RESEARCH ARTICLE

Monitoring the Prophylactic Enoxaparin Therapy on Orthopedic Patients

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ABSTRACT

Background: Fixed daily enoxaparin dose is used as anticoagulant prophylaxis despite variations in body weight and unknown renal function

Aim of the Study: Monitoring prophylactic enoxaparin therapy through Anti-Xa measurement and evaluating the adequacy of fixed single daily dose (40 mg s.c) for 4 weeks in the prevention of venous thromboembolism (VTE) in patients with total hip or knee surgery.

Patients and Method: The study included 52 patients admitted to the Basrah Teaching Hospital for total hip and knee surgeries, 43 patients for Total Knee Replacements (TKR), and nine for Total Hip Replacement (THR). Blood parameters measured were D-dimers, anti-factor Xa activity, serum potassium, activated partial Thromboplastin Time (APTT), blood urea and platelets count for all patients according to the schedule at the pre-operative time, 4 hours after the second dose of enoxaparin, 2 weeks, and 4 weeks after surgery.

Results: The majority of the patients were overweighted**.** In patients with knee and hip replacement, the serum level of anti-factor Xa was found to be lower than the therapeutic level in most of the patients (0.08 ± 0.12 mean $\pm$ sd). However, it was significantly changed between the pre-operative, 4 hours, 2weeks, and four weeks after surgery; the D-Dimer value was significantly increased overtime between the pre-operative, 4 hours after the second dose of the enoxaparin therapy, and at 2 and 4 weeks after surgery, while the patients continued to receive 40 mg enoxaparin once daily as anticoagulants prophylaxis. There were significant changes over time regarding the APTT in knee replacement patients. There were no significant changes in serum potassium levels over the study time.

Three patients (5.8%) developed venous complications, one patient (1.9%) developed a fatal pulmonary embolism, and two patients (3.8%) developed venous thromboembolism (DVT)

Conclusion: The dose of the enoxaparin of 40 mg once daily was inadequate in the majority of the patients, and the risk of DVT is still high with a high mortality rate; however, the use of the thromboprophyl axis.

The D-Dimer test can predict the occurrence of the DVT and might be a helpful screening parameter in patients undergoing joint arthroplasty.

Keywords: Anti-Xa, Enoxaparin, Hip surgery, Knee surgery.

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INTRODUCTION

Venous thromboembolism (VTE) is a clot that prevents blood flow in a vein and might dislodge and result in pulmonary embolism (PE).[1] The VTE is A silent killer,[2] approximately 80% of VTE are asymptomatic, and 20% symptomatic, VTE incidence is about 1 per 1,000 people. It's leads to about 60,000–100,000 deaths annually.[3] The annual deaths related to VTE in the European countries exceed combined deaths due to AIDS, breast cancer, prostate cancer, and transport accidents.[4]

Virchow's Triad includes three risk factors: venous stasis, vascular damage, and hypercoagulability in developing thrombosis;[5] the short term complication is pulmonary thromboembolism, while the severe long-term complications of VTE include recurrent VTE, Post Thrombotic Syndrome (PTS), Chronic Thromboembolic Pulmonary Hypertension (CTPH) and venous ulcers.[6] there are two types of risk factors, genetic (primary) and acquired (secondary) risk factors.[7]

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In addition to pharmacological prophylaxis, according to the latest available recommendations from the American College of Chest Physicians (ACCP) in 2012, recommend using mechanical methods, Intermittent Pneumatic Compression Devices (IPCDs) with portable batteries[8] but decreasing complication following major orthopedic surgery. This guideline focuses on optimal prophylaxis to reduce postoperative pulmonary embolism and DVT. *Methods*: The methods of this guideline follow those described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement. *Results*: In patients undergoing major orthopedic surgery, we recommend the use of one of the following rather than no antithrombotic prophylaxis: low-molecular-weight heparin; fondaparinux; dabigatran, apixaban, rivaroxaban (total hip arthroplasty or total knee arthroplasty but not hip fracture surgery.

