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EVALUATION OF PREDICTORS FOR THE OCCURRENCE OF ENOXAPARIN BRUISING SIDE EFFECT

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ABSTRACT: Enoxaparin is useful in the treatment of unstable angina, but its use is associated with many hematological side effects principally bruising appearance. A prospective comparative study was designed to evaluate the effects of certain predictors on the occurrence of bruising side effect of enoxaparin during the administration of two different subcutaneous (SC) doses (prophylactic vs. therapeutic) of enoxaparin injection among patients with unstable angina. Patients were divided into two groups, 60 patients served as A group given a prophylactic dose 40mg q12h. The other 60 patients served as the B group given 1mg/kg q12h. Area of the bruising was measured by disposable measuring tape as mm^2. A significant higher occurrence in the mean of bruising area was found in males (P=0.014), geriatrics (P=0.001), patients with body weight more than 76 kg (P=0.007), therapy of 5-day duration (P=0.01), hypertensive patients and those treated with captopril (P=0.001) while receiving the therapeutic dose (B group) than those receiving the prophylactic dose (A group). In conclusion, certain predictors significantly affect the occurrence of enoxaparin bruising and could be considered clinically during the evaluation of bruising side effect of enoxaparin injection.

INTRODUCTION: Enoxaparin is a low-molecular-weight heparin (LMWH) produced from unfractionated heparin by depolymerization [1]. Different coagulation disorders are benefiting from the use of LMWH to initiate anticoagulation like atrial fibrillation, unstable angina, and non–Q-wave myocardial infarction (MI), deep-vein thrombosis, and pulmonary emboli [2]. Enoxaparin has multiple clinical advantages as a more predictable dose response, a longer half-life for outpatient use, no obvious drug or food interactions, and lower risk of osteoporosis [3].

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It is given by SC injection once or twice daily in the management of unstable angina [4]. However, enoxaparin can cause many side effects, particularly bruising and pain at the injection site [5]. Most studies believe that the incidence of enoxaparin bruising at the injection site can be affected by several factors such as needle gauge, proper injection site, decreasing the volume of solution, and the mode of anticoagulant injection can affect the incidence of enoxaparin bruising at the injection site [6, 7].

The objective of this study was to investigate the effects of certain predictors on the occurrence of bruising side effect of enoxaparin during the administration of two different SC doses (prophylactic vs. therapeutic) of enoxaparin injection.

MATERIALS AND METHODS:

Patients' Selection: A prospective observational clinical study was carried out on newly 120 hospitalized patients suffered from unstable angina and prescribed enoxaparin sodium SC injection as a part of normal clinical care for the treatment or prophylaxis of this condition. Patients eligible for the study were under specialized medical supervision at the Intensive Care Unit (ICU) of Al-Kahdumyia Teaching and Training Hospital in Baghdad-Iraq. Approval of this study was granted by the Ethical Committee of the hospital and all patients were signed the related consent form. Patients were divided into two groups, 60 patients served as a prophylacticgroup (A group) given a prophylactic SC dose of enoxaparin for ischemic complications of unstable angina at 40 mg (0.4 ml volume) q12h for 3 days. The other 60 patients served as a treatment group (B group) given 1mg/kg (0.6 ml volume) q12h SC dose for 5 days. Inclusion criteria included patients over the age of 18 years, patients newly diagnosed with unstable angina and treated with enoxaparin sodium SC injection, and those agree to follow this study.

Exclusion criteria included patients with a history of unstable angina previously received therapy for this condition, hepatic or blood disorders, patients taking previous or current anticoagulant medications, injury or trauma at the injection sites and patients took medications other than those prescribed in the research.

Enoxaparin Administration: All the SC injections were manufactured by Sanofi-Aventis Company (Lovenox®) containing enoxaparin sodium as a syringe ready for injection. Enoxaparin injection technique was done by trained nurses and an appropriate injection site was selected in the thigh or in the lateral part of the abdomen. The injection site was sterilized with alcohol, and a 27-gauge needle was inserted at 90° angle during 30 seconds after pinching up the skin on the site of injection without aspiration and by holding the skin of the injection site between the thumb and index finger. Area of the bruising was measured 24-48 h after starting therapy with enoxaparin injection till the end of the study (3- day and 5-day duration) by disposable measuring tape as mm^2. SPSS version 18 was used in the analysis the collected results.

