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Research Article

# The Effects of Heparinized Normal Saline Flushing and Prophylactic Enoxaparin on Central Venous Catheter Thrombosis in PICU Hospitalized Pediatric

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**ABSTRACT**

**Background:** Central venous catheter (CVC) thrombosis is one of the most common complications of CVC that occurs in children and adults. Prevention of this blockage improves the treatment process and reduces treatment costs. Due to the lack of studies on preventive methods of CVC thrombosis, this study aimed to examine the effect of NS flushing heparinized and prophylactic dose of enoxaparin in prevention of CVC induced thrombosis in hospitalized patients in pediatric intensive care unit (PICU).

**Methods:** Eighty pediatrics with Central venous catheter admitted to the PICU enrolled in this trial and were divided into two groups as receiving heparinized normal saline was flushed every 8 hours under sterile conditions and receiving enoxaparin trough injection subcutaneously every 12 hours. The incidence of CVC-related thrombosis, diagnosed using color Doppler ultrasound of the vein containing the catheter was measured. Patients were monitored daily in terms of clinical symptoms related to thrombosis.

**Results:** There was no statistically significant difference in gender, age, anthropometric findings and vital sign as well as risk factors between two groups of the trial (P>0.05). Additionally, the finding showed a statistically significant relationship between major surgery (P=0.01) and heart disease (P=0.03) with symptomatic and asymptomatic thrombosis between the enoxaparin and heparinized normal saline groups. The rate of sepsis and bleeding were lower in enoxaparin group but it was not significant between study groups.

**Conclusion:** These findings indicate that enoxaparin may be considered as a clinical approach in thrombosis management and more clinical trials are needed.

## Introduction

Vascular access devices are widely utilized in the field of healthcare. This category of devices encompasses central venous catheters (CVCs) [1]. CVCs enable the measurement of hemodynamic variables that cannot be accurately assessed through noninvasive methods. Moreover, they facilitate the safe delivery of blood, drugs, and nutritional support that cannot be administered through peripheral vein catheters. However, the utilization of CVCs is associated with various side effects. Mechanical complications during insertion (such as arterial puncture, hematoma, and pneumothorax) occur in approximately 5% to 29% of cases, while infectious complications arise in about 5%

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to 26% of cases. Additionally, thrombosis, which is one of the most common complications, occurs in approximately 2% to 26% of cases [2-4]. CVC-related thrombosis is a significant cause of morbidity and mortality in patients with high-risk diseases. This is attributed not only to the inherent risks associated with thrombosis but also to its role in creating a conducive environment for bacterial proliferation, which in turn accelerates sepsis [5]. Moreover, pulmonary embolism, a highly perilous medical condition, affects approximately 15% of patients with CVC-related upper extremity deep vein thrombosis [6].

The utilization of CVCs carries a risk of vascular thrombosis due to vessel wall damage during catheter placement, hypercoagulation, and alterations in normal blood flow. The balance between the hemostatic systems that generate thrombin and the fibrinolytic systems that dissolve blood clots regulates blood vessel patency. However, the placement of a CVC can disrupt this regulated process, resulting in a persistent thrombotic state. The presence of the catheter itself exacerbates this thrombotic situation by allowing the absorption of fibrin and fibrinogen on its surface [7]. Heparin, with its anticoagulant properties, is commonly used in the form of flushes to prevent thrombus formation and prolong the catheter's open-time. However, the rationale for using heparin in peripheral venous catheters may be flawed, as no benefit has been demonstrated when compared to normal saline (NS). Nonetheless, further studies are necessary in this area [8-9]. Heparin locking is a standard method for maintaining CVCs, but its effectiveness has not been proven [10-11]. Additionally, there are potential risks associated with heparin use, such as heparin-induced thrombocytopenia [12].

Enoxaparin belongs to the family of low-molecular-weight heparins (LMWHs) and is commonly used as an anticoagulant. LMWHs work by inhibiting the final stage of the coagulation cascade, which involves the conversion of fibrinogen to fibrin through thrombin activity. LMWH achieves this by activating antithrombin III [13]. LMWH offers several advantages, such as a longer half-life, improved bioavailability, easy administration, and the ability to be closely monitored in pediatric patients [14].

Considering the significance of preventing thrombosis in central venous lines and the limited research on the use of enoxaparin in various doses for preventing thrombosis in children, this study seeks to compare the efficacy of normal saline flushing with heparinized flushing and a prophylactic dose of enoxaparin administered via subcutaneous injection in preventing CVC-induced thrombosis in hospitalized patients within the pediatric intensive care unit (PICU).

