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Research Article

Comparison of Intravenous Enoxaparin with Subcutaneous Enoxaparin in Preventing Venous Thromboembolism in Patients Admitted to Intensive Care Unit

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ABSTRACT

Background: The use of subcutaneous enoxaparin is a usual method for preventing venous thromboembolism (VTE) in the intensive care unit (ICU) patients, but adequate absorption of the drug is not reliable due to the illness intensity, existing edema and hypoperfusion in these patients. The aim of this study was to compare the effect of intravenous enoxaparin with subcutaneous enoxaparin to prevent VTE in ICU patients.

Methods: The current double-blind Randomized clinical trial was performed on 64 patients admitted to the ICU at Khatam- Al- Anbia Hospital in Zahedan, southeast of Iran. The patients were randomly assigned into each of the subcutaneous enoxaparin and the intravenous enoxaparin groups. The blood sampling was performed aseptically and then active factor Xa level was measured. Next, the intervention group received 0.5 mg/kg of intravenous enoxaparin for 10 days and the control group was injected subcutaneously the same dosage of drug. Four hours after the first injection and 12 hours after the last injection on the tenth day, the factor Xa level and the frequency of VTE incidence was measured again.

Results: In all three measurement times, the active factor Xa level in the intravenous enoxaparin group was lower than that of the subcutaneous group, but no significant difference was observed between the two groups and different times (P> 0.05).

Conclusion: The results of this study showed that the use of intravenous enoxaparin is an effective way to prevent the VTE development in the ICU patients.

The risk of developing venous thrombosis is very high in the intensive care unit (ICU) patients [1]. Prophylactic drugs for thrombosis are one of the essential treatments needed for these patients [2-3]. Venous thromboembolism (VTE), which consists of deep vein thrombosis and pulmonary embolism, not only affects the hospitalized ill patients but also may influence the fit and seemingly healthy people. Most diseased patients die from pulmonary embolism suddenly or within two hours of the onset of a vascular event before starting treatment or the therapeutic effect. Therefore, preventing VTE is more effective in preventing death than treatment [4]. Over the years, numerous clinical trials have been conducted to prevent VTE, and various ways have been proposed, including anticoagulants, mechanical preventive measures, and inferior vena cava (IVC) filters to prevent thromboses. Existing pharmaceutical agents include heparin, low-molecular-weight heparin (LMWH), and coagulation factor X inhibitors [5]. The anticoagulant effects of LMWHs are

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equivalent to that of heparin, while they are less attached to plasma proteins, and have more plasma half-life and more active anticoagulation factor Xa and IIa inhibition compared to thrombin inhibition, monitoring of their anticoagulant activity is often unnecessary [6]. Cardiac patients who have not received anticoagulant preparation for cardiac catheterization are advised to use intermittent intravenous enoxaparin with or without the use of glycoprotein (IIb/IIIa) inhibitor [7] because of its intravenous infusion causing better and faster plasma levels [8]. Other studies also compared intravenous and subcutaneous enoxaparin injections in children and concluded that both types of injections produced the same anti-factor Xa level after four hours in the body of patients [9].

In general, the experience of using intravenous enoxaparin versus subcutaneous enoxaparin is very limited; the restricted experience with taking intravenous enoxaparin and its unusual use in preventive therapy of VTE have created an incentive for further studies on the use of this therapy. Therefore, this study was conducted to compare the effect of intravenous enoxaparin and subcutaneous enoxaparin on the prevention of VTE in the ICU patients.

Methods

(A) Ethical Considerations

The present clinical trial was performed after approval by the Deputy of Research and Technology of Zahedan University of Medical Sciences and obtaining permission from the Ethics Committee of the University (Code:IR.ZAUMS.REC.1392.6030), registered on Iran clinical trial website with code (IRCT20191012045075N1) and informed consent from legal guardians of the ICU patients admitted at Khatam-Al-Anbia Hospital in Zahedan, southeast of Iran in 2014.

(B) Sample Size and Randomization

We estimated that 64 patients, 32 in each group, would need to be enrolled for the trial to have 90% power to detect a difference of at least 2 IU points in the amount of factor Xa level, assuming a 5% loss to follow-up. The sample size was estimated based on previous studies [9-10] and considering α=0.05. The patients were selected according to inclusion criteria and then randomly divided into groups receiving subcutaneous and intravenous enoxaparin. The randomized block design was used to randomization of participants within blocks such that nearly an equal number were assigned to each intervention.

(C) Inclusion and Exclusion Criteria

Inclusion criteria were age range of 18 -60 years, hospitalization for at least 48 hours in ICU, mechanical ventilation, normal renal and hepatic function, no history of deep vein thrombosis and pulmonary embolism, no history of coagulation disorders (hemophilia, disseminated intravascular coagulation, idiopathic thrombocytopenia, heparin- induced thrombocytopenia and disruption of coagulation tests), not being treated with other anticoagulants before hospitalization, lack of prosthetic implantation (artificial heart valve, stent and IVC filter), absence of myelodysplastic syndrome and other blood dyscrasias, passing 48 hours from surgery in patients with intracerebral hemorrhage (epidural, subdural and intracerebral hematoma and hemorrhagic stroke).

