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Original Research Article

A Comparative Study on the Efficacy of Heparin Ointment and Hirudoid Cream on Treatment of Thrombophlebitis Resulted From Intravenous Catheter Insertion and Multidrug Infusion

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Abstract:

Background and Aim: Intravenous cannulation is the most common invasive procedure in hospitals. Phlebitis is the most frequent complication of intravenous therapy. We aimed to compare the effect of heparin ointment and hirudoid cream on treating intravenous catheter-induced superficial thrombophlebitis and multidrug infusions.

Methodology: This prospective randomized study was conducted on 160 patients of both genders, above 18 years of age, who had superficial thrombophlebitis and had given informed consent, were randomly assigned into two groups: Group-A (Heparin ointment) and Group-B (Hirudoid cream). Heparin ointment or Hirudoid cream was applied thrice daily over the surface of the phlebitis lesion. Phlebitis grading was assessed for each patient from the first day of treatment to the seventh day of treatment or till the complete resolution of symptoms. The effectiveness of the treatment was assessed using the Visual Infusion Phlebitis Scale (VIP).

Result: In the Heparin ointment group the mean VIP score after treatment was significantly lower (p=<0.001) than hirudoid cream group from day 3 to day 5. The quality of treatment was excellent in 77.5% of patients in the heparin group than 58.75% of patients in the hirudoid group (p=0.009). The mean duration of treatment days was significantly less p=<0.001 in the heparin group (5.79 days) compared to the hirudoid group (6.30 days).

Conclusion: Heparin ointment administered topically thrice daily is better in comparison to Hirudoid cream application for treatment of superficial thrombophlebitis due to intravenous catheter insertion.

Keywords: Superficial Thrombophlebitis, Peripheral Venous Cannulation, Heparin Ointment, Hirudoid Cream.

Introduction

For patient care, peripheral intravenous catheters (PIVCs) are the most essential tools in the healthcare center. The modern medical practice uses intravenous (IV) therapy for up to 80% of hospitalized patients during their hospital stay [1]. Intravenous access is necessary for the administration of fluids, blood, blood products, resuscitation drugs, anesthetic medications, and other therapies requiring IV access. The most common complication associated with PIVC is Phlebitis, which is defined as inflammation of a vein related to a mechanical or chemical irritation or both and is characterized by local pain, redness, and swelling [2,3]. Among hospitalized patients receiving IV therapy, the incidence of phlebitis has been reported to be as high as 80% [4]. The treatment goals of superficial thrombophlebitis are to relieve pain, reduce other symptoms, and prevent complications. Phlebitis must be treated as soon as possible, by ceasing infusion and removing the PVC [5]. The affected limb should be elevated to minimize inflammation and anti-inflammatory cream or gel applied directly over the affected surface to reduce inflammation [6,7]. The most commonly used anti-inflammatory or antithrombotic creams are heparin and heparinoid formulations. Heparin is made up of straight-chain mucopolysaccharides which reduce the blood clots formed in the blood vessels by disabling the thrombin in the formation of blood clots and also preventing new blood clot formation. Heparinoids are glycosaminoglycan which is derivatives of

heparin**.** It includes oligosaccharides and sulfated polysaccharides. Heparinoids improve blood circulation through small veins, as they dissolve small blood clots and relieve swelling caused by the clots in the veins beneath the skin surface. Furthermore, several topical formulations of heparin and heparinoids are currently available and are widely used to treat and prevent superficial thrombophlebitis[7]. These gels and creams allow heparin to penetrate through the skin and into the bloodstream at the application site, without systemic exposure in clinically relevant doses, thereby reducing the risk of the adverse effect of bleeding [8].

We aimed to compare the effectiveness of Heparin Ointment and Hirudoid Cream on the treatment of thrombophlebitis resulting from Intravenous catheter insertion and multidrug infusions. Heparin Ointment (Thrombophob ointment 20 gram) is the commercial formulation of Heparin. The active ingredients are- Heparin sodium 50IU and Benzyl Nicotinate 2gm [9]. Hirudoid cream is the commercial formulation of heparinoids. The active ingredients are- Heparinoid 0.3% w/w (Equivalent to 25000 Units per 100 g cream). Excipient(s) with known effect-Anhydrous eucerine (contains lanolin)-7.515% w/w, Cetostearyl alcohol-3.105% w/w, Methylparahydroxybenzoate-0.16%vw/w, Propyl parahydroxybenzoate-0.04% w/w[10].