## Methods

### Study design and participants

This research was conducted as a randomized clinical trial (RCT) study. Eighty children who were admitted to the PICU of Bahrami Children's Hospital of Tehran University of Medical Sciences (TUMS) in 2021-2023 participated in this clinical trial study. Inclusion criteria of this research were including aged one month to 18 years, children with central venous catheters admitted to the PICU, none of the bleeding risk factors, informed consent of the patient's parent or guardian to participate in the study. Exclusion criteria included risk factors for central venous catheter thrombosis, anticoagulant or antiplatelet medication use in the past 5 days, risk factors for cerebral hemorrhage, major surgery in the last 24 hours, glomerular filtration rate less than 30, thrombocytopenia (platelets less than 50,000), kidney, heart and liver disorders, uncontrolled blood pressure, lumbar puncture in the last 24 hours, no census of parents or guardians of the patient to participate in the study.

At the outset, written informed consent, sanctioned by the TUMS ethics committee, was obtained from all participants or their parents. The objectives, benefits, and potential risks associated with the ongoing research were thoroughly explained.

The demographic characteristics of patients (age, gender, BMI), vital sign (temperature, respiratory and heart rate) and other study parameters including any disorder, malignancy, mechanical ventilation, supportive nutrition, occurrence of thrombosis, clinical symptoms of thrombosis (if symptomatic), others complications related to CVC such as bleeding and infection, hemoglobin level and the need for blood transfusion or blood culture were recorded.

The present clinical trial study was approved by the ethics committee of Tehran university of medical sciences, as ID: IR.TUMS.CHMC.REC.1400.239 and registered in Iranian Registry of Clinical Trials (IRCT) as ID: IRCT20230428058015N1.

### Implementation of the study and outcome measurements

The sample size calculation was performed based on the incidence of thromboembolic events, which served as the main variable of the study. With a significance level of $\alpha = 0.05$ and power of 80% ($1 - \beta = 1$), and considering a 20% frequency of thrombosis, the total sample size was determined to be 80 patients. These participants were then equally divided into two groups using the Permuted Block Randomization method, with each group consisting of 40 patients.

The study groups were as follows: Group 1) After CVC insertion, participants received a flush of 2 cc of heparinized normal saline (with a concentration of 2 units of heparin per cc of NS) every 8 hours under sterile conditions. Group 2) After CVC insertion, participants received subcutaneous injections of enoxaparin at a dose

of 0.5 mg/kg every 12 hours. The incidence of CVC-related thrombosis was subsequently measured by diagnosing the presence of thrombosis using color Doppler ultrasound of the vein containing the catheter. Doppler ultrasound was performed on the fourth day after CVC insertion, as well as on the day of discharge or when symptoms of thrombosis appear (including catheter failure, limb edema, limb stiffness, discoloration, pain, and limb tenderness) by a radiologist. In case of complications of CVC due to non-thrombosis causes such as bleeding and failure of catheter or infection, the patient was excluded from the study and the relevant treatment were performed. Patients were monitored daily in terms of clinical symptoms related to thrombosis, CVC complications due to non-thrombosis and bleeding, and major bleeding was defined as a drop in hemoglobin or the need for blood transfusion. The duration of hospitalization and the time between CVC insertion and the occurrence of any complication were recorded.

**Statistical analysis**

The data was transferred to SPSS software version 22 for analysis. The normality of the data was assessed using the Kolmogorov-Smirnov distribution test. A chi-squared test was employed to compare qualitative factors between the two groups receiving enoxaparin and heparin flush. For data that was not normally distributed, the Fisher exact test was utilized. In the case of comparing the quantitative variables between the two groups, the independent t-test and Mann-Whitney U test were used for normally distributed and non-normally distributed data, respectively. The data is expressed as mean ± standard deviation (SD). A p-value of ≤0.05 was considered indicative of a statistically significant difference. It is worth noting that outliers' data were identified through ±3SD calculation, and the intention-to-treat method was used to handle missing data and outliers.

## Results

**Participant's information**

The clinical and anthropometric data of patients in the enoxaparin group and heparinized normal saline group are presented in Table 1. There were no statistically significant differences observed in age (P=0.28), gender (P=0.91), weight (P=0.59), and height (P=0.26) between the two groups. Additionally, there were no significant differences found in the clinical signs of the patients across the groups (body temperature P=0.89, respiratory rate P=0.43, and heart rate P=0.18) (Table 1).

