Heparin-induced Thrombocytopenia Monitoring in Postoperative Orthopedic Patients who Received Prophylactic Enoxaparin at Gezira Center for Trauma and Orthopedic Surgery in Wad-Medani, Sudan

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Supervision Committee:

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**Declaration**

I declare that none of the work done in this dissertation has been submitted in support of application for another degree or qualification at this or any other university or institution and it has been done at university of Gezira, Sudan.

Signature

Wafaa Mustafa Abdelrahman Mohammed
Dedication

To the loving memory of my father, it has been 17 years and yet it feels like yesterday

To my mother for her unconditional love and huge sacrifices

To my brother for his endless support

To my grandfather and my uncle who kept encouraging me to the last moment until they left our world in the past few months

To my friends and the rest of my family for being there for me
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As a final word, I would like to thank anyone who has been a source of support and helped me in completing my research successfully.
Heparin-induced Thrombocytopenia Monitoring in Postoperative Orthopedic Patients who Received Prophylactic Enoxaparin at Gezira Center for Trauma and Orthopedic Surgery in Wad-Medani, Sudan

Wafaa Mustafa Abdelrahman Mohammed

Abstract

Low molecular weight heparin can cause a serious adverse effect called heparin-induced thrombocytopenia (HIT). Monitoring of platelet count and awareness about the condition are important in early detection and in prevention of the potential thromboembolic consequences. To study the monitoring protocol of HIT in postoperative orthopedic patients who received prophylactic enoxaparin and also to explore awareness of orthopedic surgeons about HIT at Gezira center for trauma and orthopedic surgery. Fifty patients met the inclusion criteria were investigated for the performance of platelet count test for monitoring of HIT before, during and after enoxaparin use. Thereafter, ten orthopedic surgeons working at Gezira center for trauma and orthopedic surgery were interviewed to explore their awareness about HIT and its monitoring. Monitoring for platelet count before the administration of enoxaparin was done in 66% of the patients and no monitoring was done during enoxaparin use and after attending referral clinics for follow up. All of the orthopedic surgeons who were interviewed could not recognize HIT as an adverse effect of enoxaparin. Five orthopedic surgeons observed thrombosis cases in patients receiving enoxaparin before but believed it to be related to other risk factors other than HIT. The absence of monitoring of platelet count and the lack of awareness of heparin-induced thrombocytopenia among orthopedic surgeons may prevent recognition and diagnosis of the condition which in turn affects patients’ lives. Guidelines and training on heparin-induced thrombocytopenia monitoring need to put in place.
مراقبة نقص الصفائح الناجم عن الهيبارين في مرضى العظام بعد الجراحة

الذين تلقوا إنوكسابارين الوقائي في مركز الجزيرة للإصابات وجريدة العظام بود مدني، السودان

伍اء مصطفى عبد الرحمن محمد

ملخص الدراسة

الهيبارين ذو الوزن الجزيئي المنخفض يمكن أن يسبب أثر جانبي خطير يسمى نقص الصفائح الناجم عن الهيبارين. مراقبة تعداد الصفائح الدموية والوعي حول الحالة مهمان في الكشف المبكر وفي منع العواقب الخطيرة المحتملة. لدراسة بروتوكول مراقبة نقص الصفائح الناجم عن الهيبارين لمرضى العظام بعد الجراحة الذين تلقوا إنوكسابارين الوقائي وأيضاً لاستكشاف وعي جراحى العظام حول نقص الصفائح الناجم عن الهيبارين في مركز الجزيرة للإصابات وجريدة العظام. تم النقصي لخمسين مريضاً استوفوا شروط الإدخال عن أداء اختبار تعداد الصفائح الدموية لمراقبة نقص الصفائح الناجم عن الهيبارين قبل وأثناء وبعد استخدام إنوكسابارين. بعد ذلك، تمت مقابلة عشرة جراحى عظام يعملون في مركز الجزيرة للإصابات وجريدة العظام لاستكشاف وعيهم عن نقص الصفائح الناجم عن الهيبارين. تمت مراقبة تعداد الصفائح الدموية قبل إعطاء إناكسابارين في 66% من المرضى، ولم يتم إجراء أي مراقبة أثناء استخدام إنوكسابارين وبعد حضور العيادات المحولة للمتابعة. كل جراحى العظام الذين تمت مقابلتهم لم يستطيعوا التعرف على نقص الصفائح الناجم عن الهيبارين كأثر جانبي لانوكسابارين. خمسة جراحى عظام لاحظوا حالات خطر من قبل في مرضى متلقين لانوكسابارين ولكنهم اعتقدوا أنها مرتبطة بعوامل خطر أخرى غير نقص الصفائح الناجم عن الهيبارين. غياب مراقبة تعداد الصفائح الدموية وعدم وجود وعي حول نقص الصفائح الناجم عن الهيبارين بين جراحى العظام قد يمنع تطبيق وتشخيص الحالة والذي بدوره يؤثر على حياة المرضى. التوجيهات القياسية والتدريب على مراقبة نقص الصفائح الناجم عن الهيبارين في حاجة إلى التنفيذ.
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<tr>
<td>ACCP</td>
<td>American College of Chest Physicians</td>
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<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
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<td>DVT</td>
<td>Deep Vein Thrombosis</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>HIPA</td>
<td>Heparin-induced Platelet Activation Assay</td>
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<tr>
<td>HIT</td>
<td>Heparin-Induced Thrombocytopenia</td>
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<tr>
<td>HITT</td>
<td>Heparin-Induced Thrombocytopenia With Thrombosis</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<tr>
<td>LMW-HIT</td>
<td>Low Molecular weight Heparin-Induced Thrombocytopenia</td>
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<tr>
<td>PE</td>
<td>Pulmonary Embolism</td>
</tr>
<tr>
<td>PF4</td>
<td>platelet factor 4</td>
</tr>
<tr>
<td>TECs</td>
<td>Thromboembolic Complications</td>
</tr>
<tr>
<td>THR</td>
<td>Total Hip Replacement</td>
</tr>
<tr>
<td>TKR</td>
<td>Total Knee Replacement</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated Heparin</td>
</tr>
<tr>
<td>UF-HIT</td>
<td>Unfractionated Heparin-Induced Thrombocytopenia</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous Thromboembolism</td>
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Chapter One

1. Introduction
1. Introduction

1.1. Background

Orthopedic surgical procedures are widely known to cause venous thromboembolism (VTE) as a postoperative complication such as deep vein thrombosis (DVT) and pulmonary embolism (PE). Major orthopedic surgery and trauma are both considered risk factors for developing VTE (Lapidus, 2007). VTE occurs due to the activation of the clotting cascade and the promotion of endothelial injury during surgery. The immobility state that follows the surgery, the advanced age and obesity also contribute in increasing the risk of VTE (Muntz, 2009). The incidence of VTE in orthopedic patients who do not receive thromboprophylaxis may occur up to 60% of patients within 2 weeks after lower extremity orthopedic surgery (Kakkar et al., 2013), it is also estimated to be around 40% - 70% and occurs within 7-14 days postoperatively (Muntz, 2009). Because the patients who undergo major orthopedic surgery of lower extremities belong to a very high risk group for VTE: they are candidates for high risk thromboprophylaxis (Eichinger et al, 2004). Hence, the use of pharmacologic thromboprophylaxis has shown remarkable reduction in the risk for developing VTE. (ACCP, 2012; Muntz, 2009). Low molecular weight heparins (LMWHs) are the most common anticoagulant agents that are used in the prophylaxis of VTE in orthopedic surgery. They have been studied extensively in this area especially enoxaparin and they have been compared to unfractionated heparin (UFH) and Warafrin. These studies have demonstrated the selectivity, the efficacy and the safety of LMWHs compared to other anticoagulant alternatives. However, UFH and LMWHs share a common serious adverse drug reaction called heparin-induced thrombocytopenia (HIT) (Gray et al., 2008).

