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Original Article

Investigating and Comparing the Serum Level of Active Anti-factor 10 in Selected Patients Treated With Adjusted and Unadjusted Doses of Noxprin Based on Age and Creatinine Clearance in Farshchian Heart Hospital of Hamadan, 1395

Shahram Homayounfar[1], MD; Jila Hashemi*[2], MD;
Azam Ali Zamir[3], MD; Mohammad Ali Saif Rabiei[4], MD

ABSTRACT

Background: Enoxaparin is known to be a low-molecular-weight heparin used in the treatment of patients with deep vein thrombosis, pulmonary embolism, unstable angina, and acute myocardial infarction. The serum level of anti-factor 10, a biomarker, can be used to assess the anticoagulant effects of noxprin**.**

Methods: This clinical quasi-experimental trial recruited patients with a diagnosis of the acute coronary syndrome who were under treatment with adjusted and unadjusted doses of noxprin. Immediately before the administration of the next dose of noxprin, the serum level of activated anti-factor 10 in the patients was measured and compared with the value obtained via a fully automated chromogenic method.

Results: The study population was comprised of 107 patients: 68.2% male and 31.8% female. The mean and standard deviation of the patients' age was 11.13±36.61 years. Based on the study's inclusion criteria of age and the level of creatinine clearance, 35.5% and 64.5% of the patients received adjusted and unadjusted doses of noxprin. The attainment rate of the appropriate level of active ani-factor10 was 81.2% and 62.6%, respectively, in the patients who received the adjusted and unadjusted doses of noxprin (*P*=0.364).

Conclusions: The adjustment of the dose of noxprin in our patients based on their age and creatinine clearance level increased the attainment level of anti-factor 10. ***(Iranian Heart Journal 2018; 19(4): 47-53)***

KEYWORDS: Noxprin, Enoxaparin, Anti-factor 10, Adjusted dose, Unadjusted dose, Age, Creatinine clearance

[1]Department of Cardiology, Faculty of Medicine, University of Medical Sciences, Hamadan, Iran
[2]Farshchian Cardiac Research Development Center, Department of Heart, Faculty of Medicine, Hamadan University of Medical Sciences , Hamadan, Iran
[3]Department of Pathology , Faculty of Medicine , Hamadan University of Medical Sciences , Hamadan, Iran
[4]Department of Community Medicine, Faculty of Medicine, University of Medical Sciences, Hamadan, Iran

***Corresponding Author**: Jila Hashemi, Assistant of cardiology, Hamadan University of Medical Sciences, Faculty of Medicine .
Email: mehdief@ymail.com **Tel:** 09188735206

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Coronary artery disease (CAD) is considered the main cause of death in developing and developed countries. According to the World Health Organization (WHO), mortality due to CAD tops the list of the mortality rate (7.4 million) in the world.[1] It is predicted that 16.7 million deaths due to heart disease in 2002 will reach 23.3 million in 2030. CAD-induced deaths are estimated to increase by about 82% in developed countries.[2] According to the latest report by the WHO, around 45% of deaths in Iran are due to cardiovascular diseases.[3]

CAD is caused by atherosclerosis and venous thrombosis and affects the 2 organs of heart and brain through stenting blood vessels and reducing blood and oxygenation. Angiographic studies performed in the early hours after the onset of a heart infarction have determined the definite role of thrombosis in the development of acute myocardial infarction.[2]

Several clinical trials have shown the efficacy of thrombolytic therapy (streptokinase) in reducing mortality.[4] It is likely that releasing and exposing the roots of thrombin, followed by thrombolytic therapy, may activate the coagulation system. Nonetheless, the value of treatment with heparin, followed by fibrinolytic therapy, is unclear.[5]

Enoxaparin (noxprin) is a low-molecular-weight heparin (LMWH) used in the treatment of patients with deep vein thrombosis, pulmonary embolism, unstable angina, and acute myocardial infarction. The anti-thrombocytopenic activity of noxprin is the result of its binding to antithrombin 3, which inhibits coagulation factor 10 and thrombin (2 active). Thus, the antioxidant activity of active anti-factor 10 can be used in the assessment of the anticoagulant effect in patients receiving enoxaparin.[6] LMWH has high bioavailability, constant anticoagulant effects, low risks of creating heparin-dependent thrombocytopenia, and low risks of the occurrence of bleeding.[7]

