Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

Mayank Mukeshbhai Baloo

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

Johannesburg, 2020

Declaration

I, Mayank Mukeshbhai Baloo, declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

13 November 2020

Abstract

Background

Veno-thromboembolism is a well-known complication in the peri-operative period. The aim of this study was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit (ICU).

Methods

A cross-sectional study was conducted in the multi-disciplinary ICU at Chris Hani Baragwanath Academic Hospital affiliated with the University of the Witwatersrand. Seventy-three patients admitted to the ICU receiving 40 mg enoxaparin sodium daily were enrolled into this study. Anti-factor Xa level samples were taken from patients receiving prophylactic enoxaparin following the second dose administered in the ICU. The prophylactic and the sub-prophylactic groups of patients were also compared for age, sex, weight, body mass index, total bilirubin, serum albumin and APACHE II score.

Results

Anti-factor Xa levels were prophylactic (0.2 – 0.6 IU/ml) in 44 (60.3%) patients and sub-prophylactic (< 0.2 IU/ml) in 29 (39.7%) patients. The mean (SD) actual delivered dose of enoxaparin per kilogram body weight was significantly higher, at 0.59 (0.11) mg/kg in the prophylactic group compared to 0.53 (0.13) mg/kg the sub-prophylactic group, (p=0,043). Patients in the sub-prophylactic group had significantly lower serum albumin levels compared to those in the prophylactic group. Total bilirubin levels were not found to be significantly different between the two groups, (p=0.110).

Conclusion

A fixed prophylactic 40 mg dose of enoxaparin was associated with a high proportion of sub-prophylactic anti-factor Xa levels. Weight-based dose and serum albumin level were independent predictors of achieving the prophylactic target range.

Acknowledgements

I would like to thank my supervisors Professor Juan Scribante, Ms Helen Perrie and Dr Daren Calleemalay for their guidance and patience.

I would like to express my gratitude to Professor Shahed Omar for the help and guidance he has provided.

I am also grateful to the Department of Critical Care at Chris Hani Baragwanath Academic Hospital for allowing me to conduct my study.

Table of contents

List of figures

List of tables

Section 1: Review of the literature

Section 2: Draft article

Abbreviations

ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
BMI	Body mass index
CHBAH	Chris Hani Baragwanath Academic Hospital
COX	Cyclo-oxygenase
DVT	Deep vein thrombosis
eGFR	Estimated glomerular filtration rate
HITT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IQR	Inter-quartile range
LMWH	Low molecular weight heparin
NHLS	National Health Laboratory Service
SD	Standard deviation
VTE	Veno-thromboembolism

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the Critical Care and Resuscitation, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

Section 1: Review of the literature

1.1 Introduction

Veno-thromboembolism (VTE) is a well-known complication in the peri-operative period in patients with decreased mobility in hospitals (1). A standardised drug regimen is used in VTE prophylaxis along with non-pharmacological methods. The drug of choice is a low molecular weight heparin (LMWH) such as enoxaparin sodium, which will now be referred to as enoxaparin and the standard of practice is to use a dose of 40 mg of enoxaparin subcutaneously daily (2). Enoxaparin is used due to its ease of subcutaneous administration, monitoring is not routinely required and the side effect profile is less than with the use of intravenously administered unfractionated heparin (2,3). Despite VTE prophylaxis, there are still numerous incidents of VTE complications in immobile hospitalised patients (4).

In this literature review VTE and LMWH will be discussed, regarding patients at risk of VTE, the incidence of VTE, preventative strategies, pharmacology of LMWH, tests for LMWH efficiency, complications and factors affecting LMWH efficacy.

1.2 Veno-thromboembolism

The risk factors, the incidence and preventative strategies for VTE will be discussed.

1.2.1 Patients at risk of veno-thromboembolism

The majority of patients at risk of developing a VTE have an identifiable source such as surgery, disease states and immobility (5). VTE occurs when there is disturbance of either the blood flow in the vessel such as stasis, endothelial injury or by a hypercoagulable state (6). These three factors are commonly known as Virchow's triad which was described and named after Rudolf Virchow, a German pathologist (5,7). With injury or disturbance to one or more of the risk factors, thrombi develop either at the site of vascular trauma, artificial catheters or in areas where blood flow is reduced, for example, valves in veins, venous sinuses, the hepatic portal system or central veins such as the superior vena cava (5,8). Risk

factors are identified by their ability to induce the coagulation cascade, causing the formation of thrombi and potentially disrupting venous return to the heart and causing the formation of a deep vein thrombosis (DVT) or VTE (5,8).

Identifying patients that are at risk of developing VTE is important in determining who should be receiving prophylaxis. Anderson et al (7) studied the patient risk factors for VTE that were treated for acute DVT and pulmonary embolism or both and observed the following VTE risk factors in 1 231 patients:

- age > 40 years (88.5%)
- obesity (37.8%)
- history of venous thromboembolism (26.0%)
- cancer (22.3%)
- bed rest > 5 days (12.0%)
- major surgery (11.2%)
- congestive heart failure (8.2%)
- varicose veins (5.8%)
- fracture (hip or leg) (3.7%)
- oestrogen treatment (2.0%)
- stroke (1.8%)
- multiple trauma (1.1%)
- childbirth (1.1%)
- myocardial infarction (0.7%) (7).

These risk factors can be further classified into low, moderate, high and very high risk without VTE prophylaxis, as shown in Table 1.1.

Table 1.1: Classification of VTE risk factors (6,7,9)

Risk	Risk factors	Approximate VTE risk without prophylaxis
Low	Surgical duration < 30 minutes Age < 40 years Fixation of small fractures Obesity Laparoscopic surgery Pregnancy	< 10%
Moderate	Age 40 – 60 years Arthroscopy or repair of lower leg fractures Congestive cardiac failure Hormone replacement therapy Stroke Cancer Previous VTE	10 – 40%
High	Age > 60 years Age 40 – 60 years, with additional risk factors Immobilisation > 4 days	40 – 80%
Very high	Arthroplasty Hip fractures Compound fracture Reductions and fixations Major trauma Spinal cord injury Multiple risk factors for VTE	40 – 80%

The human immunodeficiency virus (HIV) is also known to cause a hypercoagulable state (6). HIV is particularly prevalent in South Africa where there

are a large number of patients being treated (10). The associated risk of VTE in HIV patients may be as high as 18% of all HIV infected individuals (6).

1.2.2 Incidence of VTE

VTE risk is increased in surgical patients and is a preventable cause of death and morbidity (11). A study in Australia (12) was performed in 2014 to look at the incidence of VTE in surgical patients. The study was done over a period of seven years among elective surgical patients in 82 hospitals (12). The incidence of VTE was found to be 2 per 1 000 patients annually, with a mortality of 8% (12).

The incidence of VTE has been noted to increase with age in both men and women. Incidence rates were found to be higher in women of childbearing age as compared to men, but after the age of 45, the incidence of VTE in men increased and was found to be higher than that of women (13). The incidence of survival following VTE from either a DVT or pulmonary embolism is shown in Table 1.2.

Table 1.2: Incidence of survival following a VTE event (13)

Time	Survival following DVT (%)	Survival following pulmonary embolism (%)
0 days	97.0	76.5
7 days	96.2	71.1
14 days	95.7	68.7
30 days	94.5	66.8
90 days	91.9	62.8
1 year	85.4	57.4
2 years	81.4	53.6
5 years	72.6	47.4
8 years	65.2	41.5

1.2.3 Preventative strategies

Appropriate thromboembolic prophylaxis will depend on the patient's risk. There are three types of VTE prophylaxis used, namely mechanical, pharmacological and surgical (5).

Mechanical prophylaxis

Mechanical prophylaxis of VTE include the use of anti-embolism stockings, intermittent pneumatic compression and foot impulse devices (5,9). Anti-embolism stockings have been the mainstay of treatment in a large number of hospital settings. They work by exerting circumferential pressure to the leg from distal to proximal, thereby increasing the blood flow and promoting venous return to the heart (5,9). Anti-embolism stockings are contra-indicated in patients with peripheral vascular disease, neuropathy, oedema, acute stroke and soft tissue diseases (5).

Intermittent pneumatic compression devices work by intermittently compressing the calf or thigh muscles, which simulate the muscle pump effect of walking, promoting fibrinolysis (5). Venous foot impulse devices are designed to simulate the activity of walking, thereby increasing venous return in immobilised patients (5). The advantages and limitations of mechanical VTE prophylaxis should be accounted for in choosing the correct VTE prophylaxis for patients (9).

Advantages of mechanical VTE prophylaxis include they can be used in patients with a high risk of bleeding and they have a synergistic effect with pharmacological prophylaxis (9). Limitations include them not being as effective as pharmacological VTE prophylaxis, not as effective in reducing proximal DVT compared to calf DVT and having no standardised features for size, pressure or physiological parameters. Further limitations are due to poor patient and staff compliance, the cost associated with use of each device and there not being enough data from clinical trials as to their efficacy (9)

Geerts et al (9) recommend mechanical VTE prophylaxis in patients with a high risk of bleeding and as an adjunct to pharmacological VTE prophylaxis. Though all three mechanical methods of VTE prophylaxis have been shown to reduce the risk of VTE, they are not as effective as pharmacological prophylaxis (9).

Pharmacological prophylaxis

There are many different pharmacological modalities available for VTE prophylaxis (5,9). In South Africa the pharmacological therapies available are unfractionated

heparin, LMWH, pentasaccharides, vitamin k antagonists and aspirin salicylate (2,5). LMWH will be discussed in Section 1.3, as this is the focus of the study.

Unfractionated heparin is a naturally occurring anti-coagulant produced from either bovine lung or porcine intestine (5,14). Due to its large molecular structure, it binds to both factors Xa and IIa (thrombin) (5,14). Unfractionated heparin has a short half-life of 1 – 2 hours compared to other pharmacological anti-coagulants (14). Even though unfractionated heparin is effective in VTE prophylaxis and used prior to LMWHS and easier to reverse, it is not as predictable as LMWHs in VTE prophylaxis (5).

Synthetic pentasaccharides, for example fondaparinux bind to factor Xa and are given subcutaneously and reach peak plasma levels two hours post-administration with a half-life of 17 – 21 hours (14). Due to their activity on factor Xa, their efficacy can be measured by monitoring anti-factor Xa assays (5,14). Pentasaccharides are renally excreted and, therefore, should not be used in patients with a creatinine clearance of less than 30 ml/minute (14). Pentasaccharides are useful in patients who have developed complications following the administration of unfractionated heparin and LMWH (5,14).

The mechanism of action of vitamin k antagonists is the inhibition of the production of vitamin k-dependent coagulation factors (5). Vitamin k-dependant coagulation factors are II, VII, IX and X. Warfarin is the most commonly used vitamin k antagonist (5,6). Vitamin k antagonists act on the extrinsic component of the coagulation cascade and are monitored by the international normalised ratio (5,6). Vitamin k antagonists are frequently the drug of choice in the long term prevention of VTE (6). The main disadvantages of vitamin k antagonists are their associated toxicity, bleeding risks, unpredictable effect, prolonged time to reach therapeutic effect and drug-drug interactions (5).