1.2. Heparin-Induced Thrombocytopenia

HIT is an immune mediated reaction that occurs due to heparin exposure. It is a clinical pathological condition that is characterized by a decrease in platelet count below the normal range which is 150,000 – 450,000 per cubic milliliter (Cooney, 2006). The degree of the thrombocytopenia determines the incidence of HIT: a sudden fall in platelet
count by 50% or more from the baseline indicates an incidence of HIT, it typically occurs within 5-14 days after initiation of heparin (Gupta et al., 2008; Cooney, 2006). HIT is a serious and potentially life threatening condition because it can lead to thrombotic complications that occur in 30% - 70% of the cases such as deep vein thrombosis (DVT) and pulmonary embolism (PE) (Cervellione et al., 2012). HIT occurs due to the binding of the negatively-charged heparin compound to platelet factor 4 (PF4) to form heparin/PF4 complexes. These complexes initiate an immune response which leads to platelet activation, platelet aggregation and thrombotic state (Franchini, 2005). The length of the heparin molecule is proportionally linked to the incidence of HIT; the longer the chain of the molecule, the more it wraps more PF4 particles which explains the increased risk with UFH compared to LMWHs (Shaikh, 2011). Additionally, patients who have been exposed to heparin in the past three months are more susceptible and can develop HIT more rapidly due to the presence of antibodies (Gupta et al., 2008). HIT can be unpredictable among patients, but there are a few risk factors to be considered: patients who receive UFH for instance are more susceptible than those who receive LMWHs, the severity of the trauma is also a risk factor; major trauma is more risky than minor trauma (Warkentin, 2012). Age and gender are other important risk factors; patients older than 40 years of age are more susceptible and female patients develop HIT more than male patients. Also, surgical patients are at higher risk than medical and obstetric patients (Shantsila et al., 2009; Warkentin et al., 2006). Duration of heparin use is also an important risk factor; patients who use heparin for six days and more are more likely to develop HIT (Cervellione et al., 2012; Martel et al., 2005).

1.3. Diagnosis of Heparin-Induced Thrombocytopenia

The diagnosis of HIT has two main components. First, the monitoring of platelet count for early detection of HIT and second, the performance of immunological assays to confirm the incidence of HIT (Gupta et al., 2008; Cooney, 2006). Monitoring of platelet count is very substantial, in order to determine the timing and the severity of thrombocytopenia that pinpoints HIT (ACCP, 2012). The timing of platelet drop occurs between day 5 and day 14 of heparin treatment in patients, who have not been exposed previously to heparin, the severity of thrombocytopenia is described by an unexplained
drop in platelet count by 50% or more from the baseline after initiation of heparin therapy (LaMuraglia et al., 2011). A diagnostic algorithm has been developed to provide more accurate diagnosis to exclude any other causes of thrombocytopenia. It is a systematic approach called the “4Ts” probability system. This system is based on four main points; the degree of thrombocytopenia, the timing of the platelet count drop, the presence of thrombosis, and the exclusion of other causes of thrombocytopenia. Each point has a score that classifies the patients into three categories, high risk, intermediate risk and low risk (Cuker et al., 2012). The second component of the diagnosis is the immunological assays which are performed to detect the presence of Heparin/PF4 antibodies after applying the “4Ts” scoring system that suspects the incidence of HIT. There are two groups of tests which are available: the first one is the antigen test which consists of ELISA test that detects anti-PF4/heparin antibodies. The other test is the particle gel immunoassay that also detects the presence of antibodies by binding of the PF4Heparin complex to red high-density polystyrene beads. The second group is the washed platelet assays which consist of the serotonin release test and heparin-induced platelet activation assay (HIPA), both of these tests detect the platelet activation and aggregation in the patient’s serum. (Leo et al., 2003).

1.4. Awareness about Heparin-Induced Thrombocytopenia

Thromboembolic consequences of HIT are significantly reduced when it is diagnosed and treated as recommended by evidence-based guidelines. The guidelines recommend that, HIT should be suspected in a patient who develops thrombosis or thrombocytopenia 5 - 14 days after heparin initiation (Keeling et al., 2006). In many cases, HIT is related to the thrombosis in a recently hospitalized or heparin-exposed patient but little is known about HIT awareness and practices in emergency departments (Levine et al., 2004). Generally, there is a gap between HIT guidelines and clinical practice for heparin exposed hospitalized patients. This indicates a lack of awareness among medical practitioners about the serious complications of HIT (Crespo et al., 2009). Increasing the awareness of HIT among practitioners is essential in early recognition and documentation of HIT and it can be achieved by developing clinical approaches to facilitate efficient and accurate HIT risk assessment (Levine et al., 2010).
1.5. Rationale

Low molecular weight heparins (LMWHs) have been used frequently in the past decades as a thromboprophylactic measure in surgical and hospitalized patients to reduce the risk of venous thromboembolism (VTE) after surgery (Gray et al., 2008). Orthopedic surgery requires thromboprophylaxis due to the high risk of VTE that may occur postoperatively. However, thromboprophylaxis using LMWHs results in the paradoxical effect of heparin-induced thrombocytopenia (HIT) that may lead to devastating thrombotic events. Despite being rare, HIT is considered a serious and a life-threatening condition and it is associated with significant increase in morbidity, disability and mortality (DiGiovanni, 2008). Therefore, the role of HIT monitoring is very crucial in early detection and diagnosis of the condition. Regular monitoring of platelet count during the use of heparin is recommended by evidence based clinical practice guidelines. The frequency of platelet count monitoring recommended by American College of Chest Physicians (ACCP) guidelines depends on the risk factors involved. Early platelet count monitoring allows further clinical assessment to be made if HIT is suspected (ACCP, 2012).
1.6. Objectives
1.6.1. General Objective

To investigate monitoring of heparin-induced thrombocytopenia in postoperative orthopedic patients who received prophylactic enoxaparin and to explore the awareness of orthopedic surgeons about HIT at Gezira center for trauma and orthopedic surgery in Wad-Medani.