The therapeutic dosage is defined in the guidelines released in the year 2012 as 1 mg/kg subcutaneously every 12 hours. This dose for patients with a creatinine clearance (CrCl) level of above 30 cc/min is changed to 1 mg/kg daily.[8] In some studies, the use of the enoxaparin dose of 1 mg/kg every 12 hours has been accompanied by a higher risk of bleeding in patients whose weight exceeds 150 kg.[9]

The enoxaparin dose should be adjusted according to age, weight, and the level of CrCl. In individuals younger than 75 years, 15 minutes after the initial intravenous dose, a subcutaneous dose of 1 mg/kg is administered every 12 hours. In individuals older than 75 years, the initial dose of venous enoxaparin is not administered, and the subcutaneous dose is reduced to as low as 0.75 mg/kg every 12 hours.[10]

Some studies have shown that the standard dose (40 mg/d) has a low efficacy in getting the active anti-factor 10 to the therapeutic level among patients admitted to the intensive care unit (ICU).[11] In a previous study, patients with different degrees of renal failure (CrCl<30 cc/min) presented increased levels of enoxaparin compared with those receiving the adjusted dose.[12] Despite the adjustment of enoxaparin in some studies, the level of active anti-factor 10 was not within the appropriate range. Accordingly, in the present study, we sought to compare the serum level of active anti-factor 10 in selected patients under treatment with adjusted and unadjusted doses of enoxaparin based on age and CrCl.

METHODS

The present semi-experimental clinical trial recruited 107 patients with a diagnosis of the acute coronary syndrome admitted to Farshchian Heart Hospital in the Iranian city of Hamadan in 2016. The inclusion criteria of the study were comprised of admission to the coronary care unit due to a diagnosis of the acute coronary syndrome/myocardial infarction, age over 18 years, and written informed consent. Patients were excluded if they were

aged over 75 years or had CrCl levels of less than 30 cc/min, low platelets, heparin-induced thrombocytopenia, severe uncontrolled hypertension, bacterial endocarditis, hemorrhagic cerebrovascular accidents, bleeding or ulcer of the stomach or duodenum, severe renal dysfunction (CrCl<10) and being on dialysis, coagulation disorders, and a high risk of bleeding.

In the absence of a similar study, in order to determine the sample size, we carried out a pilot study with a sample size of 30 subjects (15 adjusted persons) (the test group) and 15 unadjusted subjects (the control group) and calculated the frequency of attaining an appropriate level of active anti-factor 10 in both groups at 85% and 57%, respectively (α=0/05 and B=20%). Consequently, the sample size in the test and control groups was calculated to be 38 patients; and in the study, there were 38 subjects in the test group and 69 in the control group.

Implementation

Based on the criteria of age (>18 and <75 y) and CrCl (≤30 cc/min), the patients in the test group received an adjusted dose of noxprin and the control group received an unadjusted dose of noxprin. The adjustment of the noxprin dose was based on the level of CrCl (1 mg/kg/sc every 12 hours to 1 mg/kg/sc daily) and based on age (from 1 mg/kg/sc every 12 hours to 0.75 mg/kg/sc every 12 hours). Before the administration of the next dose of noxprin, the patients were given a blood test in order to determine the level of active anti-factor 10. The samples were sent to the laboratory under the cold chain and were measured with a TAP300 device (Italy) via a fully automated chromogenic method, preventing the passing of light, and a kit IL (Italy). The expected outcomes in this study were active anti-factor 10 plasma levels in patients treated with noxprin. The serum levels ranging from 0.5 to 0.7 U/mL were regarded as appropriate and less than 0.5 U/mL and more than 0.7% U/mL as inappropriate. The purpose of the administration of noxprin was to attain the serum level of active anti-Factor 10. The patients' levels of CrCl were also measured with a Biotech device (BT 3500, Italy) and a kit (Pars Azmoon, Iran).

This project was approved by the Research Council of Hamadan University of Medical Sciences (contract No.: 9507063891) and approved by the ethics committee of the university (IR.UMSHA.REC.1395.177).

The data were analyzed with the SPSS software, version 16. The appropriate and inappropriate titrations of anti-factor 10 were compared between the test and control groups with the χ^2 test. The first type error of .05 and the test power of 80% were considered.