**Thrombosis risk factors**

As shown in Table 2, the most risk factors in both enoxaparin and heparinized normal saline groups are related to immobility (73.75%), total nutrition parenteral need (63.75%), inotropic drugs consumption (61.25%) and loss of consciousness (57.50%). However, based on statistical analysis, no significant difference (P>0.05) found in the risk factors of thrombosis including deep vein thrombosis, malignancy, chemotherapy, major surgery, sepsis, mechanical ventilation, steroid consumption, dehydration, anemia and heart disorder between two groups of study (Table 2).

**The complications incidence**

The overall incidence rate of complications in the current study was 33.75%. Out of the 80 patients who participated in the study, 15 experienced thrombosis. Of these, 8 patients (20%) were in the enoxaparin group, and 7 patients (17.5%) were in the heparinized normal saline group. Additionally, 9 patients had sepsis, with 3 patients (7.5%) in the enoxaparin group and 6 patients (15%) in the heparinized normal saline group. Lastly, 3 patients experienced bleeding, with 1 person in the enoxaparin group and 2 in the heparinized normal saline group. Statistical analysis revealed that there was no statistically significant relationship between the two study groups in regards to any of the complications (P > 0.05) (Figure 1).

**The symptomatic and asymptomatic thrombosis**

The rate and time of occurrence of symptomatic and asymptomatic thrombosis in enoxaparin and heparinized normal saline groups as well as the relationship between thrombosis and risk factors are shown in Tables 3 and 4.

In the current study, no statistically significant difference was observed between the two study groups in the rate of total thrombosis included symptomatic and asymptomatic (P=0.81), or the time of thrombosis, which is categorized into three time periods: first three days, the fourth day, and after the fourth day (P=0.82) (Table 3).

In addition, none of the gender (P=0.57), age (P=0.78) or risk factors including deep vein thrombosis (P=0.18), malignancy (P=0.16), chemotherapy (P=0.28), sepsis (P=0.54), immobility (P=0.24), mechanical ventilation (P=0.29), total nutrition parenteral (P=0.26), inotropic drugs consumption (P=0.89), steroid consumption (P=0.36), dehydration (P=0.59), loss of consciousness (P=0.66) and anemia (P=0.37) related to thrombosis showed significant differences in the two study groups. Based on the results, a significant relationship between major surgery and thrombosis was observed between enoxaparin and heparinized normal saline groups (P=0.01). In the case of heart disease also, there was significant difference between the incidence of thrombosis between the two study groups (P=0.03) (Table 4).

**Table 1- Baseline characteristics of participants**

| Characteristics | | Enoxaparin group (n=40) | Heparinized normal saline group (n=40) | P value |
|---|---|---|---|---|
| Age (month) | | 7.5±11.5 | 9.50±50 | 0.28[a] |
| Gender | Girl | 10 (25%) | 10 (25%) | 0.91[b] |

| | | | |
|---|---|---|---|
| Boy | 30 (75%) | 30 (75%) | |
| Mean± SD | | | |
| Weight (kg) | 8.5±7.5 | 8.5±9.5 | 0.59[a] |
| Height (cm) | 70.82±25.58 | 71.50±47.10 | 0.26[a] |
| Body Temperature ($^oC$) | 38.32±1.14 | 37.79±1.11 | 0.89[a] |
| Respiratory rate (number/minute) | 42.10±16.65 | 39.85±16.73 | 0.43[a] |
| Heart rate (bpm) | 141.95±24.67 | 137.17±20.63 | 0.18[a] |

All values are expressed as means ± SD or numbers.
[a]Independent t test
[b]Chi-squared test

**Table 2- Thrombosis risk factors in the study groups**

| Risk Factor | Enoxaparin group (n=40) Number | heparinized normal saline group (n=40) Number | P value |
|---|---|---|---|
| Deep vein thrombosis (DVT) | 0 | 1 | 0.66[a] |
| Malignancy | 1 | 3 | 0.54[a] |
| Chemotherapy | 1 | 2 | 0.55[a] |
| Major Surgery | 21 | 15 | 0.21[a] |
| Sepsis | 14 | 15 | 0.87[a] |
| Immobility | 30 | 29 | 0.91[a] |
| Mechanical Ventilation | 16 | 12 | 0.65[a] |
| Total Nutrition Parenteral | 25 | 26 | 0.90[a] |
| Inotropic drugs consumption | 26 | 23 | 0.76[a] |
| Steroid consumption | 16 | 20 | 0.46[a] |
| Dehydration | 8 | 5 | 0.67[a] |
| Loss of consciousness | 20 | 26 | 0.47[a] |
| Anemia | 13 | 19 | 0.40[a] |
| Heart disorder | 3 | 5 | 0.78[a] |

[a]Independent t test
All values are expressed as numbers.