The results were expressed as mean± SD, Univariate analysis (p=0.001), independent t-test were used to examine the degree of significance which is considered significant as p- value <0.05.

RESULTS AND DISCUSSIONS: The characteristics of various predictors that affect the the bruising area during the administration of two different SC doses (prophylactic vs. therapeutic) of enoxaparin injection are presented in **Table 1**. The majority of patients were non-geriatrics, nonsmokers, suffering from hypertension, on enoxaparin administration for 5 days and with concurrent aspirin therapy. A significant higher difference was found in the mean of bruising area in males (p=0.014), and geriatric patients (p=0.001) of the B group compared with those of the A group. Although, no significant difference was found in the bruising area between smoker patients of both groups, but the overall mean was higher in nonsmokers compared with smokers (p = 0.038). In the B group, patients with body weight more than 76 kg were more sensitive to the bruising side effect of enoxaparin (p=0.007) than patients of the A group. Duration of therapy for 5 days significantly showed a higher area of bruising in patients of the B group than those of the A group (p=0.01).

Additionally, hypertensive patients of the B group were significantly (p=0.001) more susceptible to have a higher mean of bruising area compared to those of the A group. Patients treated with captopril while using the treatment dose of enoxaparin had significantly a higher mean (p=0.001) of the bruising area than those using the prophylactic dose.

The development of bruising induced by enoxaparin injection is usually happened following the blood outflow from the damaged vessels into the SC tissue. This condition usually peaks within 48 hours and starts to decline after 60-72 h [8]. In our study, one of the predictors that can influence the bruising side effect of enoxaparin is patients' gender as presented in **Table 1** which was significantly higher (p=0.001) in males of the B group than those of the A group (2.54 ± 2.42) vs. (1.20 ± 1.53) mm^2 as well as than females of both groups. The results of our study were in contrast with that reported by Khadije Dehghani *et al.*, [9],

which showed no significant association between bruise size and subjects' gender. As observed in **Table 1**, the patients' age was another predictor in this study which showed a higher significance (p=0.001) among patients aged more than 65 years old of the B group than in patients of the A group (2.38 ± 2.36) vs. (0.59 ± 0.70) mm^2 compared with those aged less than 65 years old within both groups. The findings of this study were in accordance with a study by Marwa Shoeb, and Margaret C. Fang. [10] who found that increased age was associated with an increased risk of bleeding in patients with an acute coronary syndrome treated with enoxaparin. A possible explanation may be related to the fact that elderly patients have decreased renal function activity since enoxaparin is excreted mainly by the kidneys. Thus LMWH should be used with care in patients with impaired renal function because it may bio-accumulate and may cause bleeding, particularly with enoxaparin [11].