1.6.2. Specific Objectives

1- To determine the performance of baseline platelet count for included patients.
2- To determine the performance of platelet count during enoxaparin use.
3- To determine the performance of platelet count in the first post-discharge follow up.
4- To determine awareness about HIT and HIT monitoring among orthopedic surgeon.
5- To highlight the unrecognized area of HIT among orthopedic surgeons.
Chapter Two

2. Literature Review
2. Literature Review

2.1. Use of LMWHs in Orthopedics

The incidence of venous thromboembolism (VTE) is very common in orthopedic patients who undergo major surgical operations like total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery in the absence of thromboprophylaxis (Kakkar et al., 2013). Low molecular weight heparins (LMWHs) are currently the mainstay in orthopedic thromboprophylaxis to reduce VTE following orthopedic surgery and they have replaced unfractionated heparin (UFH) in clinical practice due to their efficacy, safety and ease of administration (Solayar et al., 2014). In the USA, (Kalyani et al., 2011) reviewed the most recent evidence-based practice guidelines for the most current recommendations for the application of LMWHs in orthopaedic surgery. Thirty five prospective and randomized controlled clinical studies were identified; they compared LMWHs with other treatments in orthopaedic surgery patients. The studies assessed the efficacy of LMWH thromboprophylaxis following orthopaedic surgery in comparison with placebo and other prophylactic treatments. The results showed clinical significant reduction in VTE following THR, TKR and hip fracture surgery. However, these studies demonstrated the clear supporting evidence for the application of LMWHs for thromboprophylaxis in orthopaedic surgery.

2.2. Incidence of Heparin-Induced Thrombocytopenia

UFH and LMWHs can cause HIT with varying incidence, being higher with UFH therapy compared to LMWHs therapy (Shaikh, 2011). UFH and LMWHs are structurally different; these differences, somehow affect the incidence of HIT: the extent of binding of heparins and platelet factor 4 depends on heparin’s chain length and molecular weight (Gray et al., 2008). This resultant complex of binding produces antibodies that activate platelet causing thrombocytopenia and thrombotic state (Franchini, 2005). LMWHs have a less frequent incidence of HIT by 2 - 3 fold compared to thrombocytopenia-induced by UFH (UF-HIT). However, thrombocytopenia-induced by LMWH (LMW-HIT) is considered as severe as HIT resulting from UFH, in terms of thrombocytopenia,
thrombosis, and death. The difference is; LMWH-HIT has longer onset of symptoms, more severe thrombocytopenia, and longer platelet recovery (Walenga et al., 2005).

2.3. Incidence of HIT with the Use of UFH

HIT is the most significant immune mediated-drug thrombocytopenia that may cause venous and arterial thrombosis: several studies have been conducted to determine the incidence of HIT with both UFH and LMWHs (Franchini, 2005). In Germany, (Girolami et al., 2003) reported an incidence of HIT in hospitalized medical patients treated with subcutaneous UFH. The study included 598 patients who received prophylactic and therapeutic doses of UFH. The baseline platelet count was performed and then repeated every 1-3 days after UFH administration. Patients were diagnosed with HIT when there was a 50% or more drop in platelet count occurred and patients tested positive for HIT. HIT developed in 5 patients who received UFH for prophylactic indications and thromboembolic complications (TECs) occurred in 60% of the cases. These findings suggested the prevalence of HIT with the use of UFH in medical patients and the high rate of TECs.

2.4. Incidence of HIT with the Use of LMWHs

Incidence of HIT in patients using UFH is generally higher than in those who use LMWHs, but it is clear that HIT still can occur with LMWHs. This incidence has been documented in the few past decades (Gray et al., 2008). In Italy, (Prandoni et al., 2005) determined an incidence of HIT prospectively in both hospitalized and non-hospitalized medical patients. These patients received prophylactic and therapeutic doses of LMWHs. 1754 patients with normal platelet count and no previous exposures to heparin were enrolled in the study. The baseline platelet count was performed and thereafter at least every 2 or 3 days of LMWH administration. The study confirmed the incidence of HIT in 14 patients within the first two weeks. HIT was more frequent in patients who had been exposed previously to UFH or LMWH (1.7%) than in those who had not (0.3%). The study findings suggested that the frequency of LMW-HIT is not different from UF-HIT. (Giuliani et al., 2015) in Italy reported a case of HIT in a single patient treated with
enoxaparin in intensive care unit (ICU). The patient was a 63 year old woman that brought to ICU because of worsening respiratory failure in an underlying severe pancreatitis. The patient was on enoxaparin 4000 IU daily for 10 days after surgical operation. HIT was diagnosed with a detailed platelet count analysis over the time and with detection of platelet antibodies. The recovery of platelet count after discontinuation of enoxaparin strongly supports the diagnosis of HIT. These report findings suggested that although HIT is more frequent in patients treated with UFH, but it can also be induced by LMWHs.