Aspirin salicylate inhibits cyclo-oxygenase (COX) enzymes (5). There are three types of COX enzymes. Aspirin salicylate irreversibly inhibits both COX 1 and 2 enzymes. COX 1 inhibition prevents thromboxane A2 production needed in platelet aggregation, therefore reducing the risk of VTE, although its effect on

prophylaxis is significantly lower than the use of other pharmacological methods (5,9,15).

Surgical prophylaxis

Vena caval filters may either be permanent or retrievable filters (16). Placement of vena caval filters is indicated for patients with a known large proximal DVT and in whom anti-coagulation is contraindicated (5). Vena caval filters may also be inserted prophylactically in patients with a high risk of developing a DVT where anti-coagulation is contradicted for VTE (16). The filters are usually placed under radiological guidance percutaneously in the inferior or rarely the superior vena cava (5). Evidence as to their efficacy is limited and they are associated with a high rate of recurrent DVT (5).

1.3 Low molecular weight heparin

The pharmacology of LMWH, tests for LMWH efficiency, complications and factors affecting LMWH efficacy will be discussed.

1.3.1 Pharmacology of low molecular weight heparin

LMWH is produced by either chemical or enzymatic depolymerisation of unfractionated heparin (17). LMWH is made up of smaller chains and with a lower molecular weight than unfractionated heparin. Its weight is approximately 4 000 – 6 000 Daltons as compared to unfractionated heparin, which is 12 000 – 15 000 Daltons (17). The understanding of the pharmacology of LMWH is informed by the coagulation cascade shown in Figure 1.

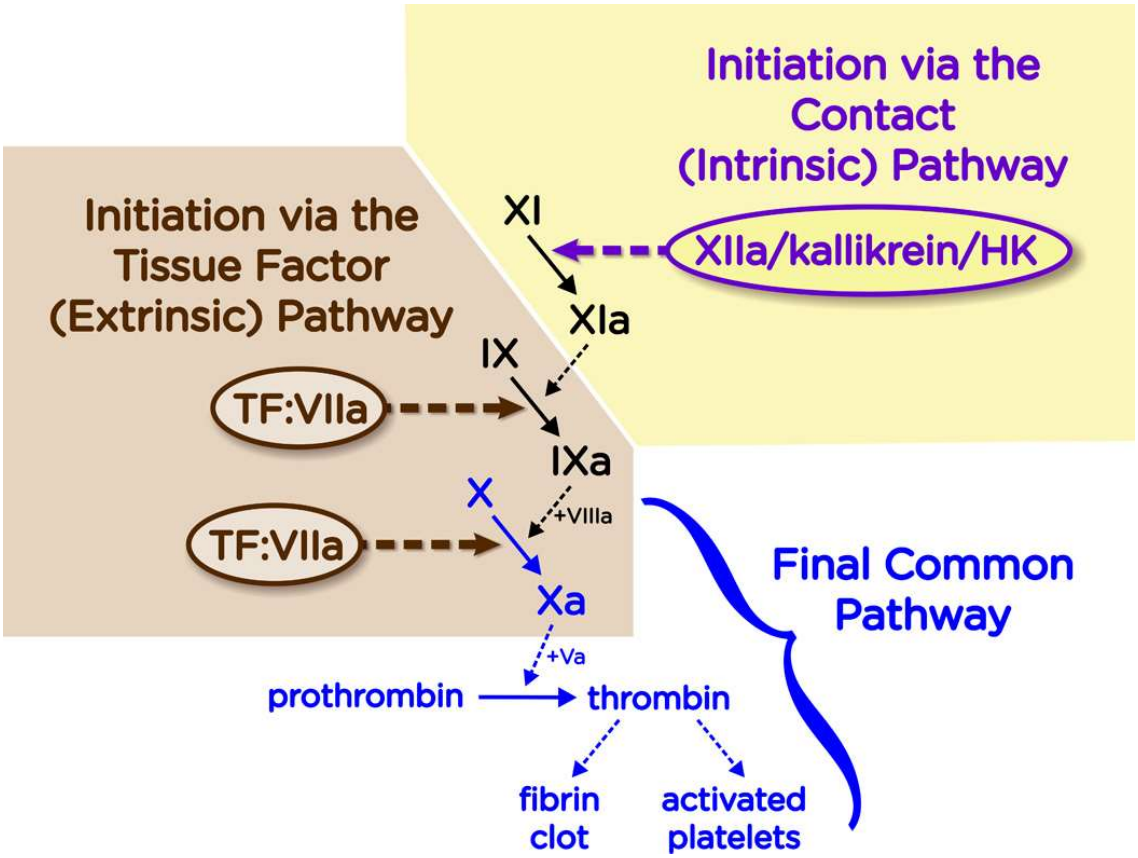

Figure 1: The coagulation cascade (18)

Unfractionated heparin, due to the size of its molecules, works on both factors Xa and IIa (thrombin) (17,19). Unfractionated heparin combines with anti-thrombin to inactivate factors Xa and IIa (20,21). LMWH, due to its smaller chain structure, has more effect on anti-factor Xa activity than anti-factor IIa activity (17,19).

LMWH has a higher bioavailability than unfractionated heparin, 90% versus 20% (11,12). LMWH are administered subcutaneously and have a longer half-life than unfractionated heparin at four hours compared to 1 – 2 hours (17,19). Maximal plasma levels after a subcutaneous dose are reached within two hours, with the peak effect at four hours (17,19). LMWH in the blood plasma are bound to the protein fibronectin and are distributed systemically. LMWH is eliminated renally, therefore, clearance may be impaired in patients who suffer from impaired renal function (17). The reversal of LMWHs by protamine sulphate is only partial and, therefore, inadequate (17). Table 1.3 compares unfractionated heparin and LMWH.

Table 1.3: Comparison between unfractionated heparin and LMWH (17)

	Unfractionated heparin	LMWH
Source	Biological	Biological
Molecular weight	12 000 – 15 000 Daltons	4 000 – 6 000 Daltons
Co-factor	Anti-thrombin III	Anti-thrombin III
Factor inhibition	IIa, Xa, IXa, XIa, and XIIa	IIa and Xa
Anti-Xa and anti-IIa activity	1:1	2:1 – 4:1
Common assays	aPTT, anti-Xa, ACT	anti-Xa
Bioavailability	20%	90%
Clearance	Rapid, saturable (non-renal) and first-order kinetics (renal)	Renal
Half-life (hours)	1 – 2	4
Reversibility	Protamine sulphate (100%)	Protamine sulphate (<75%)
HITT incidence	1 – 5%	0.1%

aPTT - activated partial thromboplastin time, ACT - activated clotting time, HITT - heparin-induced thrombocytopenia

1.3.2 Tests for low molecular weight heparin efficiency

The specific tests for LMWH efficiency are limited by the structure of the drug (22), therefore, it is important for the clinician to understand the pharmacokinetics and pharmacodynamics of the drug to determine which assays are appropriate for monitoring (23). Compared to unfractionated heparin, LMWH is smaller in size; thus, its effect on factor II is less than its effect on factor Xa (17,19,22). As compared to unfractionated heparin, LMWH has less prolongation of the aPTT and ACT (20). Therefore, measuring aPTT and ACT levels does not help determine the efficacy of LMWH and, therefore, anti-factor Xa levels are monitored (20). Factor Xa assays are measured by taking the blood plasma of the patient and then adding a known concentration of anti-factor Xa. The residual anti-factor Xa is measured using a chromogenic substrate and then quantified to produce a result (3).

Limitations of laboratory testing include that anti-factor Xa assays do not refer to the anti-thrombotic function of the LMWH but indicate the amount of LMWH present (24). The time at which the blood samples are taken is important due to the pharmacokinetics of the drug (24). LMWH levels should be drawn 3 – 4 hours after administration (23). Although these investigations exist, they are not a good predictor of the anti-thrombotic efficacy in VTE prophylaxis (24). Another limitation is the lack of assay standardisation and differences between different laboratories with differences in results of up to 30% (23).

1.3.3 Complications of low molecular weight heparin

The major complications of LMWHs are bleeding (19,25). Although the incidence of bleeding is decreased as compared to unfractionated heparin, the incidence still ranges from 0 – 3% of patients with up to 0.8% of these patients suffering from fatal bleeds (19,25). VTE prophylaxis with LMWH is thus determined by a bleeding risk assessment and the patient profile. LMWH prophylaxis should be discontinued at least 12 – 24 hours before surgery and should not be restarted for at least 24 hours post major surgery to reduce the risk of bleeding (19,26).

HITT is a documented complication of LMWH (19). HITT occurs when the immune system forms antibodies to the platelet surface antigen platelet factor IV (19,27). The incidence of HITT with the use of LMWH is much lower compared to the use of unfractionated heparin (19,28). HITT usually occurs within 5 – 7 days of onset of administration but may occur sooner if the patient has previously suffered from HITT or has been previously exposed to an LMWH (19,28). Table 1.4 may be used in the diagnosis of HITT with three or fewer points being a low probability of HITT, 4 – 5 points being a moderate probability and 6 – 8 points a high probability (29).

Table 1.4: Probability of HITT (29)

Category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ $20 \times 10^9\,L^{-1}$	Platelet count fall 30 – 50% or platelet nadir $10 – 19 \times 10^9\,L^{-1}$	Platelet count fall < 30% or platelet nadir < $10 \times 10^9\,L^{-1}$
Timing of the decrease in platelet count	Clear onset 5 – 10 days or platelet fall ≤ 1 day with prior heparin exposure within 30 days	Consistent with days 5 – 10 fall in platelets, but not clear (e.g. missing platelet counts) or onset after day 10 or fall ≤ 1 day (prior heparin exposure 30 – 100 days ago)	Platelet count fall < 4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or non-necrotising (erythematous) skin lesions or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None	Possible	Definite

Long-term therapy with LMWH may also be associated with osteoporosis though the incidence is lower when compared to unfractionated heparin (19).

1.3.4 Factors that influence factor Xa levels in patients receiving low molecular weight heparin

The mainstay of prophylaxis is fixed LMWH dosing (30–32). The doses being used for VTE prophylaxis are non-weight based dosing of enoxaparin 40 mg subcutaneously daily or 30 mg subcutaneously twice a day (3,21,31,32). The South African Venous thromboembolism: Prophylactic and Therapeutic Practice Guideline (2) recommends 40 mg enoxaparin subcutaneously daily as prophylaxis. The recommended anti-factor Xa levels for VTE prophylaxis vary (3,21,32).

Wall et al (33) described anti-factor Xa levels in acute care surgical patients receiving a standard dose of 30 mg twice daily. Anti-factor Xa levels were drawn at four hours post-administration. The results showed that 56.4% of patients had sub-prophylactic anti-factor Xa levels (<0.2 IU/ml) and 41.8% of patients had prophylactic anti-factor Xa levels (0.2 – 0.4 IU/ml) and one patient had a therapeutic level according to their reference range. The authors concluded that with fixed dosing, the majority of patients are not achieving adequate VTE prophylaxis (33).