Anti-Xa assay is designed to test the levels of plasma Unfractionated heparin and Low Molecular Weight Heparin (LMWH) and track therapy with anticoagulants; the levels of Anti-Xa should be tested at their highest level 4 hours after dosing time. Pharmacological prophylaxis includes; aspirin, unfractionated heparin (UH), low molecular weight heparin (LMWH), adjusted dose vitamin K antagonists, synthetic pentasaccharide factor Xa inhibitor (fondaparinux) and newer oral anticoagulants.[9] Usually, a single daily dose of enoxaparin is used in the prophylaxis for VTE; the adequacy of such treatment has not been thoroughly studied

PATIENT'S MATERIALS AND METHODS

There were 52 patients, 37 females and 15 males; 43 had a total knee replacement, and nine had total hip replacements.

Blood samples (4 mL) were collected from each patient according to the dosing schedule at the pre-operative time, 4 hours, 2 weeks, and four weeks.

The blood parameters measured: D-dimers test, Anti-factor Xa activity, Serum Potassium, Activated Partial Thromboplastin Time (APTT), Blood urea, Platelets count. According to the standard laboratory methods, All patients were followed up by full medical examination, and information for each patient was recorded in a special form.

RESULTS

The study was conducted from January 2020 to July 2020, and it was ethically approved by the Ethical Committee of the College of Medicine, University of Basrah, and Basrah Health Directorate. Written informed consent was obtained from all patients after a full explanation of the study in the Arabic language.

In patients with knee replacement, the Anti-Xa value was significantly changed over time, between the pre-operative level of 0.07 ± 0.08 IU/mL to 0.12 ± 0.20 IU/mL, 4 hours after the second dose of the enoxaparin therapy. After two weeks, the level of anti-Xa was 0.09 ± 0.10, which was decreased to 0.04 ± 0.02 IU/mL 4 weeks after surgery, as in Table 1.

The D-Dimer value was significantly increased overtime between the pre-operative level of 1.37 ± 1.18 µg/mL to 1.51 ± 0.59 µg/mL 4 hours after the second dose of the enoxaparin therapy and then increased to become 3.34 ± 0.56 and 3.49 ± 0.83 µg/mL at 2 and 4 weeks after surgery while the patients continued to receive 40 mg enoxaparin once daily as anticoagulants prophylaxis. Regarding the APTT, there were also significant changes over time starting from 33.40 ± 3.48 seconds before operation and staying around this level 4 hours after the second dose of enoxaparin (34.20 ± 3.34 seconds). However, two and four weeks after the operation (33.05 ± 3.84 seconds and 35.17 ± 3.11 seconds, respectively), There were no significant changes in serum potassium levels in patients with total knee replacement over the study time.

In hip replacement patients, the anti-Xa value was significantly changed from a pre-operative value of 0.04 ± 0.02 to 0.19 ± 0.27 IU/mL at 4 hours after the second dose of enoxaparin. Then, it started to decrease 2 and 4 weeks after surgery to be 0.09 ± 0.01 and 0.04 ± 0.02, respectively, as in Table 2.

Table 1: Measured parameters in 43 patients with total knee replacement

Parameter	*Pre-operative*	*4 hours after the second dose*	*2 wks postop*	*4 wks postop*	*P-value**
Anti-Xa (IU/mL)					
mean ± Sd	0.07 ± 0.08	0.12 ± 0.20	0.09 ± 0.10	0.04 ± 0.02	0.042**
Median	0.05	0.05	0.07	0.04	
D-Dimer (µg/mL)					
mean ± Sd	1.37 ± 1.18	1.51 ± 0.59	3.34 ± 0.56	3.49 ± 0.83	0.0001**
Median	0.88	1.29	3.36	3.7	
APTT(seconds)					
mean ± Sd	33.40 ± 3.48	34.20 ± 3.34	33.05 ± 3.84	35.17 ± 3.11	0.003**
Median	33.6	33.65	32.8	34.6	
S.K(mmol/mL)					
mean ± Sd	3.70 ± 0.26	3.50 ± 0.42	3.74 ± 0.33	3.71 ± 0.33	0.177
Median	3.7	3.5	3.7	3.7	