Methodology

After the institutional ethical committee approval clearance (083/ 19-I-S-084/ Dt-25.01.2019), this prospective randomized study was conducted on 160 patients who had developed signs and symptoms of phlebitis due to peripheral IV cannulation, admitted to ICU and various wards in our institution from April 2019- January 2023.

As per the result of the previous study [11] (an improvement of 99% with heparin gel 1000 IU/g compared with 63% with mucopolysaccharide cream), using the formula for sample size calculation to compare 2 proportions:- $n=[p_1\times(100-p_1) + p_2\times(100-p_2)](Z_{1-\alpha/2} + Z_{1-\beta})^2 / (p_2-p_1)^2$, with 95% confidence interval and 80% power, the calculated minimum sample size for each group was 15, so we included 80 patients in each group.

The inclusion criteria were: patients of both genders, who were over 18 years of age, with thrombophlebitis caused by IV cannula, and were conscious, oriented, and gave their consent to participate. Exclusion criteria were: patients with phlebitis along with skin disorders, critically ill, unconscious, having associated vascular disorders, having hypersensitivity to heparin ointment or hirudoid cream, and who refused to take part in the study.

In the patients receiving IV infusions, the presence of thrombophlebitis was screened. Once superficial phlebitis had been diagnosed, the patients were briefed about the study. Consent was obtained from each patient and they were then randomly assigned to either a Heparin ointment application (Group A) or a Hirudoid cream application (Group B). Heparin ointment or Hirudoid cream was applied three times daily (morning, afternoon, and night) with an amount sufficiently covering the surface of the phlebitis lesion.

Phlebitis grading was assessed for each patient from the first day to the seventh day of treatment or till the complete resolution of the symptoms. The patient's variables recorded were age, gender, occupation, diagnosis, the purpose of intravenous infusion, site of IV cannula, number of pricks during the IV cannulation, size of peripheral IV cannulas, type of medication infused, duration of peripheral IV cannulation, and grading of phlebitis. As per modified Jackson's visual infusion phlebitis scale (VIP scale), grading of phlebitis was measured based on local signs and symptoms (redness, pain, edema, increased local temperature, venous induration, and palpable venous cord) [12] [Table-1].

Quality of treatment was graded as Excellent-resolution of all symptoms within 5 days, Good-resolution of all symptoms within 7 days, Fair-symptoms not resolved after 7 days, and Poor- if any complications.

Table 1: Visual infusion Phlebitis scale [12]

Grade	Clinical criteria	Stage and Action Required
0	I.V site appears healthy	No Signs of Phlebitis
1	One of the following is evident • Slight pain near the I.V site • slight redness near the I.V site	Possible first signs of phlebitis. • Observe cannula
2	Two of the following are evident • Pain near the I.V site • Erythema • Swelling	Early stage of phlebitis. • Resite the cannula
3	All of the following are evident • Pain along the path of the cannula • Erythema	Medium stage of phlebitis • Resite cannula • Consider treatment

	• Induration	
4	All of the following are evident and extensive • Pain along the path of cannula • Erythema • Induration • Palpable venous cord	Advanced stage of phlebitis or start of thrombophlebitis • Resite cannula • Consider treatment
5	All of the following are evident and extensive • Pain along the path of cannula • Erythema • Induration • Palpable venous cord • Pyrexia	Advanced stage of thrombophlebitis • Initiate treatment • Resite cannula

Continuous variables were presented as mean, standard deviation, and categorical variables as frequency and percentages.

A Chi-square test was performed to compare the qualitative data and an independent t-test was performed to compare continuous data between the groups.

Paired t-test was used for comparison in the group. The confidence level of the study was kept at 95%. A p-value of <0.05 was considered statistically significant. SPSS version 23 was used for statistical analysis.

Results

The demographic parameters and medical details of patients were comparable in both groups.

The degree of superficial phlebitis VIP-2 and VIP-3 was 60(75%), 20(25%) in Group-A and 54(67.5%), 26(32.5%) in Group-B were comparable (p=0.295) [table-2].