Anti-factor Xa levels in intensive care patients receiving a fixed dose of 40 mg of enoxaparin within the first 24 hours of admission were described by Mayr et al (34). Samples were drawn at 4-, 12- and 24 hours post-administration. At four hours, the highest percentage of patients were found to have adequate prophylactic levels, 56,5%, with a decreased percentage of patients still having adequate prophylactic levels at 12 and 24 hours. It was concluded that standard dosing was ineffective in achieving adequate VTE prophylactic levels (34).

Riha et al (30) studied the incidence of VTE using the 30 mg twice daily administration as compared to 40 mg once daily administration of enoxaparin. The patient sample was of similar age, body mass index, of a similar disease profile and had no renal impairment. The results showed that there was an increase in VTE in patients receiving enoxaparin twice daily. This was due to the inadequate prophylactic levels required to prevent VTE phenomena. The authors concluded

that single dosing of enoxaparin yielded higher peak anti-factor Xa levels and thus is better suited for VTE prophylaxis (30).

Chapman et al (32) evaluated the non-weight based dosing of enoxaparin and its associated VTE prophylaxis levels. The study included trauma patients over the age of 18, with a hospital stay of more than three days and a creatinine clearance of more than 30 ml/minute. The patients received a fixed dose of 30 mg of enoxaparin twice daily and anti-factor Xa levels were measured 3 – 5 hours post-administration. The results showed that in 72.5% of the patients, the anti-factor Xa levels were below the recommended prophylactic range of 0.2 – 0.5 IU/ml (32). Using these results, the dose was adjusted according to the weights of the patients. The dose was adjusted incrementally to 0.5 mg/kg of actual body weight to achieve the desired prophylactic levels. In this study, 4 of the 51 patients had VTE events and this was related to their anti-factor Xa levels being < 0.2 IU/ml. It was found that in patients who had a higher creatinine clearance (131 ml/minute) their prophylactic levels were < 0.2 IU/ml and they made up the majority of the patients in the study who were below the recommended prophylactic range (32).

Freeman et al (31) compared three enoxaparin dosing regimens, a fixed dose of 40 mg daily, a low weight-based dose of 0.4 mg/kg daily and a higher weight-based dose of 0.5 mg/kg daily. The sample group used were ill medical patients with an increased body mass index of > 40 kg/m^2. The study showed that the higher weight-based dose was superior to the other regimens and achieved adequate levels (31). This was confirmed by Celik et al (35), in obese patients, who found that an increased weight-based dose of enoxaparin resulted in a reduced number of patients, approximately 10%, having inadequate levels (35).

Pannucci et al (36) investigated whether anti-factor Xa levels should routinely be measured in patients receiving enoxaparin VTE prophylaxis in a burn unit. It was found that there was increased benefit and effectiveness of altering the dose based on anti-factor Xa levels in preventing VTE complications as compared to fixed dosing (36). LMWH is a protein-bound drug (17). Therefore protein levels may impact on free drug concentration and rate elimination constants, thereby affecting the drug's efficacy (37,38).

1.4 Summary

VTE is a well-known complication in the peri-operative period despite VTE prophylaxis (1). Pharmacological VTE prophylaxis using enoxaparin as the drug of choice is the mainstay of treatment in hospital (5,9). The fixed non weight-based dosing of 40 mg daily subcutaneously suggested by Jacobson et al (2), has been shown by studies to be ineffective in achieving prophylactic levels (31–34).

1.5 References

1 Kopelman TR, Walters JW, Bogert JN, Basharat U, Pieri PG, Davis KM, et al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. Injury. 2017;48(5):1088–92. https://doi.org/10.1016/j.injury.2016.10.039

2 Jacobson BF, Louw S, Büller H, Mer M, De Jong PR, Rowji P, et al. Venous Thromboembolism: Prophylactic and Therapeutic Practice Guideline. S Afr Med J. 2013;103(4):261–267. https://doi.org/10.7196/SAMJ.6706

3 Wei MY, Ward SM. The anti-factor Xa range for low molecular weight heparin thromboprophylaxis. Hematol Rep. 2015;7(4):80–83. https://doi:10.4081/hr.2015.5844

4 Pannucci CJ, Rondina MT. Should we be following anti-factor Xa levels in patients receiving prophylactic enoxaparin perioperatively? Surgery, 2017;161(2):329–331. doi:10.1016/j.surg.2016.07.038

5 Barker RC, Marval P. Venous thromboembolism: Risks and prevention. BJA Educ. 2011;11(1):18–23. https://doi.org/10.1093/bjaceaccp/mkq044

6 Johnston L. Deep vein thrombosis after surgery. SA Pharm. J. 2011;78:18-21.

7 Anderson FA. Risk factors for venous thromboembolism. Circulation. 2003;107(90231):9–16. https://doi.org/10.1161/01.CIR.0000078469.07362.E6

8 Johnson SA, Eleazer GP, Rondina MT. Pathogenesis, diagnosis, and treatment of venous thromboembolism in older adults. J Am Geriatr Soc. 2016;64(9):1869–78. https://doi.org/10.1111/jgs.14279

9 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. Chest. 2008;133(6):381S-453S. https://doi.org/10.1378/chest.08-0656

10 Satoh S, Boyer E. HIV in South Africa. Lancet. 2019;394(10197):467. https://doi.org/10.1016/S0140-6736(19)31634-4

11 Amaral C, Guimarães Pereira L, Moreto A, Sá AC, Azevedo A. The postoperative venous thromboembolism (TREVO) study – Risk and case mortality by surgical specialty. Rev Port Cardiol. 2017;36(9):609–16. https://doi.org/10.1016/j.repce.2016.11.016

12 Assareh H, Chen J, Ou L, Hollis SJ, Hillman K, Flabouris A. Rate of venous thromboembolism among surgical patients in Australian hospitals: A multicentre retrospective cohort study. BMJ Open. 2014;4(10):e005502. https://doi.org/10.1136/bmjopen-2014-005502

13 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):3–14. https://doi.org/10.1007/s11239-015-1311-6

14 Hogg K, Weitz JI. Blood coagulation and anticoagulant, fibrinolytic, and antiplatelet drugs. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. Goodman Gilmans Pharmacol. Basis Ther. 13th ed., New York, NY: McGraw-Hill Education; 2017.

15 Hull RD, Raskob GE, Hirsh J. Prophylaxis of venous thromboembolism. Chest 1986;89(5):374S-383S. https://doi.org/10.1378/chest.89.5_Supplement.374S

16 DeYoung E, Minocha J. Inferior vena cava filters: Guidelines, best practice, and expanding indications. Semin Interv Radiol. 2016;33(2):065–70. https://doi.org/10.1055/s-0036-1581088

17 Heit, JA. Low-molecular-weight heparin: Biochemistry, pharmacology, and concurrent drug precautions. Reg Anesth Pain Med. 1998;23(6):135–139. https://doi:10.1016/s1098-7339(98)90138-9

18 Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. Crit Rev Biochem Mol Biol. 2015;50(4):326–36. https://doi.org/10.3109/10409238.2015.1050550

19 Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: A review of the pharmacology, dosing, and complications. Curr Emerg Hosp Med Rep. 2013;1(2):83–97. https://doi.org/10.1007/s40138-013-0014-6

20 Linkins LA, Julian JA, Rischke J, Hirsh J, Weitz JI. In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. Thromb Res. 2002;107(5):241–4. https://doi.org/10.1016/S0049-3848(02)00340-7

21 Pannucci CJ, Prazak AM, Scheefer M. Utility of anti-factor Xa monitoring in surgical patients receiving prophylactic doses of enoxaparin for venous thromboembolism prophylaxis. Am. J. Surg. 2017;213(6):1143–1152. https://doi:10.1016/j.amjsurg.2016.08.010

22 Hemker HC, Al Dieri R, Beguin S. Laboratory monitoring of low molecular weight heparin therapy part II. J Thromb Haemost. 2005;3(3):571–3. https://doi.org/10.1111/j.1538-7836.2005.01206.x

23 Funk DMA. Coagulation assays and anticoagulant monitoring. Hematol Am Soc Hematol Educ Program. 2012;2012:460–5. https://doi.org/10.1182/asheducation-2012.1.460

24 Greaves M. Limitations of the laboratory monitoring of heparin therapy: Scientific and standardization committee communications: On behalf of the Control of Anticoagulation Subcommittee of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. Thromb Haemost. 2002;87(1):163–4. https://doi.org/10.1055/s-0037-1612960

25 Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment. Chest. 2008;133(6):257S-298S. https://doi.org/10.1378/chest.08-0674

26 Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy. Chest. 2012;141(2):e326S-e350S. https://doi.org/10.1378/chest.11-2298

27 Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients: Crit Care Med. 2007;35(4):1165–76. https://doi.org/10.1097/01.CCM.0000259538.02375.A5

28 Martel N. Risk for heparin-induced thrombocytopenia with unfractionated and low molecular weight heparin thromboprophylaxis: A meta-analysis. Blood. 2005;106(8):2710–5. https://doi.org/10.1182/blood-2005-04-1546

29 Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: A systematic review and meta-analysis. Blood. 2012;120(20):4160–7. https://doi.org/10.1182/blood-2012-07-443051

30 Riha GM, Van PY, Differding JA, Schreiber MA. Incidence of deep vein thrombosis is increased with 30 mg twice daily dosing of enoxaparin compared with 40 mg daily. Am J Surg. 2012;203(5):598–602. https://doi.org/10.1016/j.amjsurg.2011.12.008

31 Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am. J. Hematol. 2012;87(7):740–743. https://doi:10.1002/ajh.23228

32 Chapman SA, Irwin ED, Reicks P, Beilman GJ. Non-weight-based enoxaparin dosing subtherapeutic in trauma patients. J Surg Res. 2016;201(1):181–7. https://doi.org/10.1016/j.jss.2015.10.028

33 Wall V, Fleming KI, Tonna JE, Nunez J, Lonardo N, Shipley RW, et al. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. Am J Surg. 2018;216(2):222–9. https://doi.org/10.1016/j.amjsurg.2017.07.014

34 Mayr AJ, Dünser M, Jochberger S, Fries D, Klingler A, Joannidis M, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. Thromb Res. 2002;105(3):201–4. https://doi.org/10.1016/S0049-3848(02)00028-2

35 Celik F, Huitema ADR, Hooijberg JH, van de Laar AWJM, Brandjes DPM, Gerdes VEA. Fixed-dose enoxaparin after bariatric surgery: The influence of body weight on peak anti-Xa levels. Obes Surg. 2015;25(4):628–34. https://doi.org/10.1007/s11695-014-1435-3

36 Pannucci CJ, Rondina MT. Should we be following anti-factor Xa levels in patients receiving prophylactic enoxaparin perioperatively? Surgery. 2017;161(2):329–31. https://doi.org/10.1016/j.surg.2016.07.038

37 Wagner JG. Simple model to explain effects of plasma protein binding and tissue binding on calculated volumes of distribution, apparent elimination rate constants and clearances. Eur J Clin Pharmacol. 1976;10(6):425–32. https://doi.org/10.1007/BF00563079

38 Gurevich KG. Effect of blood protein concentrations on drug-dosing regimens: Practical guidance. Theor Biol Med Model. 2013;10(1):1–7. https://doi.org/10.1186/1742-4682-10-20

Section 2: Author guidelines

Critical Care and Resuscitation

Critical Care and Resuscitation is the official journal of the College of Intensive Care Medicine of Australia and New Zealand. It is a research and educational journal for those interested in critical care and intensive care medicine and related subjects.