RESULTS

The present study recruited 107 patients: 73 (68.2%) men and 34 (31.8%) women. The mean and standard deviation of the patients' age was 61.36±13.11 years (minimum age=21 y and maximum age=91 y), and 15% of the patients were aged 75 years and older. According to the criteria of age and the level of CrCl, 38 (35.5%) patients received the adjusted dose and 69 (64.5%) patients received the unadjusted dose.

The result of the administration of the adjusted dose of noxprin showed that based on age, of the 16 patients aged over 75 years who received the adjusted dose of noxprin, 13 (81%) had the appropriate serum level of active anti-factor 10 (between 0.5 and 0.7 U/mL) and 3 (8.18%) had the inappropriate level (<0.5 and >0.7 U/mL); and of the 91 patients aged under 75 years who received the unadjusted dose of noxprin, 57 (62.6%) had the appropriate serum level of active anti-factor 10 (between 0.5 and 0.7 U/mL) and 34 (4.37%) had the inappropriate level (<0.5 and >0.7 U/mL); the difference was not statistically significant (*P*=364.0) (Table 1).

Table 1. Frequency of the level of active anti-factor 10 in the patients based on age and the dose received

Serum Level of Active Anti-factor 10 (U/mL)	No (%)		*P*
	Control group	Test group	
<0.5	26(28.6)	3(18.8)	0.364*
0.5-0.7	57(62.6)	13(2.81)	
>0.7	8(8.8)	0(0)	
Total	91(100)	16(100)	

*. Fisher exact test

Based on the level of CrCl, of the 22 patients who had a CrCl level less than 30 cc/min and received the adjusted dose, 12 (54.4%) had the appropriate serum level of active anti-factor 10 and 10 (45.6%) had the inappropriate level; and of the 87 patients who received the unadjusted dose of noxprin, 56 (64.4%) had the appropriate serum level of active anti-factor 10 and 31 (35.6%) had the inappropriate level; the difference did not constitute statistical significance (*P*=.174) (Table 2).

Table 2. Frequency of the level of active anti-factor 10 in the patients based on creatinine clearance and the dose received

Serum Level of Active Anti-factor 10 (U/mL)	Creatinine Clearance		*P*
	Under 30	Above30	
<0.5	10(45.6)	31(35.6)	0.174*
0.5-0.7	12(54.4)	56(64.4)	
>0.7	0(0)	0(0)	
Total	22(100)	87(100)	

*. Fisher exact test

The average serum level of active anti-factor 10 in the patients who received the adjusted and unadjusted doses of noxprin based on age and CrCl was 0.25±0.575 and 0.25±0.479, correspondingly.

According to the nonparametric test of the Mann–Whitney *U* test, there was no significant difference concerning the mean serum level of anti-factor 10 between the patients who received the adjusted dose of noxprin and those who received the unadjusted dose of noxprin based on age and CrCl (*P*=.176) (Table 3).

Table 3. Comparison of the mean and standard deviation of active anti-factor 10 in the patients based on the dose of noxprin

Noxprin Dose	Serum Level of Active Anti-factor 10 (U/mL)			*P*
	mean	SD	median	
Adjusted	0.575	0.25	0.57	0.176*
Unadjusted	0.479	0.25	0.55	

Mann–Whitney *U* test

DISCUSSION

In the present study, the difference was not statistically significant between the patients who were at least 75 years old with a CrCl level of under 30 cc/min who received the adjusted dose of noxprin and those who were under 75 years old with a CrCl level of over 30 cc/min who received the unadjusted dose of noxprin. This means that a significant percentage of both groups of patients, who received the adjusted and unadjusted doses of 30 cc/min, attained the appropriate level of anti-factor 10 (0.5–0.7 U/mL).

In 2004 in France, Hulot et al[12] studied 60 patients (60% male) with the acute coronary syndrome (mean age=70±10 y, mean weight=72±15 kg, and mean CrCl level=56±24 cc/min) and concluded that the maximum level of active anti-factor 10 could be predicted by weight and sex up to 1.5 U/mL when there was a moderate rise in the level of CrCl. In addition, the renal function was the most important factor in the pharmacokinetics of enoxaparin.

In patients with a reduced renal function, the optimal level of anticoagulants measured by active anti-factor 10 requires the adjustment of the dose of enoxaparin based on the body weight, sex, and CrCl.[13]

We adjusted the dose of enoxaparin in our patients based on age and CrCl. Our measurements of active anti-factor 10 showed that more than 80% of our patients had attained the optimal level of the anticoagulant.