*Friedmans Test, ** Statistically significant

Table 2: Measured parameters in nine patients with total hip replacements

Parameter	*Pre-operative*	*4 hours after the second dose*	*2wks postop*	*4wks postop*	*p-value**
Anti-Xa IU/ML					
mean ± Sd	0.04 ± 0.02	0.19 ± 0.27	0.09 ± 0.01	0.04 ± 0.02	0.004*
Median	0.04	0.11	0.09	0.05	
D-Dimer:µg/mL					
mean ± Sd	0.84 ± 0.34	1.39 ± 0.48	3.66 ± 0.33	3.46 ± 0.16	0.004*
Median	0.82	1.2	3.7	3.5	
APTT sec					
mean ± Sd	32.92 ± 2.69	33.13 ± 3.11	32.39 ± 4.66	35.21 ± 4.41	0.106
Median	32.1	32	30.2	36.2	
S.Kmmol/L					
mean ± Sd	4.14 ± 0.69	3.46 ± 0.51	3.63 ± 0.26	3.55 ± 0.22	0.251
Median	3.9	3.4	3.7	3.6	

* statistically significant

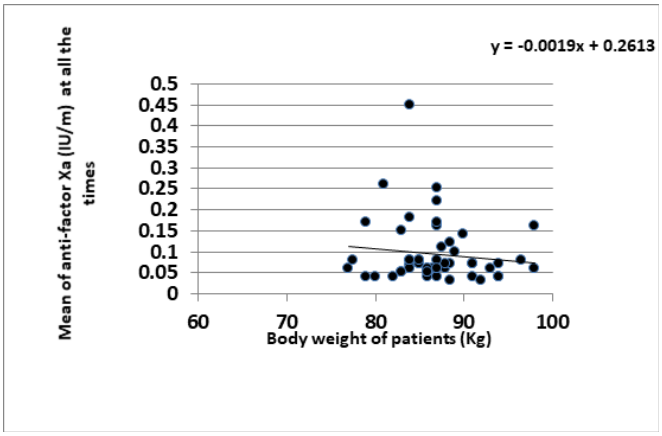

Figure 1: Correlation between the mean value of anti-factorXa measured at all times and the patients body weight

The D-Dimer value was significantly increased from a level of 0.84 ± 0.34 µg/mL pre-operatively to 1.39 ± 0.48, four hours after the second dose of the enoxaparin. This level also increased to 3.66 ± 0.33 and 3.46 ± 0.16 µg/mL 2 and 4 weeks after surgery, respectively. Serum potassium levels and APTT levels had not changed in these patients over the time of the study.

There was no correlation between Anti-Xa and APTT at any time of the study (pre-operative, 4 hours after the second enoxaparin dose, two weeks, and four weeks after the operation) for total hip replacement and total knee replacement patients.

There was no correlation between levels of D-Dimer and Anti-Xa at any time of the study (pro-operative, 4 hours after the second enoxaparin dose, two weeks and four weeks after the operation) for both total hip replacement and total knee replacement patients.

The serum level of anti-Xa in various individual patients was consistently below the expected therapeutic range for anti-Xa, and the Anti-Xa level was negatively correlated to the patient's body weights as in (Figure 1).

During the present study and despite the anticoagulant therapy, three patients (5.8% of the patients) have established DVT, one patient (1.9%) died due to pulmonary embolism, and two patients (3.8% of patients) developed DVT.

DISCUSSION

Venous thromboembolism is a dangerous condition with an incidence of 40 to 60% in orthopedic surgery. However, with routine VTE prophylaxis, this number drops from 1.3 to 10%.[9]

The average weight of patients in this study was more than 80 kg. This matches the previous studies as obesity is one of the well-known and modifiable risk factors for both progression and the incidence of osteoarthritis.[10] Compared to adults of similar age in the general population, obesity, and overweight were significantly associated with the need for a TKR or THR.[11] Being overweight and obese can affect drug distribution and kinetics.