Manuscripts

All manuscripts to be submitted via the online submission system, which can be accessed here: https://ccr.cicm.org.au/submissions

Manuscripts should be prepared largely in accordance with the Uniform requirements for manuscripts submitted to biomedical journals (Ann Intern Med 1997; 126: 36-47).

Articles are accepted with the understanding that they have not been, nor will be, published elsewhere. This does not refer to abstracts or oral communications presented in the proceedings of societies or symposia. The editor reserves the right to alter and shorten material accepted for publication and to determine the priority and time of publication.

All articles should be submitted online at ccr.submissions.cicm.org.au, along with a covering letter and competing interests' statement by the primary author on behalf of all authors, signed electronically. The last should declare any competing interests as described in the British Medical Journal 1998; 317: 291-2. Any substantially revised versions of the original manuscript should be approved by all authors, and signed to that effect by the primary author. A letter of permission from the copyright holder is required for the use of images from other publications.

Studies on human subjects must comply with the Helsinki Declaration of 1975, and those on animals must comply with National Health and Medical Research Council Guidelines. A statement affirming Ethics Committee (Institutional Review Board) approval should be included in the text. A copy of that approval should be available if requested.

Receipt of the article will be acknowledged, and two or more experts will review the manuscript. Authors are invited to suggest names (and email addresses) of two potential reviewers, and also any reviewers they would prefer did not see the manuscript. Authors will be advised of the outcome within 6 weeks of receipt of the manuscript.

Preparation of manuscripts

All articles must be written in English. Submit manuscripts electronically (maximum fi le size, 5 MB). Microsoft Word is the preferred word processing program. The document should be unformatted, and the text should be single-word and double line spaced, with 2.5 cm margins on an A4 sized page.

On a single separate page there must be:

- title
- each author's given name, middle initial, surname, and appointments
- institution and department in which work was performed
- up to five keywords chosen from the keyword list
- (see https://ccr.cicm.org.au/submissions); and
- name, email address and telephone and fax numbers of the author to whom correspondence and requests for reprints should be directed, plus an email address for another author or nominated person as a back-up. The proofs will be sent to the nominated author unless contrary instructions are given.

Abstracts

Articles should have an abstract of appropriate format and length as follows:

Original article or survey:

Structured abstract (up to 250 words) with headings, Objective; Design; Setting; Participants; Interventions (if any); Main outcome measures; Results; and Conclusions.

Structured review or meta-analysis:

Structured abstract (up to 250 words) with headings, Objective; Design; Data sources; Review methods; Results; and Conclusions.

Other review:

Non-structured narrative or dot point abstract (up to 250 words).

Point of view:

No abstract, or non-structured narrative or dot point abstract (up to 100–150 words), depending on article length.

Case report:

Non-structured narrative abstract (up to 100 words) summarising case and reason it is notable.

Editorial, Pro-con debate, Letter, Book review, Obituary: No abstract.

Article formats

Original articles and surveys should be in IMRAD format (Introduction, Methods, Results and Discussion) (word limit, 2500 words).

Introduction (approximately 400 words) should cover why this topic is important (background); what is known and gaps in knowledge (unanswered questions); how this study will fill the gap (question addressed or relevant to this study); and specific aim and hypothesis of this study.

Methods should be clear and reproducible and include the start and end dates of the study; any equipment (including statistical software) should have manufacturer and city of manufacture in parentheses.

Results should be presented in the most meaningful way (text, table or figure). Results presented in tables and figures should not be repeated in the text (text should cite the table or figure and highlight only its most important features).

Present results in the same order as the methods, and ensure all results have a method described.

Discussion should discuss only results already presented in the results section. It should include a statement of the principal findings; how the findings fit with previous knowledge and data, including any important differences in results; what new and relevant data the study provides; meaning and implications of the study, especially for clinicians and policymakers; strengths and weaknesses of the study; relevant unanswered questions and future research; and conclusion.

Case reports should have an introduction of less than 100 words followed by the case report and discussion. In general, they should not exceed 2500 words in length.

Style

Use abbreviations sparingly and define each at first mention. Give measurements in SI units (except blood pressure in mmHg; if blood gases are given in mmHg, then include kPa in parentheses). Supply reference ranges for measurements. Refer to drugs by their Australian approved generic, not proprietary, names.

References

Number references consecutively in the order in which they are first mentioned in the text. References in tables and figures should be numbered as if mentioned where the table or figure is first cited. Identify references in text, tables and legends by superscript Arabic numerals.

Use the form of references adopted by the Vancouver style. Abbreviate journal names as in Index Medicus. List all authors when four or fewer; when five or more, list only the first three and add et al. For example:

Journal article:

Alten JA, Klugman D, Raymond TT, et al. Epidemiology and Outcomes of Cardiac Arrest in Pediatric Cardiac ICUs. Pediatr Crit Care Med 2017; 18: 935-43.

References to personal communications and unpublished observations should not be listed as references but should be noted in the text in parentheses: eg, “(personal communication)”. Articles that have been accepted for publication but not yet published should be included in the references with the words “In press” included in place of volume and page numbers.

Tables

Present all tables in double-spaced type on separate pages. Do not submit tables as images. Information in tables should not be duplicated in the text. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations that are used in each table. Cite each table in the text in consecutive order.

Standard deviation (SD) is the accepted measure of variation in text and tables. Standard error of the mean (SEM) is acceptable in fi gures for the sake of graphical clarity, provided that the number of observations is clearly stated. Omit internal horizontal and vertical rules.

Figures and illustrations

Figures and illustrations should be submitted in electronic format. Two versions of each image are required:

1. A print-quality (high resolution) image. An acceptable image must be at least 3.5 inches (8.75 cm) across when printed at 300 dots per inch (dpi). Computer screen resolution only requires 72 dots per inch (dpi), which is not suitable for print. If the image is small to begin with, it cannot be turned into a high-resolution image: it is not effective to “blow up” an image using image editing software to increase the size.

Images should be submitted in their original fi le format. Preferred image fi le formats are EPS, TIFF, Adobe Illustrator or Adobe Photoshop. JPEG images may be acceptable but should be saved at their maximum size, as JPEG compression reduces image quality. ZIP compression is acceptable. Microsoft

Excel format is acceptable for graphs; it is important to provide the data table from which the graph was generated.

2. A lower-quality image that can be viewed with standard software is also required for review purposes. For example, a copy of the image may be embedded in the Word document at the relevant position or provided in TIFF format.

Figures should be drawn professionally or in a computer graphics program; freehand or typewritten lettering is unacceptable. Letters, numbers and symbols should be clear throughout, and of sufficient size that when reduced for publication each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves. Figures depicting two dimensions of data should be presented with simple vertical and horizontal axes. Framing, shading, icons and fanciful typefaces are unacceptable.

Cite each figure in the text in consecutive order. Arabic numerals should be used to number the figures. Include legends for illustrations on a separate page. When symbols, arrows, numbers or letters are used to identify parts of the illustration, identify and explain each one clearly in the legend. Colour reproduction of figures is available, although the authors may be required to bear the cost.

Letters to the Editor

Letters to the Editor are welcomed and will be published if appropriate. They should be presented in single-word, double line spaced type and generally be no more than two pages in length. All authors must sign, and an email address for publication must be given. The Editor reserves the right to style or shorten any letter. Major changes will be referred back to authors for their concurrence. When letters refer to an earlier published paper, it must be one published within the previous 6 months. Its authors will be offered right of reply.

Proofreading

Contributors of original articles are provided with proofs and are asked to proofread them for typesetting errors and return them as soon as possible. Important corrections are allowed, but authors will be charged for extensive changes to text at this stage. Proofs are not provided for abstracts of scientific meetings or for letters to the Editor.

Reprints

Reprints can be ordered from the publisher.

Section 3: Draft article

Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

Mayank Mukeshbhai Baloo, MBChB, DA (SA)

Juan Scribante, PhD

Helen Perrie, MSc

Daren Calleemalay, MBChB, DA (SA), MMed (WITS), FCA (SA), Critical Care (SA)

Department of Anaesthesiology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding Author

MM, Baloo

Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
26 Chris Hani Rd
Diepkloof, Soweto
Johannesburg
1860

mayankbaloo@gmail.com

011 933 9335

Key words: Veno-thromboembolism, anti-factor Xa levels, enoxaparin, prophylactic, low molecular weight heparin

Abstract

Objective: The aim of this study was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit (ICU).

Design: A cross-sectional study design was followed.

Setting: Multi-disciplinary ICU at Chris Hani Baragwanath Academic Hospital affiliated with the University of the Witwatersrand.

Participants: Seventy-three patients admitted to the ICU receiving 40 mg enoxaparin sodium daily were enrolled into this study.

Interventions: Anti-factor Xa level samples were taken from patients receiving prophylactic enoxaparin following the second dose administered in the ICU. The prophylactic and the sub-prophylactic groups of patients were also compared for age, sex, weight, body mass index, total bilirubin, serum albumin and APACHE II score.

Main outcome measures: Anti-factor Xa levels after receiving the second prophylactic dose of enoxaparin sodium in ICU.

Results: Anti-factor Xa levels were prophylactic (0.2 – 0.6 IU/ml) in 44 (60.3%) patients and sub-prophylactic (< 0.2 IU/ml) in 29 (39.7%) patients. The mean (SD) actual delivered dose of enoxaparin per kilogram body weight was significantly higher, at 0.59 (0.11) mg/kg in the prophylactic group compared to 0.53 (0.13) mg/kg the sub-prophylactic group, (p=0,043). Patients in the sub-prophylactic group had significantly lower serum albumin levels compared to those in the prophylactic group. Total bilirubin levels were not found to be significantly different between the two groups, (p=0.110).

Conclusion: A fixed prophylactic 40 mg dose of enoxaparin was associated with a high proportion of sub-prophylactic anti-factor Xa levels. Weight-based dose and serum albumin level were independent predictors of achieving the prophylactic target range.

Introduction

Veno-thromboembolism (VTE) is a well-known complication in the peri-operative period in patients with decreased mobility in hospital and standardised drug regimen is recommended in VTE prophylaxis (1). The drug of choice is a low molecular weight heparin (LMWH) such as enoxaparin sodium, commonly known as enoxaparin, and the standard dose is 40 mg subcutaneously daily (2). Enoxaparin is used due to its ease of subcutaneous administration, monitoring is not routinely required and it has a more advantageous side effect profile when compared to intravenously or subcutaneously administered unfractionated heparin (2,3). Despite prophylaxis, VTE remains a significant complication among immobile hospitalised patients (4). The incidence of VTE in Australia in 2014 was 2 per 1 000 patients annually, with a mortality of 8% despite prophylaxis (5). The survival following VTE is shown to be worse if the patient suffered a pulmonary embolism compared to a deep vein thrombosis (6).