**Table 3- The rate and time of occurrence of symptomatic and asymptomatic thrombosis in study groups**

| Thrombosis | | Enoxaparin group (n=40) Number (%) | heparinized normal saline group (n=40) Number (%) | P value |
|---|---|---|---|---|
| Thrombosis incidences | General | 8 (20%) | 7 (17.5%) | 0.81[a] |
| | Symptomatic | 4 (10%) | 5 (12.5%) | |
| | Asymptomatic | 4 (10%) | 2 (5%) | |
| Time of incidence | The first three days | 2 (5%) | 1 (2.5%) | 0.82[a] |
| | The fourth day | 4 (10%) | 2 (5%) | |
| | After the fourth day | 2 (5%) | 4 (10%) | |

[a]Independent t test

**Table 4- The incidence of symptomatic and asymptomatic thrombosis according to gender, age and risk factors in in study groups**

| Features | Enoxaparin group (n=40) | | | Heparinized normal saline group (n=40) | | P value[a] |
|---|---|---|---|---|---|---|
| | Thrombosis | symptomatic | asymptomatic | symptomatic | asymptomatic | |
| Gender | Girl | 3 | 1 | 1 | 1 | 0.57 |
| | Boy | 1 | 3 | 4 | 1 | |
| Age | <1 | 4 | 4 | 3 | 0 | 0.78 |
| | ≥ 1 | 0 | 0 | 2 | 2 | |
| Risk Factors | Deep vein thrombosis (DVT) | 2 | 0 | 0 | 0 | 0.18 |
| | Malignancy | 0 | 0 | 1 | 1 | 0.16 |
| | Chemotherapy | 0 | 0 | 0 | 1 | 0.28 |
| | Major Surgery | 2 | 0 | 5 | 1 | 0.01 |
| | Sepsis | 2 | 4 | 2 | 1 | 0.54 |

| | | | | | |
|---|---|---|---|---|---|
| Immobility | 4 | 4 | 5 | 2 | 0.24 |
| Mechanical Ventilation | 2 | 4 | 4 | 2 | 0.29 |
| Total Nutrition Parenteral | 2 | 4 | 5 | 2 | 0.26 |
| Inotropic drugs consumption | 0 | 2 | 4 | 2 | 0.89 |
| Steroid consumption | 0 | 2 | 0 | 1 | 0.36 |
| Dehydration | 2 | 0 | 0 | 0 | 0.59 |
| Loss of consciousness | 0 | 4 | 4 | 1 | 0.66 |
| Anemia | 4 | 4 | 4 | 1 | 0.37 |
| Heart disorder | 0 | 0 | 3 | 1 | 0.03 |

[a]Independent t test

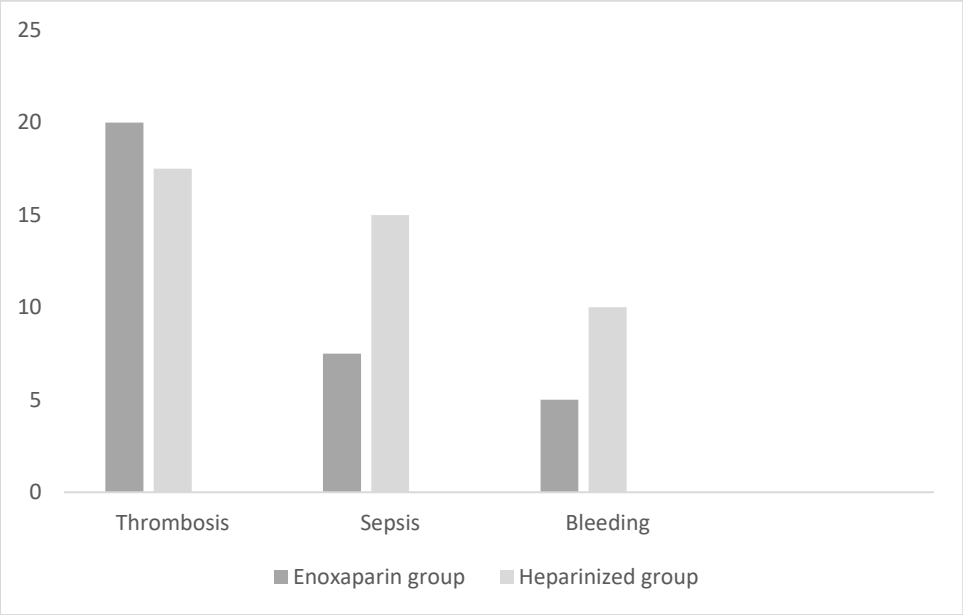


**Figure 1- Incidence of complications in study groups (%)**

## Discussion

In the current clinical trial study, our objective was to compare the efficacy of heparinized normal saline flushing with prophylactic enoxaparin injection in preventing central venous catheter thrombosis in pediatric patients admitted to the PICU. A total of 80 children participated in this study. The patients were randomly assigned to two groups: one group received heparinized NS flushing, while the other group received prophylactic enoxaparin. Subsequently, both symptomatic and asymptomatic complications were recorded and analyzed.