Monitoring of enoxaparin can be measured by quantifying the presence of Anti-factor Xa (Anti-Xa) for dose adjustment, as this activity represents the drug's serum concentration. A reasonable anti-Xa target range for deep vein thrombosis prevention for enoxaparin could be 0.2–0.5 IU/mL.[12]

Enoxaparin pharmacokinetic properties, as absorption at the site of the injection and elimination half-life, are predictable and well-characterized in non-obese healthy individuals. However, in obese patients, pharmacokinetic parameters such as rate of absorption, the volume of distribution, and renal clearance may be changed, and this study found that standard enoxaparin doses did not always result in therapeutic anti-Xa levels.[13] Peak anti-Xa levels of 0.6–1.0 IU/mL and 1.0–2.0 IU/mL have been suggested for once and twice daily subcutaneous enoxaparin dosage, respectively.[12]

In this study, only a small percentage of patients reached this therapeutic level. However, while most of the patients didn't achieve the therapeutic level, Patients' compliance is another major factor contributing to anti-Xa serum levels below the therapeutic range.

In addition, we found that only 13% of the patients reached the therapeutic level after four weeks of the operation, so the more time passed since the operation, the more patients

had subtherapeutic serum levels. Therefore, missed doses or irregular dosing intervals could be the cause of our patient's noncompliance at the same time. It was found that only about 20% of patients follow their thromboprophylaxis instructions after being discharged from the hospital following hip surgery, which increases the risk of DVT.[14] another type of anticoagulant, pentasaccharide, an indirect factor Xa inhibitor, has shown good anticoagulative effect in clinical trials. Three types of pentasaccharides are available: short-acting fondaparinux, long-acting idraparinux and idrabiotaparinux. Pentasaccharides cause little heparin-induced thrombocytopenia and are better tolerated than unfractionated heparin, LMWH and warfarin. However, no consensus has been reached on whether pentasaccharides are superior or inferior to other anticoagulative methods. *Objectives*: To assess effects of pentasaccharides versus other methods of thromboembolic prevention (thromboprophylaxis Therefore, continuous anti-Xa monitoring can also help in the early detection of patient noncompliance.

D-dimer can be used as a screening test to diagnose DVT, and a negative result can effectively rule out the condition.[15] The risk of DVT was still high in this study as D-dimer levels were shown to rise considerably after 2 and 4 weeks following surgery.

Patients with a high D-dimer value were proposed to be subjected to further DVT investigations. The importance of using the D-dimer test to follow-up patients who have had orthopedic surgery to detect DVT early requires more studies.

We couldn't find a significant correlation between the various clotting parameters and the level of anti-Xa in the blood.

The current study shows that the DVT rate (5.8%) is higher than prior studies, such as Mula et al., 2020, who found a 0.77% rate of symptomatic DVT following THA and 0.05% after TKA. THA had a 0.46% rate of proven symptomatic pulmonary embolism, while TKA had a 0.27% rate. The high prevalence of DVT is due to anti-Xa serum levels that are below therapeutic ranges. Patients who developed DVT in our study were not different from the rest of the patients; however, two of them were females and had knee surgery.

We had a high mortality rate in this study as one patient (1.9%) died due to DVT in the present study, which is higher than what's mentioned in the last studies like Mula *et al*.,2020 in which the Mortality rate post-THA was 0.6, and 0.6% for TKA.[16]

CONCLUSIONS

The dose of the low molecular weight anticoagulant, enoxaparin 40 mg once daily, was inadequate in most of our patients; patients' compliance with thromboprophylaxis is probably not adequate, especially with a prolonged period of administration. While monitoring of prophylactic Anti-Xa levels may not be needed in the majority of patients, it may still be required in specific patient groups and in some practices to optimize treatment. D-D-Dimer test can predict the occurrence of the DVT and might be a helpful screening parameter of all patients subjected to joint arthroplasty.

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