Enoxaparin is a low molecular weight heparin (LMWH) (7). LMWHs have a smaller chain structure than unfractionated heparin, therefore, they have more anti-factor Xa activity (7,8). Maximal plasma doses are reached within two hours with a peak effect at four hours and a half-life of four hours (7,8). The tests to determine the efficacy of LMWH are limited by their structure (9). Factor Xa assays are used to monitor anti-factor Xa levels in the blood plasma (10).

VTE prophylaxis using enoxaparin 40 mg subcutaneously daily is standard treatment in adult patients in the intensive care unit (ICU) at Chris Hani Baragwanath Academic Hospital (CHBAH), provided there are no contraindications. However, it is not known whether this dose provides adequate prophylactic levels in these patients. The aim of this study was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin in the ICU.

Methods

A cross-sectional study was conducted in the multi-disciplinary ICU at CHBAH. CHBAH is a 2 888-bed central academic hospital affiliated to the University of the

Witwatersrand. The ICU has 27 beds and admits both adult and paediatric patients, with approximately 750 admissions annually.

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190833). Written informed consent was obtained from each patient or their surrogate before enrolment into this study. Deferred consent was obtained from all patients who had surrogate consent when they were able to give informed consent.

All adult patients admitted to the ICU between November 2019 and to January 2020, receiving 40 mg enoxaparin daily were considered for enrolment into the study. The exclusion criteria in this study were patients with an eGFR of < 60 ml/minute, patients who did not receive a 06:00 dose of enoxaparin, blood samples collected or stored incorrectly and patients' receiving therapeutic enoxaparin dosing. A time of 06:00 was used to allow for a standard time of collection. Patients were classified into two groups, prophylactic and sub-prophylactic.

All ICU admissions were screened daily and blood samples were taken in a sterile standardised manner three hours post the second prophylactic enoxaparin dose by one author (MB). Blood was collected in a 5 ml citrate tube from preferentially an arterial line or if not possible by venipuncture, stored at -20° C and analysed by an accredited laboratory in batches of ten. For this study the prophylactic range was regarded as an anti-factor Xa level 0.2 – 0.6 IU/ml (3).

The primary objective was to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin following the second dose administered in the ICU. The secondary objectives were to describe and compare the following factors between the prophylactic and the sub-prophylactic groups; age, sex, weight, body mass index (BMI), total bilirubin, serum albumin and severity of illness using the APACHE II score. Independent predictors of a prophylactic level were also determined.

Analysis was done in consultation with a statistician using the statistical program STATA version 13.1 (StataCorp, USA). Categorical data were described using frequencies and percentages. Independent t-tests were used to compare normally

distributed data and Mann-Whitney tests for data not normally distributed. Regression analysis was performed on significant predictors of prophylactic anti-factor Xa levels. A p-value of 0.05 or less was considered statistically significant.

Results

A total of 77 patients were assessed for eligibility. Bloods for anti-factor Xa levels were taken from each patient. Four patients were excluded, one patient due to laboratory error and three patients were later found to have received therapeutic enoxaparin sodium dosing. A total of 73 patients were thus included in the study.

The anti-factor Xa levels of all patients and for those falling in the prophylactic and sub-prophylactic ranges are shown in Table 1. A comparison of patient characteristics between the prophylactic and sub-prophylactic groups is provided in Table 2. There was a statistically significant difference between the two groups regarding weight, BMI and APACHE II score, with those in the prophylactic group having lower values for all three.

The mean (SD) actual delivered dose of enoxaparin per kilogram body weight was significantly higher, at 0.59 (0.11) mg/kg in the prophylactic group (n=44) compared to 0.53 (0.13) mg/kg the sub-prophylactic group (n=29), (p=0,043).

Patients in the sub-prophylactic group were found to have significantly lower serum albumin levels compared to those in the prophylactic group, while total bilirubin levels were not found to be significantly different between the two groups. See Table 3.

Using a multiple regression model that included total bilirubin, serum albumin, weight-based delivered dose of enoxaparin and Apache II score, only a higher serum albumin (p=0.013) and a greater weight-based delivered dose (p=0.033) were independent predictors of being in a prophylactic range.

Discussion

The main finding of this study was that the standard dosing of enoxaparin of 40 mg daily did not always achieve its intended prophylactic range. Only 60.3% of patients were found to be within the prophylactic range. In a group of surgical and

trauma patients, Wall et al (11) found that 41.8% of patients had an anti-factor Xa level in the prophylactic range. Their patients had a similar BMI to our patients. The lower proportion of patients that reached the prophylactic target range in their study is likely explained by the difference in the study population and dosing. Their study included only surgical and trauma patients while our study included medical, surgical and obstetric patients (11). With regards to dosing of enoxaparin, our study used a 40 mg dose of enoxaparin compared to 30 mg twice daily used by Wall et al (11). It has been demonstrated that trauma patients have a higher risk of developing augmented renal clearance (12,13). This higher renal clearance could result in an increase clearance of enoxaparin and hence a lower proportion of patients reaching the desired prophylactic level. Mayr et al (14) studied similar patients to ours, receiving 40 mg enoxaparin daily and found 56.5% of patients to be within the recommended prophylactic range (14). This is similar to our finding of 60.3%.

When calculating the delivered dose of enoxaparin per kilogram body weight in our study group, a significant difference was found with the group achieving prophylactic levels receiving a dose of 0.59 mg/kg, while the sub-prophylactic group received only 0.53 mg/kg. The relevance of this weight-base delivered dosing is confirmed by Celik et al (15). Using a morbidly obese group of patients with a mean BMI of 42.2 kg/m^2, the authors showed that a daily dose of 0.63 mg/kg was able to reduce the sub-prophylactic group to 11.8% (15), which is lower than found in our study (39.7%) and other studies (11,14). Lim et al (16) also found that a daily weight-based dose of enoxaparin 0.7 mg/kg in a population with a mean BMI of 21.7 kg/m^2 was able to reduce the sub-prophylactic group to approximately 5% (16).

Freeman et al (17) compared three dosing regimens, a fixed-dose of 40 mg enoxaparin daily, a low weight-based dose of 0.4 mg/kg daily and a higher weight-based dose of 0.5 mg/kg daily (17). Only 18% of the fixed-dose group achieved target anti-factor Xa levels compared to 64% of the low dose and 87% of the high dose group (17). Chapman et al (18) demonstrated that by changing the dosing strategy from a fixed-dose to a weight-based dose, the proportion of patients in the sub-prophylactic range could be reduced (18).

In our study, a sub-prophylactic anti-factor Xa level was associated with a lower serum albumin level (mean 27.8 g/l) when compared to patients who achieved a prophylactic anti-factor Xa level (mean serum albumin 34.4 g/l). Pharmacokinetic studies for protein-bound drugs indicate that protein levels impact on free drug concentration and on elimination rate constants (19,20). Chi et al (21) showed an increasing incidence of VTE from 3.5% among medical patients with serum albumin levels greater than 45 g/l to 20% among patients with serum albumin levels of less than 25 g/l (21). Regression analysis in our study confirmed that low serum albumin level was an independent predictor of a sub-prophylactic anti-factor Xa level.

APACHE II score is used as a surrogate for severity of illness in ICU patient and in this study was significantly associated with low anti-factor Xa levels. However, APACHE II score was shown not to be an independent predictor of anti-factor Xa prophylactic levels by regression analysis. The mean APACHE II score in this study was low, mean 11.5, as patients with a higher APACHE II score did not meet the inclusion criteria for the study.

A limitation to this study was that it was a single centre, which may reduce generalisability to other populations. The authors suggest weight-based dosing and cognisance of lower serum albumin levels may provide solutions to adequate dosing and recommend further research in this regard.

Conclusion

In this study, a fixed prophylactic 40 mg dose of enoxaparin was associated with a high proportion of sub-prophylactic anti-factor Xa levels. Weight-based dose and serum albumin level were independent predictors of achieving the prophylactic target range.

Conflict of interest

The authors declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

Acknowledgment

The authors would like to thank Dr Gill Hendry for her statistical support and Prof Shahed Omar for his clinical expertise and support.

References

1 Kopelman TR, Walters JW, Bogert JN, et al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. Injury. 2017;48(5):1088–92. https://doi.org/10.1016/j.injury.2016.10.039

2 Jacobson BF, Louw S, Büller H, et al. Venous thromboembolism: prophylactic and therapeutic practice guideline. S Afr Med J. 2013;103(4):260-267. https://doi.org/10.7196/SAMJ.6706

3 Wei MY, Ward SM. The anti-factor Xa range for low molecular weight heparin thromboprophylaxis. Hematol Rep. 2015;7(4):80–83. https://doi.org/10.4081/hr.2015.5844

4 Pannucci, CJ, Prazak, AM, Scheefer M. Utility of anti-factor Xa monitoring in surgical patients receiving prophylactic doses of enoxaparin for venous thromboembolism prophylaxis. Am. J. Surg. 2017;213(6):1143–1152. https://doi:10.1016/j.amjsurg.2016.08.010

5 Assareh H, Chen J, Ou L, et al. Rate of venous thromboembolism among surgical patients in Australian hospitals: A multicentre retrospective cohort study. BMJ Open. 2014;4(10):e005502. https://doi.org/10.1136/bmjopen-2014-005502

6 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):3–14. https://doi.org/10.1007/s11239-015-1311-6

7 Heit JA. Low-molecular-weight heparin: Biochemistry, pharmacology, and concurrent drug precautions. Reg Anesth Pain Med. 1998;23(6):135–139. https://doi:10.1016/s1098-7339(98)90138-9

8 Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: A review of the pharmacology, dosing, and complications. Curr Emerg Hosp Med Rep. 2013;1(2):83–97. https://doi.org/10.1007/s40138-013-0014-6

9 Hemker HC, Al Dieri R, Beguin S. Laboratory monitoring of low molecular weight heparin therapy part II. J Thromb Haemost. 2005;3(3):571–3. https://doi.org/10.1111/j.1538-7836.2005.01206.x

10 Linkins LA, Julian JA, Rischke J, et al. In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. Thromb Res. 2002;107(5):241–4. https://doi.org/10.1016/S0049-3848(02)00340-7

11 Wall V, Fleming KI, Tonna JE, et al. Anti-factor Xa measurements in acute care surgery patients to examine enoxaparin dose. Am J Surg. 2018;216(2):222–9. https://doi.org/10.1016/j.amjsurg.2017.07.014

12 Udy AA, Putt MT, Shanmugathasan S, et al. Augmented renal clearance in the intensive care unit: An illustrative case series. Int J Antimicrob Agents. 2010;35(6):606–8. https://doi.org/10.1016/j.ijantimicag.2010.02.013

13 Minville V, Asehnoune K, Ruiz S, et al. Increased creatinine clearance in polytrauma patients with normal serum creatinine: A retrospective observational study. Crit Care. 2011;15(1):R49. https://doi.org/10.1186/cc10013

14 Mayr AJ, Dünser M, Jochberger S, et al. Antifactor Xa activity in intensive care patients receiving thromboembolic prophylaxis with standard doses of enoxaparin. Thromb Res. 2002;105(3):201–4. https://doi.org/10.1016/S0049-3848(02)00028-2