Sacha et al[13] in 2016 studied 273 patients with renal dysfunction (weight=45–150 kg) and reported that only half of their patients had

attained the peak level of active anti-factor 10 after 4 hours. Totally, the monitored level of active anti-factor 10 was low. The obese patients with a lower dose attained the recommended level of the coagulant. The low-weight patients, at the recommended doses, were often at low therapeutic levels. Additionally, the serum level of active anti-factor 10 in the patients with impaired renal function was either lower than or at the therapeutic level. Finally, the researchers concluded that the pharmacokinetics of enoxaparin could not be predicted and in patients with all 3 risk factors (weight<45 kg, weight>150 kg, and impaired renal function), monitoring the serum levels of active anti-factor 10 was necessary to ensure the desired therapeutic level and the optimal dosage of the drug. In our study, one of the criteria for adjusting the dose of enoxaparin was the renal function, consistent with the findings of Sacha and colleagues, who reported that in the monitoring of the serum level of active anti-factor 10, a high proportion of their patients had attained favorable therapeutic levels. The second variable of adjusting the enoxaparin dosage in the present study, in contrast to the dose adjustment in the study by Sacha and coworkers, was that instead of weight, we took into account the age of the patients. The results showed that the dose adjustment of enoxaparin based on the renal function and age was effective in achieving the therapeutic level of active anti-factor 10.

In 2010, Lalama et al[14] proposed a treatment protocol for the enoxaparin dose based on the body mass index. Accordingly, in 31 patients with a body mass index of 40 kg/m^2 and above, with the administration of 0.75 mg/kg of enoxaparin, 48% of the patients attained the treatment level of active anti-factor 10, 36% higher than the treatment level, and 16% less. The mean dose of enoxaparin to attain the appropriate level of active anti-factor 10 was 0.71 mg/kg.

In our study, the dose of enoxaparin was adjusted based on the age of the patients. Our monitoring of the serum level of active anti-factor 10 in our study population demonstrated that 81.2% had the appropriate level and 18.8% were below the appropriate level. Moreover, none of the patients had a level of active anti-factor 10 beyond the appropriate level. The proportion of patients who attained the appropriate level was more in our study than in the study by Lalama and colleagues.[14]

In 2017, Pellizzar et al[15] conducted a prospective study on an elderly population of 98 individuals (34 women and 68 men at a mean age of 82 y) in order to assess the effects of age, the body mass index, and renal failure on the efficacy and low risk of treatment with enoxaparin in terms of the serum level of active anti-factor 10. The treatment dose of enoxaparin was between 0.2 and 0.7 U/mL. The patients with chronic renal failure were inflicted with deep vascular thrombosis or the acute coronary syndrome. The serum level of anti-factor 10 was evaluated 4 hours after the third injection of enoxaparin with the chromogenic test. The renal function to CrCl calculation was carried out according to the Cockcroft formula. Based on the findings, the mean active anti-factor 10 was 0.41 U/mL (95% CI=0.36 to 0.45). A logistic regression analysis showed that, except for the enoxaparin dose, none of the variables—including age, sex, CrCl, and the body mass index—could predict the serum level of active anti-factor 10. In their study, the level of anti-factor 10 was higher than the appropriate range in 3 patients and less than the appropriate range in 8 patients.

We adjusted the dose of enoxaparin from 1 mg/kg/sc every 12 hours to 1 mg/kg/sc in the patients with a maximum CrCl level of 30 cc/min and from 1 mg/kg/sc every 12 hours to 0.75 mg/kg/sc every 12 hours in the patients over 75 years of age. The mean level of active anti-factor 10 in our study for the patients having received the adjusted and unadjusted doses was 0.577 and 0.479, respectively.

Consistent with the findings of Pellizzar et al,[15] our adjustment of the noxprin dose by age and the renal function did not cause a statistically significant difference in the mean serum level of anti-factor 10.

CONCLUSIONS

The results of the current study showed that the adjustment of noxprin based on the renal function and age increased the attainment of the appropriate level of active anti-factor 10. The limitations of the present study are its relatively small sample size and the lack of follow-up results. We would, therefore, recommend that future interventional studies with larger sample sizes be conducted so as to examine the predictive value of the body mass index, in addition to age and the renal function, in the treatment with noxprin. What should also be assessed is the incidence of bleeding and thrombosis by specified levels of anti-factor 10.

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