Table 2: Demographic and medical details of patients in both groups

Variables	Group-A(Heparin) (n=80)	Group-B(Hirudoid) (n=80)	p-value
Age- years(mean±SD)	45.80±16.97	45.70±16.72	0.970
Sex- no (%) M, F	54(67.5%), 26(32.5%)	59(73.8%), 21(26.3%)	0.385
Weight-kg (mean±SD)	57.06±6.47	54.55±5.17	0.07
Site of IV cannula-no (%) Dorsum of hand, wrist lateral, forearm, antecubital.	14(17.5%), 37(46.3%), 17(21.3%), 12(15%)	13(16.3%), 43(53.8%), 14(17.5%), 10(12.5%)	0.811
Size of cannula-no(%) 18G, 20G	47(58.8%), 33(41.3%)	49(61.3%), 31(38.8%)	0.747
Mean no of attempts of cannulation	1.38±0.62	1.34±0.59	0.711
Mean duration IV cannulation-days	3.94±0.24	3.96±0.19	0.470
Types of drugs infused-no (%) Crystalloids, Antibiotics, Antipyretics, Analgesics, Vasopressors, Potassium, Insulin, Mannitol, Atropine, ASV, Anti-cancer drug, Hypertonic saline	80(100%), 66(82.5%), 17(21.3%),62(77.5%), 5(6.3%),5(6.3%), 5(6.3%),11(13.8%), 10(12.5%),4(5%), 12(15%), 11(13.8%)	80(100%),67(83.8%), 16(20%), 64(80%), 4(5%), 5(6.3%),5(6.3%), 11(13.8%), 8(10%), 4(5%), 8(10%), 11(13.8%)	0.432
Comorbidities-no(%) Diabetes mellitus, Hypertension, Malignancy, Dyslipidemia, Nil	13(16.3%),14(17.5%), 17(21.3%),1(1.3%), 42(52.5%)	21(26.3%),13(16.3%), 14(17.5%),4(5%), 37(46.3%)	0.467
Degree of superficial thrombophlebitis-no (%) VIP-2, VIP-3	60(75%), 20(25%)	54(67.5%), 26(32.5%)	0.295

Data are presented as mean±standard deviation or numbers (percentages). $*$ $p < 0.05$ is statistically significant.

The mean VIP score after treatment was significantly decreased from day 3, compared to their pre-treatment value (p<0.001) in both groups. The mean VIP Score difference was lower in

Group A than in Group B from the 3rd day to the 5th day which was statistically significant (p=0.001). The mean duration of treatment in Group A was 5.79 days and in Group B was 6.30 days (p=0.001).

Quality of treatment was graded as Excellent for 62 patients (77.5%), Good for 12 patients (15%) in Group A, and Excellent for 47 patients (58.75%), good for 27(33.75%) patients in Group B (p=0.009) [table-3].

Table 3: Comparison of mean VIP Score, quality of treatment, and duration of treatment after treatment

Variables		Group-A(Heparin) (n=80)		Group-B(Hirudoid) (n=80)		Comparison of mean VIP Score in Group-A and Group-B (p-value)
			p-value		p-value	
Mean VIP Score (mean±SD)	D1	2.25±0.44	1	2.32±0.47	1	0.298
	D2	2.25±0.44	1	2.32±0.47	1	0.298
	D3	1.45±0.63	<0.001*	2.14±0.49	0.0078*	<0.001*
	D4	1.29±0.45	<0.001*	1.85±0.35	<0.001*	<0.001*
	D5	0.73±0.63	<0.001*	1.02±0.31	<0.001*	<0.001*
	D6	0.38±0.58	<0.001*	0.44±0.54	<0.001*	0.485
	D7	0.15±0.35	<0.001*	0.21±0.41	<0.001*	0.308
Quality of treatment (no, %)	Excellent	62(77.5%)		47(58.75%)		0.009*
	Good	12(15%)		27(33.7%)		
	Fair	6(7.5%)		6(7.5%)		
Duration of treatment(days)		5.79±0.95		6.30±0.71		<0.001*

Data are presented as mean±standard deviation or numbers (percentages). * p<0.05 is statistically significant.

The resolution of redness (p=0.001) and the pain (p=0.001), was significantly better in Group A than in Group B from day 3 onwards [Fig-1 and Fig-2].

In terms of resolution of swelling with treatment, the difference was statistically significant on day 5(p=0.002) and day 7 (p=0.028) [Fig-3]. There was no statistical difference seen with treatment, in terms of resolution of induration in both groups (p-value >0.05) [Fig-4].