TABLE 1: PATIENTS' DEMOGRAPHIC CHARACTERISTICS WITH VARIOUS PARAMETERS THAT AFFECT THE AREA OF ENOXAPARIN BRUISING

Predictors		Area of bruising (mm^2)				p- value
		Prophylactic Group (Group A)		Treatment Group (Group B)		
		no.	Mean ± SD	no.	Mean ± SD	
Gender	Male	30	1.20 ± 1.53	30	2.54 ± 2.42	0.014 (S)
	Female	30	1.39 ± 1.48	30	2.69 ± 4.09	0.11
Age (years)	< 65	40	1.65 ± 1.66	32	2.81 ± 4.02	0.133
	≥ 65	20	0.59 ± 0.70	28	2.38 ± 2.36	0.001 (S)
Smoking status	Yes	12	1.83 ± 1.47	23	2.70 ± 2.60	0.293
(1.5±5packet/day)	No	48	1.16 ± 1.49	37	2.56 ± 3.75	0.038 (S)
Body weight (kg)	60 – 75	24	1.60 ± 1.80	38	2.11 ± 3.03	0.464
	76 – 90	36	1.09 ± 1.24	22	3.48 ± 3.71	0.007 (S)
Duration of enoxaparin	3	28	0.98 ± 1.41	29	1.99 ± 3.59	0.171
therapy (days)	5	32	1.57 ± 1.54	31	3.19 ± 3.01	0.01 (S)
Concurrent disease	HT	18	1.22 ± 1.20	41	2.72 ± 3.71	0.024 (S)
	DM	10	1.26 ± 1.92	3	0.79 ± 0.68	0.694
	NIL	32	1.35 ± 1.54	16	2.68 ± 2.49	0.063
Antiplatelet	Aspirin (150 mg once daily)	32	1.74 ± 1.67	29	3.06 ± 3.37	0.064
	NIL	28	0.79 ± 1.08	24	2.31 ± 3.65	0.059
Captopril	Yes	16	1.33 ± 1.23	39	2.80 ± 3.58	0.027 (S)
	No	44	1.29 ± 1.59	21	2.26 ± 2.87	0.157

Each value shows mean ± SD; n=120, Univariate analysis (P = 0.001), independent t test. S = significant

The results of our study as shown in **Table 1** found that the overall mean of the bruising area was higher in nonsmokers (p=0.038*)* of both groups (2.56 ± 3.75) vs. (1.16 ± 1.49) mm^2 as compared with smoker patients of both groups. This may be related to instructions of physicians to their patients about health status. Moreover, the sample size of smokers was small which attributed to the non-significant values.

Accurate and dose adjustment is clinically important for overweight or obese patients, particularly the elders to ensure efficacy, and to minimize the risk of bruising or more severe bleeding complications. **Table 1** illustrated the significance of body weight as an important predictor when dosing enoxaparin which was higher (p=0.001) among patients with body weight over 76 kg in the B group than those of the A group (3.48 ± 3.71) vs. (1.09 ± 1.24) mm^2.

Similar finding were reported in a prior study by Lalama JT *et al.*, [12] where dose adjustments of enoxaparin in obese patients were likely to reduce the occurrence of bruising. Furthermore, the duration of enoxaparin SC injection was another predictor that affects the bruising area and was significantly higher (p=0.001) in patients of the B group than those of the A group (3.19 ± 3.01) vs. (1.57 ± 1.54) mm^2 at a 5-day duration as compared to 3-day duration as this may be attributed to increased age, renal insufficiency, and increased body weight.

A study by Natalya Thorevska *et al.,* [13], found that patients receiving enoxaparin therapy for more than 3 days experienced a higher percentage of bleeding risk compared to those receiving therapy for 1-3 days. With regard to concurrent medical diseases as shown in **Table 1**, hypertension was the sole significant concurrent condition (p=0.001) observed in patients of the B group than in patients of the A group (2.72 ± 3.71) vs. (1.22 ± 1.20) mm^2.

The long-term administration of the angiotensin-converting enzyme (ACE) inhibitors in cardiovascular events is associated with an improvement in survival and reduced morbidity and mortality including increased risk for subsequent left ventricular dysfunction [14].

The admitted patients to the ICU were principally prescribed captopril, and patients in the group B had significantly higher mean (p=0.001) of bruising area than those in the A group (2.80 ± 3.58) vs. (1.33 ± 1.23) mm^2. These results are in disagreement with that performed by Christine Macie *et al.,* [15] where the use of ACE inhibitors was associated with a lower risk of enoxaparin bleeding in patients with an acute coronary syndrome.

Limitations of the Study: Our study was the first one that assessed the effect of certain factors on the occurrence of the enoxaparin bruising side effect. However, certain limitations were observed, including a small sample size due difficulty in finding the suitable samples cited for inclusion criteria of this study. Additionally, another time of SC enoxaparin injection to 10 seconds is recommended to get more comparison in the evaluation of predictors on the bruising side effect of enoxaparin.

CONCLUSION: The results of our study showed that certain predictors significantly affect the occurrence of enoxaparin bruising side effect, particularly during the use of therapeutic SC dose injection and could be regarded clinically as additional factors in the evaluation and diagnosis of bruising side effect of enoxaparin.

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