### 2.5. Incidence of HIT with the Use of Both UFH & LMWHs

HIT is more common in patients receiving UFH than in patients receiving LMWHs: numerous studies have been performed to compare the incidence of HIT with both types of heparin (Warkentin et al., 2003). In Canada (Martel et al., 2005) determined an incidence of HIT in surgical and medical patients receiving thromboprophylaxis with either UFH or LMWH. Fifteen studies were included (7287 patients); most studies were of patients after orthopedic surgery. The analysis of all included studies showed HIT is more common with UFH compared to LMWH. The absolute risk for HIT with LMWH was 0.2% and with UFH the risk was 2.6%. A similar study was done in Brazil, in which (Junqueira et al., 2012) compared the incidence of HIT in surgical patients exposed to prophylactic UFH versus patients exposed to prophylactic LMWH. Among 923 participants, 17 patients developed HIT. The study results showed that there was a 76% relative risk reduction in developing HIT in patients used LMWH compared to patients used UFH. A recent and single study has been done in Sudan in which, (Hemadi et al., 2014) investigated the frequency of HIT among pregnant women who received UFH and LMWH in Al -Dayat labor hospital. The study compared the incidence of HIT in UFH versus LMWH in order to determine the risk of developing HIT with the type of heparin. One hundred and sixty five pregnant women included and divided into two groups, one hundred and fifteen pregnant women received UFH and fifty pregnant ladies received LMWHs. All patients had normal baseline platelet count upon inclusion. Platelet count was performed on day 7 of heparin administration. The study documented the incidence of HIT among 165 patients (10.3 %) of the study group; all of them belonged to the UFH group. Another recent study
conducted in Saudi Arabia by (Al-Eidan, 2015) concerning the rising incidence of HIT. The study retrospectively analyzed the positive HIT hospitalized patients during the period from January 2011 to December 2013. The study compared the incidence between the use of UFH and LMWH. The study findings reveled 4.09 per thousand incidence of HIT in UFH exposed patients and 0.48 per thousand in patients exposed to LMWH. In France (Gruel et al., 2003) investigated the incidence of thrombocytopenia associated with LMWHs which is less reported than the one induced by UFH. The study was carried out in 15 French centers, in which 180 patients were suspected for HIT. HIT was confirmed in 59 patients. 11 of them were received exclusively LMWH and 48 received UFH either alone or combined with LMWH. The severity of the thrombocytopenia and the length of the interval of HIT were more frequent in LMW-HIT group. The study finding reveled that; thrombocytopenia associated with LMWHs is severe and observed after a long time use and therefore the platelet count monitoring is highly recommended whenever LMWH is administered. Also, (Tian et al., 2009) in China determined the incidence of HIT among 202 patients who received LMWH and/or UFH. HIT occurred in 6 patients and the incidence we estimated to be 2.97%. HIT occurred between days 3 and 9. The study suggested a regular measuring of platelet count in patients receiving regular LMWH and/or UFH therapy and discontinuation of heparin therapy whenever a 50% drop in platelet count is observed. In Greece (Dailiana et al., 2007) reported an incidence of HIT in two patients received LMWH for prophylaxis and suffered from arterial thromboses after postoperative administration of LMWH. Thrombocytopenia was observed on day 4-7 postoperatively. The two patients showed a sign of arterial occlusions on day 9 and 10 postoperatively. The findings of this study indicate the importance of the early recognition of the syndrome by monitoring daily platelet counts during heparin therapy. In Switzerland, (Crespo et al., 2009) investigated HIT in 3,536 patients received any form of heparin. Thrombocytopenia occurred in 36.4% of patients and it was associated with an increased risk of thromboembolic complications or death. The study reveled that, despite the risk for HIT was high, the suspicion was uncommon and the patients were not evaluated until they had a thromboembolic complication. These findings suggested that
recognition and appropriate treatment for HIT was infrequent and delayed despite the presence of high risk for it.

2.6. Incidence of HIT in Orthopedic Patients

Postoperative orthopedic patients who receive heparin thromboprophylaxis are susceptible for developing HIT and its complications (Patel et al., 2007). HIT is a frequently unrecognized complication after major orthopedic surgery; it leads to potentially life threatening complications. The rate of mortality is estimated to be 30% and the estimated amputation rate is 20% (Picker et al., 2004). A study was conducted in Canada, in which (Warkentin et al., 2003) determined an improved definition of thrombocytopenia indicating HIT and investigated the frequency of HIT in postoperative orthopedic patients who received UFH or LMWH after elective hip arthroplasty. HIT was diagnosed by performing daily platelet count and detecting HIT antibodies. The study results showed that; the frequency of HIT was higher in patients received UFH compared to patients received LMWH (4.8% vs. 0.6%). It also defined a 50% or greater fall in the platelet count is a sensitive definition indicating possible HIT. (Happe et al., 2008) in the USA reported an incidence of thrombocytopenia in patients following major orthopaedic surgeries who received heparins (enoxaparin, dalteparin, and UFH) in comparison with patients who had not receive any prophylaxis. The incidence of thrombocytopenia was 1.7% in patients who received heparins and 1.0% who had not. The study suggested that the risk of thrombocytopenia is significantly increased in heparin patients group after major orthopaedic surgeries. (Mumoli et al., 2008) in Italy reported a case of HIT in a postoperative orthopedic patient associated with LMWH. The patient was a 75 year old woman who was admitted because of multiple fractures of the leg and pelvis after a road accident. The patient developed thrombocytopenia after 11 days of therapy with LMWH (Nadroparin). Nadroparin was begun on the first hospital day, 9 days after admission the patient underwent surgical repair of fractures; the platelet count was normal. 4 days after the surgical procedure, sudden dyspnea with worsening clinical status developed. The orthopedic surgeons raised the suspicion of pulmonary embolism. HIT was diagnosed with
laboratory examination that showed markedly decreased platelet (207,000/μL – 37,000/μL) and enzyme immunoassay that tested positive. The patients immediately treated once HIT was detected. This report demonstrates the incidence of HIT with LMWH although it is less common than with UFH. It also indicates the female gender and the surgery are important risk factor for HIT. (Lilikakis et al., 2007) reported 2 cases of HIT and their complication with the use of enoxaparin in 2 patients undergoing total hip replacement (THR) at the orthopaedic department in Greece. The first case was 46 year old female who had osteoarthritis of the hip. The patient was undergone THR and received a prophylactic dose of 40 mg of enoxaparin once daily. The platelet count was 126,000/mm3 and 10 days postoperatively it fell to 35,000 and paresis developed in the left arm. The enoxaparin was discontinued, but tests for antibodies to heparin were not performed. Later the investigations revealed bilateral hemorrhages that lead to rapid deterioration in her neurological status and died later the same day. The second reported case was a 47 year-old female who had osteoarthritis of the left hip with no history of coagulopathy. Total hip arthroplasty was performed and she received a regimen of 40 mg of enoxaparin once daily. After she had been discharged, she returned to the hospital on the 13th postoperatively with sensory disorders of the left arm. The platelet count was 70,000 and it kept decreasing gradually reaching 40,000. The enoxaparin was discontinued, and the presence of antibodies to heparin was investigated and confirmed. Paresis of the arms and legs developed progressively as a result of large cerebral hemorrhages. After 45 days in the intensive care unit, the patient was discharged but was quadriparetic. These two reports findings indicate that the occurrence of HIT are more frequent in orthopaedic patients than it is currently believed and it lead to increased morbidity and mortality. It also suggested that HIT is under-diagnosed which reflects a lack of awareness about the condition among orthopaedic surgeons, which necessitates clinical alertness and laboratory confirmation in order to prevent serious complications of HIT.