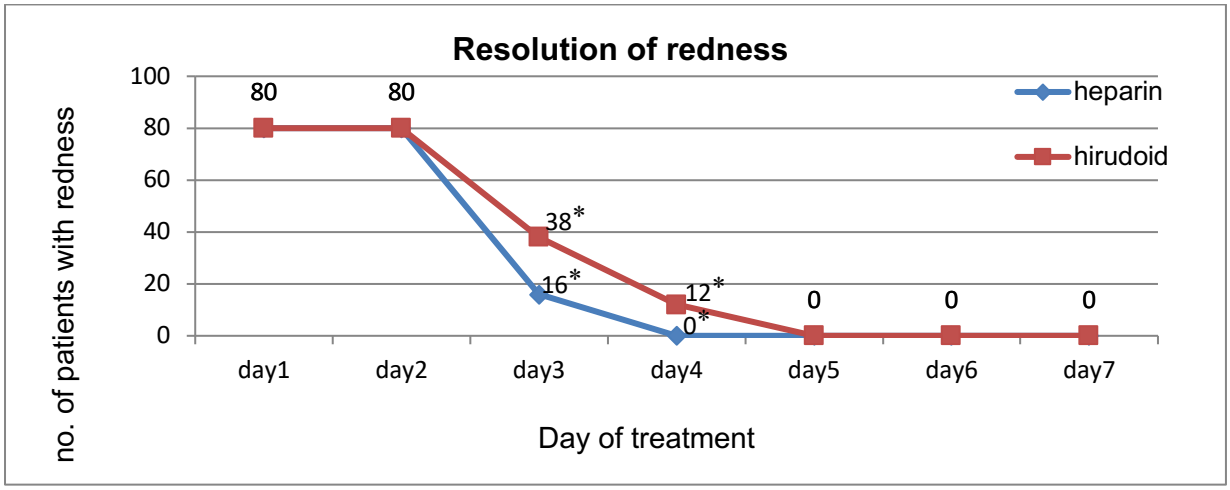


Figure 1: Resolution of redness of superficial thrombophlebitis in both groups over 7 days. *P<0.05

Figure 2: Resolution of pain of superficial thrombophlebitis in both groups over 7 days. *P<0.05

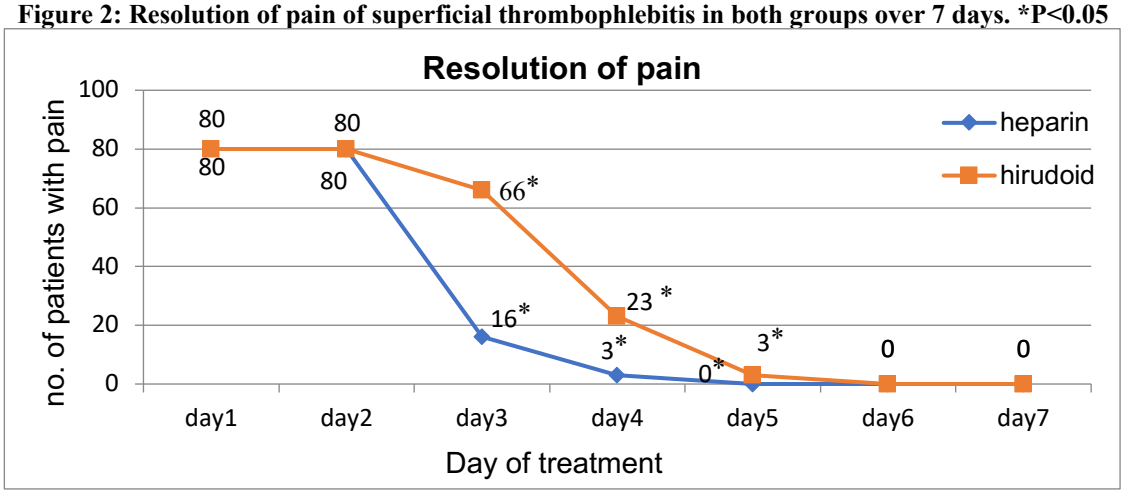


Figure 3: Resolution of swelling of superficial thrombophlebitis in both groups over 7 days. *P<0.05