The patients who died before 48 hours or those who experienced the heparin-induced thrombocytopenia syndrome after starting treatment and impaired renal function were excluded. Also excluded were patients who had edema during the intervention and treatment.

(D) Interventions

The enrolled patients were divided into two groups: subcutaneous enoxaparin and intravenous enoxaparin. Subsequently, 2cc of blood sample was taken from antecubital fossa of the patients in the two groups to measure the active factor Xa level under sterile conditions. In the first group, 0.5 mg/kg of enoxaparin (AVENTIS PHARMA Co., France) was injected subcutaneously in the deltoid region and rotationally the internal surface of the groin on both sides of the body.

In the second group, the same dose of enoxaparin was injected slowly through a peripheral vein. Repeated blood sampling was done for measuring the factor level 4 hours after the first injection. Drug injections continued for 10 days every 12 hours, then 12 hours after the last injection, both groups were retested and the active factor Xa level was measured again. It must be mentioned that none of the patients received Vasoactive drugs.

(E) Statistical Analysis

The data were presented using statistical tables and mean and Standard deviation. The repeated measurements ANOVA with several groups considering interaction between treatment and time was used to analyzing the data for Xa level. The independent t-test and Chi-square test were used to comparison of baseline data between two intervention groups. The data were analyzed in SPSS.18 software with α=0.05.

Results

Of the 64 patients, 61% were male (n=39) and 39% were female (n=25). The mean age of the patients was 37.9±11.6 years old (ranging from 18 to 51). The table 1 shows the mean age, mean duration of disease, mean BMI and sex distribution of patients in two groups. There was

no significant difference between the two groups regarding age, duration of disease, BMI and sex (Table 1).

Evaluation of the factor Xa activity level in two groups was measured in three times. The results showed that the activity level of this factor was lower in the intravenous enoxaparin group than in the subcutaneous enoxaparin group at all three times. However, the Repeated measurement ANOVA showed that there is no significant difference between two groups (P=0.65) and also there is no interaction between intervention and time (P=0.75). The independent T test with bonferroni correction indicated that there is no difference between two groups at any time separately (P>0.05) (Table 2).

To showing the data and demonstrating lack of interaction between intervention and time in diagram, the result presented in (Figure1). (Figure 1) show that the Xa level changes between two groups similarly during the time.

The (Figure 1) indicates that there is no interaction between time and intervention and the level of decrease along with the time independently from type of intervention. It must be mentioned that the Venous Thromboembolism (VTE) symptoms did not occur in any of the patients in two groups during the intervention. Also finally the power analysis was approved the sample size sufficiency with the power of 0.87.

Table 1- Comparison of the mean age, mean duration of disease, mean BMI and sex distribution of patients in two groups

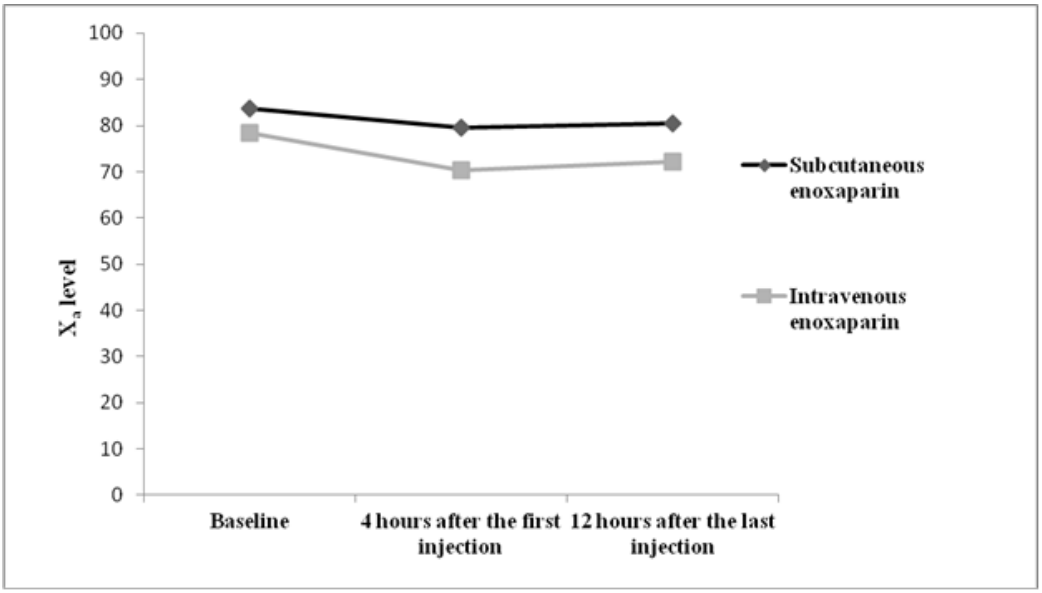
Intervention Groups	Subcutaneous enoxaparin	Intravenous enoxaparin	P value
Age (year)	38.4±7.7	37.5±14.9	0.868*
Duration of Disease(weeks)	2.1±1.9	2.1±1.7	0.91*
Sex(male(n)/female(n))	20/12	19/13	0.89*
BMI(kg/m2)	19.2±4.3	19.4±5.1	0.78**