To the best of our knowledge, this current study represents the inaugural clinical trial in children that investigates the impact of enoxaparin and heparin on thrombosis. Central venous catheter (CVC)-related thrombosis is a significant contributor to morbidity and mortality in patients with high-risk conditions. The presence of thrombosis fosters a conducive environment for bacterial proliferation, thereby escalating the risk of sepsis [5] and pulmonary embolism [6]. Enoxaparin (one of the LMWH family anticoagulants) suppresses last path of the coagulation cascade with longer half-life, more bioavailability and ease of administration [14], but there are limited studies on its use. Considering the potential risks of heparin, such as heparin-induced thrombocytopenia and accidental heparin bolus, devising a method that has fewer side effects and is safer in preventing venous thrombosis can be effective in treating and preventing complications.

Based on the results of current research, there was no statistically significant difference in gender, age, anthropometric findings (weight, height), and vital sign (body temperature, respiratory rate, heart rate) as well as risk factors between two groups of the trial (P>0.05). In addition, there was no statistically significant relationship between demographic and anthropometric characteristics or risk factors consist of deep vein thrombosis, malignancy, chemotherapy, sepsis, immobility, mechanical ventilation, total nutrition parenteral, inotropic or steroid consumption, dehydration, loss of consciousness and anemia with the occurrence of thrombosis in any of the intervention groups (P>0.05). Our finding showed a statistically significant relationship

between major surgery (P=0.01) and heart disease (P=0.03) with occurrence of symptomatic and asymptomatic thrombosis between the enoxaparin and heparinized normal saline groups that these underlying conditions should be considered in patients.

In accordance with the findings of the present study, a meta-analysis found no evidence of significant effects of LMWH prophylaxis in reducing the incidence of CVC-related thrombosis in children with CVC, compared to heparin [15]. One study (158 participants) reported symptomatic and asymptomatic CVC-related thrombosis separately and found no difference between LMWH and heparin. There is insufficient evidence to determine whether LMWH affects the risks of major or minor bleeding [16]. Another study reported minor bleeding in 53.3% of participants receiving LMWH and in 44.7% of participants receiving heparin [17], which is similar to the results of our study, as the rate of bleeding was lower in the group receiving enoxaparin, although not statistically significant between the two groups.

Most of the studies comparing normal saline and heparin have primarily focused on thrombotic complications, such as sepsis. One study demonstrated that eliminating the routine use of heparin can positively impact complications associated with central venous catheters (CVC) [18]. However, it remains unclear whether heparin is necessary to prevent occlusion, CVC-associated sepsis, or catheter effects [19]. In our study, the enoxaparin group exhibited a lower rate of sepsis, and no difference was observed in thrombosis rates between heparin and enoxaparin administration. However, the current evidence in this field is limited, and further comprehensive trials are required.

## Conclusion

In conclusion, pooling evidences did not provide sufficient data about the use of prophylactic LWMH or heparin for preventing CVC-related thrombosis in children. In general, studies in this field in children and infants are very limited, and comprehensive studies with a higher number of samples are needed in the field of enoxaparin and heparin use; the studies that examine outcomes catheter occlusion, catheter patency days and other side effects of LMWH (allergic reactions, coagulation profile, heparin-induced thrombocytopenia or osteoporosis) in addition to the consequences of thrombosis.

### Authors' contributions

MM contributes to the conception or design of the work. ESH contribute to collection and interpretation of data for the work. EHB and RM contribute to drafting manuscript. MGH contribute to analysis the data. The study was conducted under supervision of MGH. The final version of manuscript should to be published has been final approved by all authors

### Availability of data and materials

The data that support the findings of this study are available from Mohsen Sedighiyan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Maryam Ghodsi (dr.ma.ghodsi@gmail.com).

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Present manuscript was performed in Tehran University of Medical Sciences. Those was participated in this study are kindly acknowledged. The manuscript has been read and approved by all authors.

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