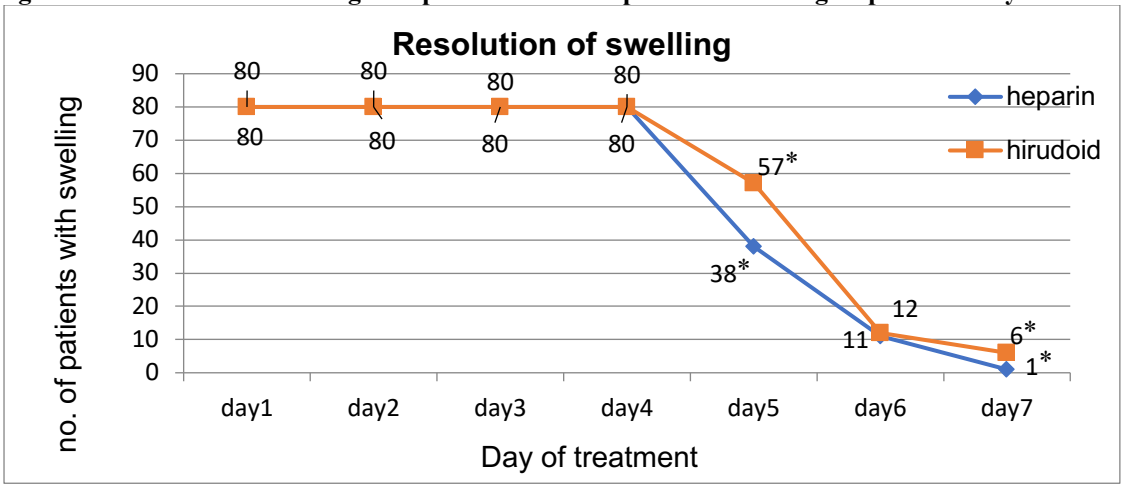
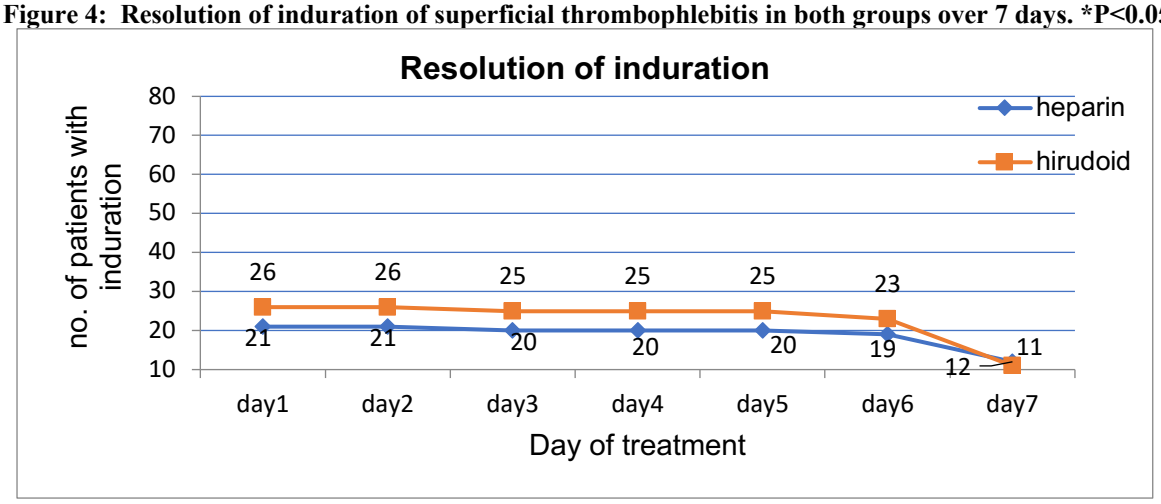


Figure 4: Resolution of induration of superficial thrombophlebitis in both groups over 7 days. *P<0.05



Discussions:

In this study, the incidence of second-degree superficial thrombophlebitis (VIP-2) was 114(71.25%) and third-degree superficial thrombophlebitis (VIP-3) was 46(28.75%). Similar observations were observed by Basanta et al., where the second degree was developed in 88.26% of patients and 11.73% developed the third degree of phlebitis [13]. Salma U et al. found that grade II phlebitis was developed in 55.26% and grade III phlebitis was developed in 22.37% of patients [14]. In both groups, drugs infused were comparable. The superficial thrombophlebitis was seen more in patients who had received vasopressors (88%), hypertonic saline (90%), mannitol (86%), potassium (80%), and insulin (80%). Gazitua et al. observed that the highest risk occurred when the solution osmolarity exceeded 600 mOsm/L [15]. In this study, the frequent site of catheterization was

the lateral side of the wrist followed by the forearm, dorsum of the hand, and antecubital area. Similar observations were found by Basanta et al. [13]. The study conducted by Cicolini et al. also observed the risk of phlebitis was higher in the antecubital fossa [16]. The mean duration of IV cannulation to the diagnosis of superficial thrombophlebitis was 3.94 days in Group A and 3.96 days in Group B. In all cases, the cannula is removed or resited on day 4. Signs of phlebitis started from day 2 in most of our subjects and the phlebitis incidence increased from the 2nd to 4th day. Cicolini et al. also concluded that phlebitis risk increases after 96 hours [16]. The cannula in our study was in situ for 72–96 hours. Our results indicate that phlebitis is more likely to occur within the fourth day of cannula insertion. This is similar to the findings of Panadero et al. [17] and Basanta et al. [13].

In the Heparin group, 60 patients had VIP score-2 and 20 patients had VIP score-3. After treatment, 12 patients had VIP score-1, and 68 patients had no superficial thrombophlebitis. The mean VIP score before the treatment was 2.25 and after treatment was 0.15. The mean VIP score after treatment was significantly less (p=<0.001) than before treatment from day 3 onwards, which indicates heparin application effectively reduced the signs and symptoms of superficial thrombophlebitis [Table 3]. The study conducted by Villardell M. et al. revealed that after 7 days of treatment, 27/61(44.3%) patients healed who received topical heparin, and 17/65(26.1%) patients healed who received placebo [18]. This concludes that topical application of heparin is effective and safe in the treatment of superficial thrombophlebitis.

In the Hirudoid group, 54 patients had VIP score-2, and 26 patients had VIP score-3. After treatment, 17 patients had VIP score-1 and 63 patients had no superficial thrombophlebitis. The mean VIP score before the treatment was 2.32 and after treatment was 0.21. The mean VIP score after treatment was significantly less from day 4 onwards [Table 3]. Thus, hirudoid cream application is also effective in the improvement of the signs and symptoms of superficial thrombophlebitis. The above finding is supported by D'Amico N et al., where heparin gel was compared with hirudoid gel and concluded that both preparations significantly improved therapeutic parameters compared with baseline [19].

In the Heparin group, the mean VIP score after treatment on day 3, day 4, and day 5 was 1.45, 1.29, and 0.72 respectively. In the Hirudoid group, the mean VIP score after treatment on day 3, day 4, and day 5 was 2.14, 1.85, and 1.02 respectively. The mean difference in VIP score for the Heparin group on day 3, day 4, and day 5 post-treatment is significantly lower (p=<0.001) than the Hirudoid application group. Thus, the heparin ointment application thrice daily produced greater improvement in signs and symptoms than the hirudoid cream application.

Moreover, in this study, we observed that Heparin ointment application results in faster resolution of symptoms compared to Hirudoid cream. Thus, the quality of treatment was better and the duration of treatment was less in Group A than in Group B. This was similar to the study conducted by De Angelis et al [11]. In their study, a proportionally greater degree of improvement was observed with heparin gel compared with mucopolysaccharide cream in terms of spontaneous pain, induced pain, edema, and heaviness in the limb. Similar results were observed by D'Amico N et al. [19].

In their study treatment with heparin gel twice daily produced a greater degree of improvement in terms of pain, erythema, hematoma, heaviness, edema and functional limitations, and night cramps, compared with the phospholipid gel, with improvements being noted after 7 days. The study conducted by Inga C et al. also found similar findings where the application of heparin gel improved symptoms of edema, pain, erythema, and heaviness in a higher proportion of patients than phospholipid gel [20].

Conclusions

From the above findings, it is evident that both Heparin ointment and Hirudoid cream applications are effective and safe in the treatment of superficial thrombophlebitis developed due to intravenous catheters. Applying heparin ointment three times a day locally resulted in a greater degree of improvement in signs and symptoms of thrombophlebitis, in terms of pain, erythema, and edema than Hirudoid cream. Hence, Heparin ointment administered topically thrice daily is better in comparison to Hirudoid cream application for the treatment of superficial thrombophlebitis due to intravenous catheter insertion.

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