution (1000 IU/ml) demonstrated superior effectiveness and safety in preventing cannula-related phlebitis compared to heparin gel (200 IU/ml). This solution proved valuable in managing patients with intravenous cannulas, significantly reducing the high incidence of infusion-associated thrombophlebitis. The primary risk factor for developing superficial thrombophlebitis identified in this study was the duration of the indwelling intravenous catheter.

7. Source(s) of Support

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8. Conflict of Interest

None.

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References

1. Endacott R. Clinical nursing skills, core and advanced. 1st ed. Oxford: Oxford University Press; 2009. p. 629.
2. Gallant P, Schultz A. Evaluation of a visual infusion phlebitis scale for determining appropriate discontinuation of peripheral intravenous catheters. *J Infus Nurs*. 2006;29(6):338–45.
3. Nagpal P, Khera GK, Kumar Y. A study to assess the clinical pattern of phlebitis among children admitted in selected hospitals of Ambala, Haryana. *Nurs Midwifery Res J*. 2015;11(2):68–77.
4. Ikeda SI, Douchi T, Nagata Y. Use of heparin to lower the incidence of phlebitis induced by anti-neoplastic agents used in ovarian cancer. *J Obstet Gynaecol Res*. 2004;30(6):427–9.
5. Babu TA, Sharmila V. Prophylactic topical heparin can prevent or postpone intravenous cannula induced superficial thrombophlebitis. *Med Hypotheses*. 2010;74(5):857–8.
6. Uslusoy E, Mete S. Predisposing factors to phlebitis in patients with peripheral intravenous catheters: a descriptive study. *J Am Acad Nurse Pract*. 2008;20(4):172–80.
7. Saini V, Samra T, Ahuja N, Sethi S. 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. *Indian J Pharmacol*. 2018;50(6):349.
8. Bansal T, Kumar P, Vashisht G. A study to evaluate the efficacy of topical quick penetrating solution of heparin in preventing thrombophlebitis. *Indian Anesth Forum*. 2019;20(2):95–8.
9. Grace SS, Segaran F, Christopher J, Samarasam I. Comparison of the effectiveness of glycerine magnesium sulphate paste vs heparinoid (Thrombophob) ointment on phlebitis among patients on peripheral intravenous therapy. *J Med Sci Clin Res*. 2020;8(4):27–34.
10. Devadas V, Rahaman H. Prevention of superficial thrombophlebitis in patients coming for surgery: Comparison of topical quick penetrating solution (QPS) of heparin versus heparin gel. *Paripex Indian J Res*. 2018;7(3):130–2.
11. Charan R, Chaurasia T. Topical heparin for infusion-associated superficial thrombophlebitis: A preventive approach. *J Indian Med Assoc*. 2018;116(12):15–6.
12. Vilardell M, Sabat D, Arnaiz JA, Bleda MJ, Castel JM, Laporte JR, et al. Topical heparin for the treatment of acute superficial phlebitis secondary to indwelling intravenous catheter. A double-blind, randomized, placebo-controlled trial. *Eur J Clin Pharmacol*. 1999;54(12):917–21.
13. Pandya JM, Gupta S, Chouhan A. Evaluation of safety and efficacy of Quick 2131 penetrating heparin solution (1000 IU/ml) in prevention of intravenous cannula-related thrombophlebitis: A prospective, randomized, comparative, parallel group clinical study. *Indian J Anesth Analg*. 2019;6(6):2129–32.
14. Akhileshwar, Singh S. Comparison of heparin quick penetrating solution and diclofenac quick penetrating solution for the prevention of superficial thrombophlebitis caused by peripheral venous cannulation: A randomized double-blind study. *Anesth Essays Res*. 2019;13(1):155–7.
15. Agarwal S, Verma NS, Singam A. Efficacy of Topical Heparin in Prevention of Superficial Thrombophlebitis before Peripheral Venous Cannulation. *J Evol Med Dent Sci*. 2020;9(23):1734–8.

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