2.7. Risk for Developing Heparin-Induced Thrombocytopenia

Postoperative orthopedic patients appear to be at higher risk for thrombosis, with an incidence of 3% to 5% with UFH and 0.9% with LMWH. The clinical presentation of the
patient, the type of heparin (UFH or LMWH) and the duration of heparin exposure are also involved in the incidence of HIT (LaMuraglia et al., 2011). Postoperative patients (trauma and orthopedic patients) who are exposed to heparin they are considered to be at higher risk than medical patients, the respective incident rates of which are 2-5% and 0.8-3%. As well as, HIT develop more frequently in patients who received LMWH who had been exposed to UFH in the past three months than in those who had not. Postoperative orthopedic patients appear to be at higher risk than obstetrical patients and long term hemodialysis patients (Arepally et al., 2006). In Germany (Warkentin et al., 2006) investigated the frequency of HIT in cardiac and orthopedic postoperative patients and evaluated the influence of gender, type of heparin (UFH vs. LMWH) and patient’s type (surgical vs. medical) in a large systematic review. The study findings revealed an overrepresentation of females which suggests that females are at greater risk for HIT. The study also demonstrated a 3-fold greater risk among surgical than medical patients and higher incidence of HIT in UFH exposed patients more than LMWH exposed patients. In the USA (Kato et al., 2011) identified the risk factors that may be associated with HIT in medical patients received heparin. The study concluded 25653 patients who received heparin (UFH or LMWH). HIT was diagnosed by the 50% drop in platelet count and by serological assays. HIT was observed in 55 patients during the study period. The study findings suggested that patients who receive heparin for more than 5 consecutive days are more likely to develop HIT and also indicated that patients who had underlying medical conditions were significantly at increased risk for HIT. Another study conducted in Germany in which (Lubenow et al., 2009) determined the influence of surgery type and heparin type on the development of HIT. The study concluded 696 patients who have been admitted to the trauma surgery department at the University Hospital Greifswald. The study findings demonstrate that patients who have undergone major surgical procedures have a much greater risk for HIT than patients who have undergone minor ones, irrespective of the type of heparin received. (Gettings et al., 2006) in the USA investigated the incidence and the risk factors for HIT in critically ill postoperative patients. The study included all patients (2046), who were suspected to have HIT and tested positive for antibodies. Risk factors are assessed and abstracted retrospectively from patients medical
records. 210 patients (10%) admitted to the ICU had HIT assays performed. 19 patients had positive tests. Patients who tested positive for HIT had an increased risk of major complication or death and prolonged length stay at ICU compared with 19 matched control. 12 of 19 (63%) who had been exposed to heparin via intravascular flushes alone developed HIT antibodies. In USA (Oliveira et al., 2008) carried out a study in 2420 patients (median age, 65.2 years; 43.8% women) and observed an incidence of thrombocytopenia in 881 patients (36.4%). 5.1% of the patients who developed thrombocytopenia died. The study findings suggested that 50% reduction of platelet count, older age and longer duration of heparin therapy (4 days or longer) were risk factors for HIT incidence.

2.8. Complications of Heparin-Induced Thrombocytopenia

HIT is a potentially catastrophic adverse effect of heparin thromboprophylaxis that can be life-threatening and often accompanied by significant clinical consequences, including arterial and venous thromboembolism. The most common ones are; deep vein thrombosis (DVT) in the lower extremities and pulmonary embolism (PE). Skin lesions and necrosis at the site of injection of heparin are less common (Davoren et al., 2006). Lower extremity surgical patients when exposed to heparins are at risk for developing HIT and its complications. These complications often manifest in the extremities with a wide range of severity (Bibbo et al., 2001). In Germany (Greinacher et al., 2005) assessed the risk factors for thrombosis that is associated with HIT. The fall in the platelet count of at least 50% occurred in 271/319 (84.9%) patients. The risk of developing thromboembolic complications (TECs) associated with HIT was strongly correlated to the relative decrease in platelet count. Thrombosis manifested in almost 60% of the patients. TECs manifested as PE which occurred in 43.6% of patients and DVT that occurred in 36.4% of patients. The most important risk factor for thrombosis in this study was orthopedic/trauma surgery. Another study was performed in Italy, in which (Prandoni et al., 2005) determined the occurrence of arterial and venous complications of HIT in 1754 patients with normal platelet count and no previous exposures to heparin. The prevalence of TECs in HIT patients (4 of 14; 28.6%) was remarkably higher than that (41 of 1740; 2.4%) observed in
the remaining patients. This suggests that the thrombocytopenia may complicate the clinical state of medical patients treated with LMWH. In Brazil (Junqueira, et al., 2012) compared the incidence of HIT and thrombosis-related complications in surgical patients exposed to prophylactic UFH versus patients exposed to prophylactic LMWH. VTE occurred in 12 of 17 patients who developed HIT among 923 patients. The study results also suggest that there was a relative risk reduction of 80% in HIT complications occurred in patients administered LMWH compared with UFH. In Australia (Sturtevant et al., 2006) described an incidence with HIT. 22 patients were identified to have HIT (the mean age was 65). All patients received UFH and 5 patients also received enoxaparin. In 2 of 5 patients, enoxaparin was the primary anticoagulant and UFH was used for central venous catheters. TECs associated with HIT were documented in 14 patients. 7 patients died (32%) and HIT was considered contributory to the fatal outcome in four of them. The study suggested that HIT is strongly associated with thrombosis and the detection of HIT is often delayed, therefore platelet count should be monitored in patients on heparin. In Germany, (Girolami et al., 2003) reported a prevalence of TECs which was higher in patients who developed HIT (60%) than in the other 593 patients who did not (3.5%).

2.9. Importance of Monitoring and Early Diagnosis of HIT

2.9.1. Using Techniques for Early Diagnosis of HIT

A diagnostic clinical system called 4Ts scoring system is used in the early diagnosis of HIT, which would have either a negative or positive predictive value for HIT. It assesses four features of HIT and each feature is assigned with a score for the probability of HIT (LaMuraglia et al., 2011). This diagnostic system has been validated in many studies for instance, in Germany (Lo et al., 2006) compared prospectively the diagnostic 4 Ts system to rule out or confirm (HIT) in two different clinical settings, Hamilton General Hospital (HGH) and Greifswald (GW) in Germany. 100 consecutive patients at HGH and 236 patients at GW who were referred for possible HIT were selected and assessed. Both groups were classified into high, intermediate, and low probability groups based mainly on timing and severity of the thrombocytopenia. The study showed that the groups with low scores were unlikely to test positive for HIT antibodies, intermediate and high score groups
were more likely to test positive for HIT antibodies. These findings suggested the suitability of the test in the importance of early detecting and/or ruling out HIT and its consequences. Also in USA (Cuker et al., 2012) estimated the predictive value of the 4Ts in patients with suspected HIT. The study suggested that, the assessment of patients with suspected HIT by the 4Ts score system may reduce over testing of HIT and provide proper diagnosis for HIT. As intermediate and high probability scores require further evaluation and the low probability 4Ts score is a strong mean of excluding HIT.

2.9.2. Frequency of Platelet Count Monitoring

Frequency of platelet count monitoring should be determined based on the risk for developing HIT. Postoperative patients are at higher risk than medical patients. Postoperative patients, who are considered at high or intermediate risk, should undergo regular platelet count with intervals assigned by clinical guidelines. (Warkentin, 2002). The ACCP in the 9th edition of the evidence-based clinical practice guidelines for treatment and prevention of HIT recommends routine platelet count monitoring for detection of HIT according to risk assessed by clinicians. They stated the recommendations for patients receiving Heparin/LMWH as follows: “For patients receiving heparin in whom clinicians consider the risk of HIT to be 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 or until heparin is stopped, whichever occurs first” (ACCP, 2012).