15 Celik F, Huitema ADR, Hooijberg JH, et al. Fixed-dose enoxaparin after bariatric surgery: The influence of body weight on peak anti-Xa levels. Obes Surg. 2015;25(4):628–34. https://doi.org/10.1007/s11695-014-1435-3

16 Lim SY, Jeon K, Kim HJ, et al. Antifactor Xa levels in critically ill Korean patients receiving enoxaparin for thromboprophylaxis: A prospective observational study. J Korean Med Sci. 2013;28(3):466. https://doi.org/10.3346/jkms.2013.28.3.466

17 Freeman A, Horner T, Pendleton RC, Rondina, MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in

hospitalized, medically ill patients with extreme obesity. Am. J. Hematol. 2012;87(7):740–743. https://doi:10.1002/ajh.23228

18 Chapman SA, Irwin ED, Reicks P, Beilman GJ. Non-weight-based enoxaparin dosing subtherapeutic in trauma patients. J Surg Res. 2016;201(1):181–7. https://doi.org/10.1016/j.jss.2015.10.028

19 Wagner JG. Simple model to explain effects of plasma protein binding and tissue binding on calculated volumes of distribution, apparent elimination rate constants and clearances. Eur J Clin Pharmacol. 1976;10(6):425–32. https://doi.org/10.1007/BF0056307

20 Gurevich KG. Effect of blood protein concentrations on drug-dosing regimes: Practical guidance. Theor Biol Med Model. 2013;10(1):1–7. https://doi.org/10.1186/1742-4682-10-20

21 Chi G, Gibson CM, Liu Y, et al. Inverse relationship of serum albumin to the risk of venous thromboembolism among acutely ill hospitalized patients: Analysis from the APEX trial. Am J Hematol. 2019;94(1):21–8. https://doi.org/10.1002/ajh.25296

Table 1: Anti-factor Xa levels

	Anti-factor Xa levels (IU/ml)		n (%)
	Mean	**SD**	
All patients	0,25	0.12	73 (100)
Prophylactic (0.2 – 0.6)	0.33	0.09	44 (60.3)
Sub-prophylactic (< 0.2)	0.13	0.03	29 (39.7)

Table 2: Comparison of patient characteristics

Characteristics	Groups			p-value
	All (n=73)	Prophylactic	Sub-prophylactic	
	n (%)			
Male	41 (56.2)	23 (56.1)	18 (43.9)	0.475
Female	32 (43.8)	21 (65.6)	11 (34.4)	
	Mean (SD)			
Age (years)	39.7 (16.2)	37.9 (16.9)	42.3 (15.0)	0.253
Weight (kg)	74.1 (19.4)	68.9 (13.4)	80.5 (25.0)	0.043
BMI (kg/m^2)	27.1 (7.8)	25.3 (5.0)	29.8 (10.3)	0.036
APACHE II score	11.5 (6.0)	10.4 (4.6)	13.2 (7.3)	0.045

Table 3: Comparisons between groups for serum albumin and total bilirubin levels

Test	Groups			p-value
	All	Prophylactic	Sub-prophylactic	
Total bilirubin (µmol/l)	**Median (IQR)**			0.110
	8.0 (5.5 – 13.0)	8.0 (5.0 – 10.0)	11.0 (6.0 – 21.5)	
Serum albumin (g/l)	**Mean (SD)**			0.007
	31 (10.4)	34.4 (10.5)	27.8 (9.0)	

Section 4: Proposal

Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

Student name: Dr Mayank Mukeshbhai Baloo

Student Number: 0600471N

Supervisor	Prof Juan Scribante Department of Anaesthesiology
Co-supervisor	Ms Helen Perrie Department of Anaesthesiology
Co-supervisor	Dr Daren Calleemalay Department of Anaesthesiology and Critical Care

4.1 Introduction and problem statement

Veno-thromboembolism (VTE) is a known complication in the peri-operative period in patients with decreased mobility in hospital (1). Despite VTE prophylaxis, patients still suffer from VTE complications (2). The incidence of VTE in Australia in 2014 was around 2 per 1000 patients annually with a mortality of 8% despite prophylaxis (3). The survival following VTE is shown to be worse if the patient suffered a pulmonary embolism compared to a deep vein thrombosis (4).

Identifying patients that are at risk of developing VTE is important in determining who should be receiving prophylaxis. Risk factors are identified by their ability to induce the coagulation cascade thereby forming thrombi (5,6). Patients with immobile states such as the critically ill or surgical patients are at an increased risk of developing VTE (5). Human immunodeficiency virus – infected patients have an increased risk of developing VTE, as high as 18%, without the peri-operative risk factors (6).

Preventative strategies can be divided into mechanical, pharmacological and surgical (5). The correct preventative strategy should be chosen according to the risk stratification of each patient (7,8). The standard practise for VTE prophylaxis is to use enoxaparin sodium (7,9), which will now be referred to as enoxaparin. The recommended dose of enoxaparin is 40 mg daily subcutaneously due to its low side effect profile and ease of administration (7).

Enoxaparin is a low molecular weight heparin (LMWH) (10). LMWHs have a smaller chain structure than unfractionated heparin, therefore, they have more anti-Xa factor activity (10,11). Maximal plasma doses are reached within two hours with peak effect at four hours with a half-life of four and a half hours (10,11). The tests for LMWHs are limited by its structure (12). Factor Xa assays are used to monitor anti-factor Xa levels in the blood plasma (13).

VTE associated events still occur despite prophylaxis. VTE prophylaxis using enoxaparin 40 mg subcutaneously is standard treatment in patients in the intensive care unit (ICU) at Chris Hani Baragwanath Academic Hospital (CHBAH), provided there are no contraindications. However, it is not known whether this

dose provides adequate prophylactic levels in these patients. The prophylactic range is described as between 0.2 – 0.6 IU per ml internationally (9). Reasons as to why patients may fall out of this described range may be due to several patient variables. These variables include the patient's age, weight, body mass index, estimated glomerular filtration rate (eGFR), liver function and severity of illness.

4.2 Aim and objectives

4.2.1 Aim

The aim of this study is to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin in CHBAH ICU.

4.2.2 Objectives

The primary objective of this study is to determine the anti-factor Xa levels in patients receiving prophylactic enoxaparin following the second dose administered in the ICU.

The secondary objectives of this study are to**:**

- describe and compare the following factors between the prophylactic and the sub- prophylactic groups:
    - age
    - sex
    - weight
    - body mass index
    - total bilirubin
    - albumin
    - severity of illness (Apache II score).

4.3 Research assumptions

The following definitions will be used in this study.

Adult: is a person 18 years and older**.**

Prophylactic enoxaparin dose: in this study it is 40 mg daily subcutaneously at 06:00 (7).

Anti-Xa reference range: ranges defined by the Coagulation Laboratory of the National Health Laboratory Service (NHLS) in IU per ml are:

- Sub – prophylactic < 0.2
- Prophylactic 0.2 – 0.6
- Therapeutic > 0.6. (9)

Prophylactic: in this study will include patients with factor Xa levels of between 0.2 – 0.6 IU.

Sub-prophylactic: in this study will include patients in the sub-therapeutic (< 0.2 IU) factor Xa levels.

Renal impairment: in this study will be an eGFR of less than 60 mls per minute (14).

4.4 Demarcation of study field

The study will be conducted in the ICU at CHBAH, affiliated to the Faculty of Health Sciences of the University of the Witwatersrand. CHBAH is a 2 888-bed central hospital. The staff complement of the department is 14 consultants, 14 fellows, 9 registrars and 17 medical officers. CHBAH ICU accommodates both adult and paediatric patients and has a total of 27 beds. On average, there are 750 admissions per year.

4.5 Ethical considerations

Approval to conduct this study will be submitted to the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Permission to conduct this study at CHBAH will be obtained from the Medical Advisory Committee (Appendix 1). Approval for this study at CHBAH ICU was obtained from the Head of the ICU (Appendix 2).

Patients who qualify for the study will be approached in CHBAH ICU and if patients are able to consent, the details of the study will be explained, and they will be given an information letter (Appendix 3.1). Informed consent will be obtained from the patient (Appendix 3.2). If the patient is unable to consent, the surrogate decision maker will be approached and asked if the family member can be included in the study. If they agree, the study will be explained, and they will be given an information letter (Appendix 4.1). Informed consent will be obtained from the surrogate decision maker (Appendix 4.2). A surrogate decision maker is defined by the National Health Act (No. 61 of 2003) (15) in this order: a spouse or partner, parent, grandparent, an adult child or sibling. When the patient can give consent, the patient will be approached, and it will be explained to them that consent was given on their behalf. The details of the study will be explained, and they will be given an information letter (Appendix 5.1). Deferred consent will then be obtained from the patient (Appendix 5.2). If the patient withdraws or is not willing to partake in the study, their decision will not influence the standard of medical care they receive, and their samples will not be used.

The anti-factor Xa levels will be done in batches, it will not be known at the time the patient is in ICU if their prophylaxis treatment is appropriate and, therefore, no adjustments to treatment can be made.

Data will be stored securely for six years after completion of the study, in a locked cupboard for laboratory result sheets and electronically on a password protected database for electronically captured data. Patients' anonymity will be ensured by allocating a study number to each patient. A list with the patients' names, hospital and study numbers will be stored separately in a secure location. Raw data will only be accessed by the researcher and supervisors to maintain confidentiality.

The study will be conducted according to the principles of the Declaration of Helsinki (16) and the South African Guidelines for Good Clinical Practice (17).

4.6 Research methodology

4.6.1 Research design

A prospective, contextual, cross-sectional research design will be followed in this study.

A prospective study collects data over a period from the commencement of the study (18). This is a prospective study as data is collected as new patients are enrolled into the study.

A contextual study is defined as a study intending to answer the research question in a specific group (19). The study that has been proposed is contextual as it aims to determine anti-factor Xa levels in critically ill patients at CHBAH.

A cross-sectional study observes variables at a fixed point in time and allows the researcher to look at a variety of variables without manipulation (18). This is a cross-sectional study as it provides information on a variety of variables and their influence on the outcome at one point in time.

4.6.2 Study population

The study population of this study is patients receiving prophylactic enoxaparin admitted to CHBAH ICU.

4.6.3 Study sample

Sample size

The minimum sample size calculated using STATA (StatSoft, USA) for the primary objective is equal to 68 based on a mean reference range of 0.50 IU and the estimated mean of 0.42 IU with a standard deviation of 0.2, a power of 90% and a significance level of 0.05. For the secondary objective, the sample size is

approximately 75 based on 10 – 15 individuals per independent variables (multiple linear regression).

Sampling method

The sampling method describes how the patients in the study are selected from the population group. The method used in this study is a convenience sampling method. Convenience sampling refers to a non-random selection of the sample as they are in the right place at the right time (18).

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- adult patients
- patients receiving 40 mg of enoxaparin.

The exclusion criteria in this study are:

- patients with renal impairment
- patients that did not receive a 06:00 dose of enoxaparin
- blood samples collected at the incorrect time
- blood samples for testing that are not stored correctly
- patients' anti factor Xa levels falling into the therapeutic range.