*P value for Independent Sample Test, ** P value for chi-square test

Table 2- Comparison of active factor Xa level in patients by activity% in two groups

Measuring time and intervention groups	Subcutaneous enoxaparin	Intravenous enoxaparin	P value
Baseline	83.8±36.6	78.3±33.1	0.824
4 hours after the first injection	79.6±22.3	70.3±31.2	0.553
12 hours after the last injection	80.4±20.1	72.1±25.9	0.534
Difference(Baseline-12 hours after the last injection	3.3±1.9	4.1±2.3	0.34

Figure 1- The mean of factor Xa level in patients by groups and time of measurement



Discussion

The VTE is one of the most common preventative causes of mortality in the hospitalized patients. Most of ICU patients are severely exposed to thromboembolism due to absolute rest and underlying illness. Failure to receive the prophylactic treatment exposes the patient to a fatal pulmonary embolism probably because of developing more dangerous and massive pulmonary embolism. However, the occurrence of pulmonary embolism in ill patients in the ICU can be very dangerous and, for this reason, the prophylactic treatment has a decisive role in reducing mortality. Therefore, all patients were given antithrombotic agents as prophylaxis. One of these drugs is enoxaparin, which is usually injected subcutaneously, but the patients with severe edema or extensive surface wounds in the body caused by burns or trauma, sepsis, septic shock and hypovolemia, and many other factors disrupting the blood supply to tissue have problems in drug absorption and subsequent judgment about drug efficacy; hence, this study utilized intravenous enoxaparin. The results showed that the factor Xa activity level and the frequency of thromboembolism did not differ in the patients receiving subcutaneous enoxaparin and intravenous enoxaparin.

Other studies also evaluated the efficacy of intravenous enoxaparin in comparison with heparin in patients undergoing carotid endarterectomy and reported that there was no difference between intravenous enoxaparin and its tough rival (heparin) in terms of incidence of complications. Although, the type and method of work were not the same in the two studies, the efficacy of using intravenous enoxaparin in patients in both studies has been proven [11]. Diab et al. showed that the use of intravenous enoxaparin is equal to or somewhat more effective than subcutaneous enoxaparin. It should be noted that the patients evaluated in this study were neonates and the anti-factor Xa level measured in the present study was conducted on adults admitted in the ICU. However, the measured active factor Xa is similar in two studies with regard to the obtained results [12]. He et al. [13] also reported that the use of heparin and enoxaparin has the same effects and complications in acute coronary syndrome without elevated ST segment while percutaneous coronary intervention (PCI). Cies et al. argued that the anti-factor Xa level at four hours after injecting intravenous and subcutaneous enoxaparin was the same in the patients. The results of both studies indicated that the intravenous enoxaparin can be an effective way to use prophylaxis in the patients at risk for deep vein thrombosis [9]. Sanchez-Pena et al. underlined that receiving a single dose of 0.5 mg/kg in the patients can increase the factor Xa level by more than 0.5 IU/ml, and only 2.5% of patients had anti-factor Xa level over 1.5 IU/ml. However, the use of 0.75 and 1 mg/kg doses causes long-term anticoagulant effects, which is unsuitable for the PCI patients. In long-term procedures, if necessary, instead of using these values, it is better to use a bolus injection dose of other 0.5 mg/kg. Despite using the dosage recommended by the mentioned study in the present research, given that none of these studies were performed in the ICU patients, we could not find a completely similar study to ours.

However, because it has been mentioned that the use of doses greater than 0.5 mg/kg can produce longer anticoagulant effects, and these long-term anticoagulant effects are of the essential requirements of the treatment team to prevent the formation of thrombosis in the ICU, it can be argued that there is no difference between the various doses in causing incidence of complications similar to the mentioned study. Perhaps these long-term effects could be used as an appropriate way to prevent the formation of thrombosis in ICU patients. Further studies are needed to examine the effect of intravenous enoxaparin on the ICU so that we can achieve more reliable results [14]. Crary et al. following the application of intravenous enoxaparin instead of subcutaneous enoxaparin showed that higher levels of anti-factor Xa were achieved within 1-2 hours after intravenous enoxaparin compared to 4-6 hours after subcutaneous enoxaparin, and this plasma level was gradually decreased within 6-8 hours after the intravenous injection [15].

Conclusion

The present study showed that the use of intravenous enoxaparin can be an effective and uncomplicated method to prevent the VTE in the ICU patients.

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Authors' contributions

Masoum Khoshfetrat: participation in implementation of research and supervision over data collection and revising this paper

Majid Khorram: participation in implementation of research and data collection

Aliakbar Keykha: Compilation of the paper and editing this paper carefully

Hossein Ansari: Analyzing the data and writing the results

All authors reviewed, commented and approved the final version.

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