2.10. Implementation of Guidelines and Compliance with Guidelines

The anticoagulation dosing and monitoring protocols are being implemented in the USA to improve the safety of anticoagulant drugs and the quality of patients care. As for LMWHs, these protocols have a policy for the necessary monitoring of platelet counts after publishing the guidelines for platelet count monitoring, diagnosis, and management of HIT in 2004. The clinicians’ awareness about HIT was lower before these guidelines; therefore, the evaluation of compliance with UFH and LMWHs platelet count monitoring and management of HIT is very essential in patient safety practice (Spinler, 2009). A study was
carried out in The Netherlands in which (Berg et al., 2009) investigated the frequency of compliance with recommendations from Summaries of product characteristics (SPCs) and clinical guidelines for platelet count monitoring in all hospitalized patients within the Utrecht Patient Oriented Database (UPOD): these patients received prophylactic and therapeutic doses of LMWHs (dalteparin and nadroparin) for at least five consecutive days. The frequency of compliance with platelet count monitoring recommendations for patients who received dalteparin, patients received nadroparin, and surgical patients with a prophylactic dose of either dalteparin or nadroparin, was 26.3%, 35.6%, and 23.0% respectively. The study revealed that compliance with recommendations of SPCs and clinical guidelines for platelet count monitoring is low at UPOD institution. A similar study in the USA where (Kim et al., 2012) evaluated the compliance by physicians with ACCP guidelines for platelet count monitoring during heparin thromboprophylaxis in a retrospective cohort study of 2350 patients. 28% of included patients, their platelet counts were not monitored as recommended. The failure of compliance was more common for hospitalized patients in the orthopedic surgery or obstetric/gynecologic services. The study demonstrated that compliance with guidelines was poor for patients receiving heparin thromboprophylaxis and routine monitoring of platelet count remains either undiscovered or ignored by clinicians at their hospital.

2.11. Physicians’ Awareness about HIT and HIT Monitoring

In UK, (Rogers et al., 2010 evaluated the implementation of the recent evidence based guidelines for routine platelet count monitoring in all postoperative patients who were at risk and received LMWH postoperatively. The study findings demonstrated a significant improvement in HIT diagnosis when the guidelines were implemented by 56%. Also an international survey evaluated the awareness of HIT and its management, the results revealed a lack of awareness towards HIT. (Levine et al., 2010) in the USA determined the frequency of emergency department (ED) physicians in documenting HIT risk assessment in thrombosis patients. 134 patients were included who had venous or arterial thrombosis. The risk assessment of HIT was undocumented by ED physicians for patients with symptoms of thrombosis who received heparin. The study suggested increasing the
awareness of HIT by developing approaches to facilitate efficient HIT risk assessment and documentations. (Tafur et al., 2012) determined the level of HIT awareness in a large teaching institution in the USA by assessing ordering behavior of health care providers when platelet counts fell from normal range. The clinicians’ awareness was determined by mentioning HIT within the hospital record by health care team and ordering platelet factor 4/heparin antibody testing when platelet count dropped by a 50% from baseline. Among 24,956 patients who received heparin, only 3,239 patients (13%) had more than one platelet count tested during their hospital stay. Of the other 199 patients who had a drop of platelet count by ≥50%, the clinician awareness was determined to be 36%. Both platelet count monitoring and HIT awareness were low at this large teaching institution.
Chapter Three

3. Materials and Methods
3. Materials and Methods

3.1. Study Area and Study Design.

The study was conducted during the period of March 1\textsuperscript{st}, 2016 through May 4\textsuperscript{th}, 2016. The study was a descriptive retrospective and prospective cross-sectional study designed to explore practices and awareness about heparin-induced thrombocytopenia (HIT) monitoring at Gezira Center for trauma and orthopedic surgery in Wad Medani, Gezira state, Sudan.

3.2. Study Population and Inclusion Criteria

The study included all consenting adult postoperative orthopedic patients who were above 40 years of age and received a prophylactic dose of low molecular weight heparin (Enoxaparin) and were admitted to Gezira Center for trauma and orthopedic surgery in Wad Medani during the period of March 2016 till May 2016. These included patients received regular prophylactic doses of Enoxaparin pre- and postoperatively and attended referral clinics for follow up after 14 days post discharge. Enoxaparin was the only low molecular weight heparin used at Gezira center during the study period. The study excluded all patients who received enoxaparin and had not undergone a surgical procedure which did not require monitoring as recommended by international guidelines and practiced by Gezira center. The study included all orthopedic surgeons working at the Gezira center for trauma and orthopedic surgery during the study period who were interviewed to obtain qualitative data regarding their knowledge and awareness about HIT.

3.3. Enoxaparin Thromboprophylaxis Policy at Gezira Center

According to the Center’s policy, after the patient is admitted and diagnosed with a condition that necessitates a surgical operation, the patient starts to receive enoxaparin as a prophylactic measure for the prevention of venous thromboembolism. The prophylactic dose used of enoxaparin is 4000 IU once daily. Enoxaparin thromboprophylaxis in the center is used only for patients who are above 40 years of age and for those who have trauma of the lower extremities. Enoxaparin usually is withheld on operation day and
reinstituted the day after the operation at the same dosage which was 4000 IU once daily. The patient will be discharged after the operation usually within 2 - 4 days and continues the use of enoxaparin with same dosage till the day of follow up after two weeks of discharge. At this point, the consultant decides whether to stop enoxaparin or to continue according to the patient’s medical status. The most common primary diagnoses of these orthopedic patients included in the study were fracture of hip femur, whether subcapital or intertrochanteric fracture of neck femur. All these orthopedic patients were admitted and underwent major surgery. The most common types of surgical operations performed in the center were; dynamic hip screw (DHS) and Austin Moore. These two types of surgical operations are orthopaedic implant designed usually to be used in the internal fixation of fractures of the hip femur (Roy, 2011).

3.4. Data Collection

The study of HIT monitoring in Gezira center for trauma and orthopedic surgery involved two parts. The first part was investigating the performance of platelet count for surgical patients who received a prophylactic enoxaparin dose while attending referral clinics for the first follow up after discharge. The second part was investigating orthopedic surgeons’ awareness about HIT and HIT monitoring through conducting in-depth interviews.

Regarding the first part, the frequency of monitoring of platelet count test was determined and expressed as percentage. The performance of platelet count monitoring involved three basic investigations, first; investigating the performance of a baseline platelet count, second; investigating the performance of platelet count during enoxaparin use and finally; investigating the performance of platelet count after attending the referral clinic for first follow up. The second part of HIT monitoring in Gezira center for trauma and orthopedic surgery in Wad Medani was conducting in-depth interviews. The purpose of these interviews was to explore orthopedic surgeons’ awareness and experience about HIT and their perspective about monitoring of platelet count for patients using enoxaparin thromboprophylaxis. The interviews were useful in providing detailed information about the orthopedic surgeons’ awareness and in exploring their opinions about monitoring of HIT in depth.
3.4.1. Patients’ Records Review

A retrospective review of patients’ medical records was used to obtain patient’s demographics such as name, age, gender and residency. Also data concerning enoxaparin dose, diagnosis, type of the surgery and dates of admission, operation, discharge and follow up were obtained. The medical records were reviewed to identify whether a baseline platelet count was done before the administration of enoxaparin. Postoperative patients were defined as patients who underwent a surgical procedure requiring an operating room (appendix 2).