4.6.4 Data collection

The data will be collected by the researcher. All patients will be screened daily for admission into the study. Relevant information from the patients will be recorded on a data collection sheet (Appendix 6). A study number will be assigned to each patient. Data will be captured onto a Microsoft excel® spreadsheet for data analysis.

Timing of blood sampling

Enoxaparin is usually administered at 06:00 to each patient and signed for by the nursing staff administering the drug. Peak plasma levels of anti-factor Xa levels are between 2 – 4 hours after administration. Blood sampling will be at 09:00, which is three hours after the second dose administered in the ICU.

Collection of blood samples

Blood samples will be collected, by the researcher in a sterile manner to prevent contamination, on the morning the patient receives the second dose of enoxaparin in ICU. The blood samples will be collected in the following standardised manner:

- using sterile non-heparinised syringes and needles
- preferentially by using the injection ports of invasive lines rather than by venipuncture, with arterial lines being the preferred choice.

If invasive lines are being used to collect blood samples. The blood samples will be collected by:

- first cleaning the ports of these lines to ensure sterility
- temporarily stopping infusions connected to these injection ports, if there is no harm to the patient in doing so, and to avoid contamination of the blood sample
- using a two-syringe technique (two sterile 5 ml syringes)
- drawing 5 mls of blood into the first syringe, which is the dead space volume of the line used
- drawing 5 mls blood into the second syringe, which will be injected into a citrated blood specimen tube.

If there are no invasive lines or an invasive line that cannot be used, venipuncture will be used. Blood samples will be collected:

- by using an aseptic venipuncture technique to obtain the required 5 ml blood sample
- one 5 ml syringe will be required for this technique
- ensuring haemostasis at the puncture site by applying manual pressure for one minute then applying a dressing.

Storage and testing of blood samples

Blood samples will be immediately be put in a -20° C freezer in ICU (20). The freezer temperature is monitored, and the ICU has a back-up generator. The researcher will transport the frozen specimens to the NHLS laboratory at CHBAH in a cooler bag in batches of 10 for testing.

4.6.5 Data analysis

A Microsoft Excel® spreadsheet will be used to capture data. Data will be analysed in consultation with a biostatistician using the statistical program STATA version 13.1 (StataCorp, USA). Categorical variables will be described using numbers and percentages and continuous variables using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. Unpaired t-tests will be used to compare normally distributed data and Mann-Whitney tests for data not normally distributed. A p-value of 0.05 or less will be considered statistically significant.

4.7 Significance of the study

This study aims to determine anti-factor Xa levels to determine if the standard dose of enoxaparin 40 mg subcutaneously is adequate to achieve prophylactic levels in critically ill patients at CHBAH ICU. Should levels not be adequate the dose of enoxaparin should be adjusted in future patients. This may help decrease VTE complications, thereby increasing patient safety and decreasing hospital stay time.

4.8 Validity and reliability of the study

Validity refers to whether the conclusions made by the study are justified according to the design and interpretation (21). Reliability of a study refers to the consistency of data obtained from the patients over the study period (22).

Validity and reliability of the study will be ensured by:

- using an appropriate study design
- applying appropriate statistical testing and sample size calculations in consultation with a biostatistician
- using a standardised blood sample collection technique
- standardised storage and transport to the laboratory
- using a single laboratory, with good laboratory practice, to process blood samples to reduce the risk of error
- analysing data in consultation with a biostatistician.

4.9 Potential limitations

The study is limited to critically ill patients at CHBAH ICU and patient numbers may be difficult to achieve due the size of the ICU. Convenience sampling of patients is not random, so there may be an element of being bias (18). The study depends on nursing staff administrating the drug at 06:00.

The timing of the collection of blood samples may influence the results of anti-factor Xa levels. To decrease the probability of this occurring, a standardised technique has been described.

4.10 Project outline

4.10.1 Time frame

Activity	2019						2020			
	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Literature review										
Proposal preparation										
Proposal submission										
Ethics approval										
Postgraduate approval										
Data collection										
Data analysis										
Draft article										
Submission										

4.10.2 Budget

The University of the Witwatersrand Department of Anaesthesiology will incur the costs of paper and printing for the postgraduate application. The Critical Care Society of Southern Africa Research and Education fund and the Jan Pretorius Research fund will be approached for funding of the proposed M Med. If applications to these two funds are unsuccessful pharmaceutical companies will be approached. Any shortfall will be covered by the primary researcher.

Item	Price per page	Number of pages	Copies	Price per patient	Total
Proposal	1	15	10		R 150
Post graduate form	1	2	6		R 12
Complete report	1	100	4		R 400
Factor Xa assays				763.40	R 57 225
Grand total					**R 57 817**

4.11 References

1 Kopelman TR, Walters JW, Bogert JN, Basharat U, Pieri PG, Davis KM, et al. Goal directed enoxaparin dosing provides superior chemoprophylaxis against deep vein thrombosis. Injury. 2017;48(5):1088–92. https://doi.org/10.1016/j.injury.2016.10.039

2 Pannucci CJ, Prazak AM, Scheefer M. Utility of anti-factor Xa monitoring in surgical patients receiving prophylactic doses of enoxaparin for venous thromboembolism prophylaxis. Am. J. Surg. 2017;213(6):1143–1152. doi:10.1016/j.amjsurg.2016.08.010

3 Assareh H, Chen J, Ou L, Hollis SJ, Hillman K, Flabouris A. Rate of venous thromboembolism among surgical patients in Australian hospitals: A multicentre retrospective cohort study. BMJ Open. 2014;4(10):e005502. https://doi.org/10.1136/bmjopen-2014-005502

4 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis 2016;41(1):3–14. https://doi.org/10.1007/s11239-015-1311-6.

5 Barker RC, Marval P. Venous thromboembolism: Risks and prevention. BJA Educ. 2011;11(1):18–23. https://doi.org/10.1093/bjaceaccp/mkq044

6 Johnson SA, Eleazer GP, Rondina MT. Pathogenesis, diagnosis, and treatment of venous thromboembolism in older adults. J Am Geriatr Soc. 2016;64(9):1869–78. https://doi.org/10.1111/jgs.14279

7 Jacobson BF, Louw S, Büller H, Mer M, De Jong PR, Rowji P, et al. Venous Thromboembolism: Prophylactic and Therapeutic Practice Guideline. S Afr Med J. 2013;103(4):260. https://doi.org/10.7196/SAMJ.6706

8 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. Chest. 2008;133(6):381S-453S. https://doi.org/10.1378/chest.08-0656

9 Wei MY, Ward SM. The anti-factor Xa range for low molecular weight heparin thromboprophylaxis. Hematol Rep. 2015;7(4):80–83. https://doi.org/10.4081/hr.2015.5844

10 Heit, JA. Low molecular weight heparin: Biochemistry, pharmacology, and concurrent drug precautions. Reg Anesth Pain Med. 1998;23(6):135–139. https://doi:10.1016/s1098-7339(98)90138-9

11 Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: A review of the pharmacology, dosing, and complications. Curr Emerg Hosp Med Rep. 2013;1(2):83–97. https://doi.org/10.1007/s40138-013-0014-6

12 Hemker HC, Al Dieri R, Beguin S. Laboratory monitoring of low molecular weight heparin therapy part II. J Thromb Haemost. 2005;3(3):571–3. https://doi.org/10.1111/j.1538-7836.2005.01206.x

13 Linkins LA, Julian JA, Rischke J, Hirsh J, Weitz JI. In vitro comparison of the effect of heparin, enoxaparin and fondaparinux on tests of coagulation. Thromb Res. 2002;107(5):241–4. https://doi.org/10.1016/S0049-3848(02)00340-7

14 Zoccali C, Kramer A, Jager KJ. Chronic kidney disease and end-stage renal disease: A review produced to contribute to the report “the status of health in the European union: towards a healthier Europe.” Clin Kidney J. 2010;3(3):213–24. https://doi.org/10.1093/ndtplus/sfp127

15 National Health Act (No. 61 of 2003). Polity org za. https://www.polity.org.za/article/national-health-act-no-61-of-2003-2003-01-01 (Accessed July 30, 2019).

16 World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191. https://doi.org/10.1001/jama.2013.281053

17 Department Of Health. 2006. Guidelines for Good Practice In the Conduct of Clinical Trials with Human Participants in South Africa. Available:

http://www.kznhealth.gov.za/research/guideline2.pdf (Accessed July 30, 2019)

18 Brink H, Van Der Walt C, Van Rensburg C. Fundamentals of Research Methodology for Healthcare Professionals. 3rd ed. Cape Town. Juta. 2012

19 De Vos A, Strydom H, Fouche C, Poggenpoel M, Schurink E, Schurinck W. Research at Grass Roots: A primer for the caring professions. 2nd ed. Pretoria. Van Schaik. 2000.

20 Details. Beaumont Lab. https://www.beaumontlaboratory.com/lab-test-directory/details (accessed August 4, 2019).

21 Botma Y, Greef M, Mulaudizi F, Wright S. Research in Health Sciences.1st ed. Cape Town. Heinemann. 2010.

22 Burns N, Grove S. The Practice of Nursing Research: Appraisal, Synthesis and Generation of Evidence. 6th ed. Missouri. Saunders Elselvier. 2009.

4.12 Appendices

Appendix 1: Letter to the Medical Advisory Committee

To the Medical Advisory Committee

I am requesting permission to perform a research project for my Master in Medicine in Anaesthesia at Chris Hani Baragwanath Academic Hospital (CHBAH) intensive care unit (ICU). Access to patient information and a blood sample will be required for this study. The study was approved by the Graduate Studies Committee and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190833 MED19-08-050). The director of CHBAH ICU, Prof Mathivha, has also approved this study.

The title of my M Med is **Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital.**

I will be looking at veno-thromboembolism prophylaxis with the use of enoxaparin sodium to determine if the current guidelines recommendation provides adequate prophylaxis for all patients. This will be done by measuring anti-factor Xa levels. The blood samples will be measured by the National Health Laboratory Service at CHBAH. There will be no cost to the hospital or the ICU.

Adequate prophylaxis may help reduce ICU stay, morbidity and mortality by veno-thromboembolism in these patients.

Yours Faithfully

Dr Mayank Mukeshbhai Baloo

Registrar

Department of Anaesthesiology

083 528 0294

Appendix 2: Approval letter to conduct research at CHBAH ICU

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Prof L.R. Mathivha
Rudo.Mathivha@wits.ac.za
Tel: 0119381596
Fax:0119381595 Office Extension:0119330270

6th August 2019

To whom it may concern

Re: Permission to conduct research for MMed in Chris Hani Baragwanath Hospital Intensive Care unit

Title of research project:
Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital.

Investigator: Dr Mayank Mukeshbhai Baloo

Permission is hereby granted for Dr **Mayank Mukeshbhai Baloo**
to access ICU for the purpose of research data collection. The data collected will be used for his MMed.

Regards

Prof L.R. Mathivha
Head of Clinical Department: Intensive Care Unit
Chris Hani Baragwanath Hospital
Soweto
& University of the Witwatersrand

Appendix 3.1: Patient information letter

Dear Sir/Madam

My name is Mayank Mukeshbhai Baloo and I am a doctor at Chris Hani Baragwanath Academic Hospital. I am training to be an anaesthesiologist who is a doctor that puts people to sleep when they come for an operation. As part of my training I need to do a research study and I would like to invite you to be a part of my study.