3.4.2. Patients’ Follow up

According to the policy of Gezira center for trauma and orthopedic surgery, all postoperative patients should return to referral clinics for follow up. The referral clinics were regularly held on Tuesdays and Wednesdays. The evaluation of Gezira center protocol regarding HIT monitoring was done by collecting data during the referral clinics to investigate the performance of platelet count during and after the use of enoxaparin. The attendance of the follow up was regular during the period of March 1st till May 4th 2016 of the referral clinics (total = 20). The data concerning the adherence to Enoxaparin during the whole period was obtained by asking the patients or the co-patients about the regular use of enoxaparin when they came for follow up (see appendix 2).

3.4.3. In-depth Interviews

All orthopedic surgeons at Gezira Center for trauma and orthopedic surgery were interviewed. Face to face interviews were carried out in October 2016. The interviews included 12 in-depth questions which explored the awareness of HIT and the importance of monitoring of platelet count for the early detection of the condition. Initial contact was made by a telephone call, and after the interviewees gave their consent, the interviews were conducted at Gezira center for trauma and orthopedic surgery or in surgeons’ private clinics. The purpose of the study was explained to them in the first contact through the telephone and then later, it was re-explained alongside the reason they have been chosen and the expected duration of the interview. The interviews were conducted in quite settings
and took between 20 to 30 minutes. The data were collected by recording and taking notes during the interviews. After the entire interviews were tape recorded, they were transcribed word for word and later the transcribed text then became the data that were analyzed using conceptual thematic analysis. The first three questions explored the practices of the orthopedic surgeons regarding the incidence of HIT in the center. The rest of the questions explored their awareness of the importance of monitoring of HIT. They also explored surgeons’ opinions on barriers of conducting regular monitoring of the platelet counts (appendix 3).

3.5. Analysis

3.5.1. Data Analysis

Data were analyzed by descriptive analysis. Frequencies were obtained for each of the categorical variables, and mean was calculated for continuous variables when needed.

3.5.2. Interviews Analysis

Transcripts of the interview data were divided into concepts and themes and processed using conceptual thematic analysis. The identified concepts were; Awareness and reporting of HIT, Opinions on importance of HIT monitoring, Awareness of HIT risk factors, Awareness of HIT monitoring protocols, Difficulties of HIT monitoring, Barrier of HIT monitoring, Suggested solutions and recommendations for HIT monitoring.

3.6. Ethical Approval

The study was conducted after approval from the ethical committee of faculty of medicine of University of Gezira (appendix 1).
Chapter Four

4. Results and Discussion
4. Results and Discussion

4.1. Patients’ demographics

The study included 50 patients who received prophylactic enoxaparin at Gezira center for trauma and orthopedic surgery.

4.1.1. Sex

Sex distribution among the surgical orthopedic samples was investigated. An overall female predominance was observed among these 50 surgical orthopedic patients. Female patients (n= 29) composed about 58 % of the overall sample. The male patients (n= 21) composed about 42% of the overall sample. The male to female ratio was 1: 1.4. Frequency and percentage of females and males distribution among the study population are presented in (Figure 1).
Figure 1: Sex distribution among the study population (n=50)
4.1.2. Age

Concerning the age distribution among the study samples; the study included surgical patients above 40 years of age. This was because; the center policy is to use enoxaparin for thromboprophylaxis only in patients who are 40 years old and above. The age of included patients varied considerably: it ranged from 41 to 92 years old. Age was divided into 6 groups representing a decade range (Figure 2). The majority (n=29, 58%) of patients’ age ranged from 60 – 80 years old with approximately half of them on either side of 70 years old. The second largest group of patients (n= 9, 18%) was in the age group 80-89 years. The median age was obtained which was almost 70 years of age.

Figure 2: Age distribution among the study population (n=50)
Residence

The patients’ residence and distance from Gezira center for trauma and orthopedic surgery were identified and grouped as: 1) living within Wad Medani city or 2) living outside Wad Medani city but in Gezira state or 3) living in another state. All patients who were located in Wad Medani (n= 19, 38%) were considered as geographically near while the rest (n= 31, 62%) were considered geographically far: as described in (Figure 3).

Figure 3: Distance from Gezira Center among the study population
(n=50)
Out of the 50 patients; 31 patients of study subjects resided outside Wad Medani city, they were from either outside Wad Medani but in Gezira state (n= 17, 34%) or were from another state (n= 14, 28%). Frequency and percentage of these geographically far patients are presented in (Figure 4).

Figure 4: Distribution of patients’ residence among the study population  
(n=50)
4.2. Platelet Counts Monitoring for HIT

4.2.1. Performance of Baseline Platelet Count

Performance of baseline platelet count was defined as performance of platelet count before administration of enoxaparin thromboprophylaxis for surgical orthopedic patients and was identified from patients’ medical records. Performance of baseline platelet count was determined and expressed as percentage; platelet count test was part of the complete blood count test (CBC). Among the 50 patients, only 33 patients which composed 66% of the whole samples who received prophylactic enoxaparin in the study period had the baseline platelet count performed. The rest of the patients had received enoxaparin without performing the baseline platelet count and they were 17 patients and composed 34% of the whole sample. Frequency and percentage of baseline platelet count performance are presented in (Figure 5).

![Figure 5: Performance of baseline platelet count among the study population (n=50) (Image)](image-url)
4.2.2. Performance of Platelet Count during Enoxaparin Use

Performance of platelet count test during the use of enoxaparin and after the patient’s discharge was determined by asking the patients or their care takers when they attended the referral clinics for their first follow up in the center. None of these postoperative orthopedic patients had performed or were asked at the discharge to perform any platelet count investigations during the period of enoxaparin use and before attending the center for follow up.

4.2.3. Performance of Platelet Count after Attendance for Follow Up

Performance of platelet count test after the patients had attended the referral clinics for the first follow up was determined by direct observation of orthopedic surgeons’ attitudes with postoperative orthopedic patients who received prophylactic enoxaparin in the first follow up. None of these postoperative orthopedic patients asked the patients to perform platelet count test during their first follow up.