Most patients in ICU are in bed and do no move a lot so blood clots can form in their legs. Patients that are very ill are admitted to the intensive care unit (ICU). These blood clots can travel to your hearts and lungs and can make them more ill. This is called a veno-thromboembolism. We do not want this to happen to you. To prevent this, we will give you an injection, which is normal practice, every morning under your skin, called enoxaparin.

We would like to do a blood test to see how much medicine is in your blood and is it enough to stop clots forming. We will need about 10 mls of blood which is about 2 teaspoons. We will try to take this blood from a drip that is already running and not prick you. If we cannot use the drip you have, we will need to take blood from a vein. This involves you getting a small prick. Taking your blood will only take 1 to 2 minutes.

It is your choice if you want to take part in my study or not. If you do not want to take part the treatment you receive will not change in any way. If you do agree to take part but change your mind later, you can tell us, and we will not use your blood. There is no cost to you if you take part in this study. We will not know the results of your blood test immediately so you will not benefit from this study, but it will allow us to help other patients in the future.

Some of your personal information will be collected but it will be kept private and stored under lock and key and no one will know your name. If you agree to take part in this study, I will ask you to sign a consent form.

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190833 MED19-08-050). They make sure there is no harm to you. If you wish to contact them, the details are as follows: Professor Penny (chairperson) can be contacted on telephone number 011 717 2301 or by email on Clement.Penny@wits.ac.za, the committee secretariats on telephone numbers 011 717 2700/1234 and the email addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mkansi@wits.ac.za. If you have any questions and wish to contact me, my telephone number is 011 933 9335.

Thank you for taking the time to read this letter.

Dr Mayank Mukeshbhai Baloo

Appendix 3.2: Patient consent form

Consent to participate in the study titled: Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

I have read the information sheet attached or it has been explained and read to me. I had a chance to ask questions and any questions that I may have had, have been answered to my satisfaction. If any more questions arise, I have been given contact details of the people to ask. I understand that my personal information will be kept private. I hereby give my consent voluntarily to participate in this study. I consent to my blood being taken and tested for anti-factor Xa levels.

Print name of participant _____

Signature _____

Date (day/month/year) _____

Print name of witness _____

Signature _____

Date (day/month/year) _____

I as the researcher/individual taking consent have accurately read out the information sheet explained the study to the patient to the best of my ability. I have explained that the study may have no direct benefit to the patient but may help patients in the future. I confirm that the patient had ample time to ask questions and any questions that may have arisen have been answered. I confirm that consent has been given freely and voluntarily.

Print name of researcher/individual taking consent

Signature of researcher/individual taking consent

Date (day/month/year)

Appendix 4.1: Family information letter

Dear Sir/Madam

My name is Mayank Mukeshbhai Baloo and I am a doctor at Chris Hani Baragwanath Academic Hospital. I am training to be an anaesthesiologist who is a doctor that puts people to sleep when they come for an operation. As part of my training I need to do a research study and I would like to invite your family member to be a part of my study.

Most patients in ICU are in bed and do no move a lot so blood clots can form in their legs. Patients that are very ill are admitted to the intensive care unit (ICU). These blood clots can travel to your hearts and lungs and can make them more ill. This is called a veno-thromboembolism. We do not want this to happen to your family member. To prevent this, ICU staff will give your family member an injection, which is normal practice, every morning under their skin, called enoxaparin.

We would like to do a blood test to see how much medicine is in your family member's blood and is it enough to stop clots forming. We will need about 10 mls of blood which is about 2 teaspoons. We will try to take this blood from a drip that is already running and not prick your family member. If we cannot use the drip they have, we will need to take blood from a vein. This involves your family member getting a small prick. Taking their blood will only take 1 to 2 minutes.

It is your choice if you want your family member to take part in my study or not. If you do not want your family member take part, the treatment they receive will not change in any way. If you do agree to take part on their behalf but change your mind later, you can tell us, and we will not use your family member's blood. There is no cost to you or your family member if they take part in this study. We will not know the results of their blood test immediately so your family member will not benefit from this study, but it will allow us to help other patients in the future.

Some of your family member's personal information will be collected but it will be kept private and stored under lock and key and no one will know their name. If you

agree to take part in this study on their behalf, I will ask you to sign a consent form.

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190833 MED19-08-050). They make sure there will be no harm to your family member. If you wish to contact them, the details are as follows: Professor Penny (chairperson) can be contacted on telephone number 011 717 2301 or by email on Clement.Penny@wits.ac.za, the committee secretariats on telephone numbers 011 717 2700/1234 and the email addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mkansi@wits.ac.za. If you have any questions and wish to contact me, my telephone number is 011 933 9335.

Thank you for taking the time to read this letter.

Dr Mayank Mukeshbhai Baloo

Appendix 4.2: Family member's consent form on behalf of the patient

Consent to participate in the study titled: Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

I have read the information sheet attached or it has been explained and read to me. I had a chance to ask questions and any questions that I may have had, have been answered to my satisfaction. If any more questions arise, I have been given contact details of the people to ask. I understand that my family member's information will be kept private. I hereby give consent on behalf of my family member voluntarily to participate in this study. I consent to my family member's blood being taken and tested for anti-factor Xa levels.

Print name of participant _____

Signature _____

Date (day/month/year) _____

Print name of witness _____

Signature _____

Date (day/month/year) _____

I as the researcher/individual taking consent have accurately read out the information sheet explained the study to the family member to the best of my ability. I have explained that the study may have no direct benefit to the family member involved but may help patients in the future. I confirm that the family

member had ample time to ask questions and any questions that may have arisen have been answered. I confirm that consent has been given freely and voluntarily.

Print name of researcher/individual taking consent

_____

Signature of researcher/individual taking consent

Date (day/month/year) _____

_____

Appendix 5.1: Patient information letter post family consent

Dear Sir/Madam

My name is Mayank Mukeshbhai Baloo and I am a doctor at Chris Hani Baragwanath Academic Hospital. I am training to be an anaesthesiologist who is a doctor that puts people to sleep when they come for an operation. As part of my training I need to do a research study and I would like to invite you to be a part of my study.

Most patients in ICU are in bed and do no move a lot so blood clots can form in their legs. Patients that are very ill are admitted to the intensive care unit (ICU). These blood clots can travel to your hearts and lungs and can make them more ill. This is called a veno-thromboembolism. We do not want this to happen to you. To prevent this, we will give you an injection, which is normal practice, every morning under your skin, called enoxaparin.

We would like to do a blood test to see how much medicine is in your blood and is it enough to stop clots forming. We will need about 10 mls of blood which is about 2 teaspoons. We will try to take this blood from a drip that is already running and not prick you. If we cannot use the drip you have, we will need to take blood from a vein. This involves you getting a small prick. Taking your blood will only take 1 to 2 minutes.

Your family member has already given consent on your behalf. It is your choice if you want to take part in my study or not. If you do not want to take part the treatment you receive will not change in any way. If you do agree to take part but change your mind later, you can tell us, and we will not use your blood. There is no cost to you if you take part in this study. We will not know the results of your blood test immediately so you will not benefit from this study, but it will allow us to help other patients in the future.

Some of your personal information will be collected but it will be kept private and stored under lock and key and no one will know your name. If you agree to take part in this study, I will ask you to sign a consent form.

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M190833 MED19-08-050). They make sure there is no harm to you. If you wish to contact them, the details are as follows: Professor Penny (chairperson) can be contacted on telephone number 011 717 2301 or by email on Clement.Penny@wits.ac.za, the committee secretariats on telephone numbers 011 717 2700/1234 and the email addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mkansi@wits.ac.za. If you have any questions and wish to contact me, my telephone number is 011 933 9335.

Thank you for taking the time to read this letter.

Dr Mayank Mukeshbhai Baloo

Appendix 5.2: Patient deferred consent form

Consent to participate in the study titled: Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

I have read the information sheet attached or it has been explained and read to me. I had a chance to ask questions and any questions that I may have had, have been answered to my satisfaction. If any more questions arise, I have been given contact details of the people to ask. I understand that my personal information will be kept private. I understand that consent has been given previously on my behalf. I hereby give my consent voluntarily to participate in this study. I consent to my blood being taken and tested for anti-factor Xa levels.

Print name of participant _____

Signature _____

Date (day/month/year) _____

Print name of witness _____

Signature _____

Date (day/month/year) _____

I as the researcher/individual taking consent have accurately read out the information sheet explained the study to the patient to the best of my ability. I have explained that the study may have no direct benefit to the patient but may help patients in the future. I confirm that the patient had ample time to ask questions and any questions that may have arisen have been answered. I confirm that consent has been given freely and voluntarily.

Print name of researcher/individual taking consent

Signature of researcher/individual taking consent

Date (day/month/year)

Appendix 6: Data collection sheet

Patient Number:

_____

Anti-factor Xa level	
Age	
Sex	
Weight	
Body mass index (BMI)	
Total bilirubin	
Serum albumin	
Severity of illness (APACHE II)	

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr M Baloo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190833

NAME: (Principal Investigator)	Dr M Baloo
DEPARTMENT:	School of Clinical Medicine Department of Anaesthesiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Factor Xa levels in patients receiving prophylatic enoxaparin sodium in the intensive care unit of an academic hospital
DATE CONSIDERED:	2019/08/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof J Scribante; Dr D Calleemalay; Ms H Perrie
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/10/31

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore reports and re-certification will be due early in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 01 November 2019

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

5.2 Permission to conduct research

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 8th October 2019

TITLE OF PROJECT:

Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr MM Baloo

Department: Anaesthesiology

Supervisor : Prof J Scribante

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 8/10/2019

Approved/~~Not Approved~~
Hospital Management
Date: 09/10/2019

5.3 Graduate studies approval

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

19 September 2019
Person No: 0600471N
PAG

Dr MM Baloo
P.o.box 1981
Brooklyn Square
0001
South Africa

Dear Dr Mayank Baloo

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Factors Xa levels in patients receiving prohylactic enoxaparin sodium in the intensive care unit of an academic hospital.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.4 Turnitin report

0600471n:For_Turn_it_In.docx

ORIGINALITY REPORT

11%	8%	8%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.mdcalc.com Internet Source	3%
2	docshare.tips Internet Source	1%
3	Submitted to Aga Khan University Student Paper	1%
4	"Abstracts", Journal of Thrombosis and Haemostasis, 2015. Publication	1%
5	Submitted to University of Arizona Student Paper	1%
6	journals.sagepub.com Internet Source	1%
7	link.springer.com Internet Source	1%
8	Submitted to Queen's University of Belfast Student Paper	1%
9	"Oral Anticoagulation Therapy", Springer	

Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital

10 November 2020

The Chairperson
Graduate Studies Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Professor Papathanasopoulos

Re: M Med: **Factor Xa levels in patients receiving prophylactic enoxaparin sodium in the intensive care unit of an academic hospital**

Dr Mayank Baloo, student number: 0600471N, has submitted his research report to Turnitin, which revealed a similarity index of 11%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the research topic.

Yours sincerely,

Juan Scribante
Supervisor