4.3. Practice Related to Enoxaparin Use
4.3.1. Duration of Enoxaparin Use

Included orthopedic patients in the study received enoxaparin when they were admitted to the center and diagnosed with situations that needed thromboprophylaxis. The duration of enoxaparin use varied according to the patients’ medical situation and the decision of performing the surgical operation. The patients who received enoxaparin regularly were 40 (80%) and these 40 patients received enoxaparin for different durations. The duration was calculated from the day of enoxaparin initiation till the day of enoxaparin cessation. Accordingly, duration of enoxaparin use among the study samples ranged from 16 days to 36 with varying frequencies as described in figure 6. The mean duration of enoxaparin use was almost 24 days and the standard deviation was 5.4. The frequencies of maximum and minimum of enoxaparin duration use in days are presented in (Figure 7).
Figure 6: Duration of enoxaparin duration use in days among the study population (n=40)

Figure 7: Maximum and minimum duration of enoxaparin use in days
4.3.2. Duration of hospitalization After Surgery

Most of the included patients in Gezira center were discharged within a few days following surgery. This was based on the type of surgical operation performed which determines the patient’s need to stay hospitalized in the center or to be discharged. In the present study, duration of hospitalization was calculated from the day of surgery till the day of discharge. The patients’ stay after surgery at the Gezira center ranged from two days to 18 days according to patient’s medical situation after the operation. Most of the patients stayed between two to four days and then discharged (Figure 8). The median of hospitalization was almost four days and the standard deviation was 2.3. Frequencies of maximum and minimum days of hospitalization after the surgery are presented in (Figure 9).

![Figure 8: Duration of hospitalization after surgery among the study](image)
population (n=50)

![Bar chart showing maximum and minimum duration of hospitalization after surgery.]

**Figure 9: Maximum and minimum duration of hospitalization after surgery**

4.3.3. Patients’ Compliance to Enoxaparin

Among the 50 postoperative orthopedic patients included in the study, it was found that enoxaparin was not being used regularly during the study period. Only 40 patients who composed 80% of the whole sample had used enoxaparin regularly prior to attending the center for follow up. The percentages of compliant and non compliant post operative use of enoxaparin are presented in (Figure10). The rest of the patients which were 10 and composed 20% of the whole sample did not use enoxaparin regularly for different reasons. These were mainly: price of enoxaparin which was not affordable for patients who did not have health insurance, dispensing of enoxaparin was done on a daily basis as the policy of the health insurance in Gezira state does not provide the whole dose for the whole duration.
of use. This was very difficult for the patients who were living outside Wad Medani. In addition the awareness of patients or the co-patients about the importance of medication compliance was low; these frequencies are described in (Figure11).
Figure 10: Patients’ compliance to Enoxaparin among the study population (n=40)
4.3.4. Patient’s Platelet Count Value and Enoxaparin Use

Most of included patients who received enoxaparin in the current study had a normal baseline platelet count (n=27, 54%). On the other hand, when reviewing the patients’ medical records, there were four cases with abnormal baseline platelet count. There of them had a low platelet count value and still received enoxaparin. As compared to normal platelet count range 150 X 10^9/L – 450 X 10^9/L: their baseline platelet count value was 136 X 10^9/L, 142 X 10^9/L, and 120 X 10^9/L respectively. They were 1 male and 2 female, one of which lived in an urban setting and 2 were from a rural area. The fourth patient was a female from rural area and had a high platelet count value of 723 X 10^9/L and still received the same prophylactic dose of enoxaparin.

4.4. Awareness About HIT Monitoring Among Orthopedic Surgeons

4.4.1. Surgeons’ Demographics

Ten orthopedic surgeons were interviewed in the current study; five of which were consultants and five were registrars. Most of the surgeons were males (n=8) while two of them were females. The doctors’ age ranged from 27 to 45 years old. They all participated in the in-depth interviews giving a response rate of 100%. The interviews were conducted in October 2016.

4.4.2. Reporting Adverse Effects with Enoxaparin Use

The first question of the in-depth interviews explored the orthopedic surgeons’ experience in noticing and reporting cases of adverse effect that developed during or after the use of enoxaparin thromboprophylaxis. In this first question; Surgeon 1 said ‘No, I have never noticed an adverse effect of enoxaparin whether with prophylactic or therapeutic dose”. Surgeon 2 said “No, I have never noticed any adverse effect of enoxaparin before”. Surgeon 3 said “I have never noticed an adverse effect caused by the
use of enoxaparin in any kind of patients”. Surgeon 4 said “No, I have never noticed an adverse effect related to enoxaparin in orthopedic patients” The rest of the surgeons stated that they have never noticed or reported any adverse effect of enoxaparin during their practices.

4.4.3. Noticing Thrombosis with Enoxaparin Use

Regarding the second question about noticing cases of thrombosis: 4 of the surgeons have never noticed such a case (they were registrars) and the other 6 (5 consultants and a register) have noticed a case of thrombosis in surgical orthopedic patients while using enoxaparin. In their opinions, causes of thrombosis were not related to enoxaparin use: surgeon 1 said “Yes I have noticed such a case and I think it was due to the prolonged bed ridden state of the patient at the hospital”. Surgeon 2 said “Yes, I have noticed that, but I think it was due to the patient’s condition as he was very obese”. Surgeon 3 said “Yes it occurred and I think it was due to the immobile status of the patient after the surgery”. Surgeon 4 said “Yes I have noticed a thrombosis case in a patient who received prophylactic enoxaparin but in my opinion it happened due to the long immobility state of the patient after the surgery”. In addition, surgeon 5 said “Yes I have noticed a thrombosis case with enoxaparin, but in my opinion it was due to the non compliance of the patient to enoxaparin during the period of use indicating a suboptimal dose that caused thromboprophylaxis failure”. Surgeon 6 said “Yes it happened in a female patient that used enoxaparin and she was old and obese as those are considered risk factors for developing thrombosis”.

4.4.4. Reporting and Awareness of HIT

Concerning the third question about being aware about incidence of HIT, they were asked about noticing or reporting thrombocytopenia with enoxaparin thromboprophylaxis: according to their responses, they were not familiar with the incidence of HIT and they indicated that: HIT never occurred during their practice, except one of the orthopedic surgeons who was a registrar. She was somewhat familiar with HIT and said that: “I read about HIT in the literature but I did not notice any cases during practice, I think HIT is rare and the doctors don’t pay attention to this condition”.

4.4.5. Opinions about Importance of HIT Monitoring
The fourth question was about the importance of platelet count monitoring in patients using prophylactic enoxaparin. All of the ten orthopedic surgeons thought that routine monitoring is not important because enoxaparin and other low molecular weight heparins are generally safe and never caused any adverse effect during their practices. Half of these surgeons thought that the routine monitoring would be needed only if the patients who use enoxaparin are assessed and considered to be at risk.

4.4.6. Opinions About Type of Patients who Need Monitoring

Regarding the fifth question, five surgeons thought that routine monitoring for platelet count would be important only for the patients who are considered to be at risk: Surgeon 1 said “monitoring would be important if the patient has a history of thrombosis within the past period”. Surgeon 4 said “monitoring is important only if the patient is on blood medications or the patient has co-morbidities such as malignancy or an autoimmune disease that may necessitate monitoring”. Surgeon 5 said “routine monitoring would be important only in the presence of risk factors such as old age of patient and incidence of thrombocytopenia”. Surgeon 6 stated that “monitoring can be considered important and should be performed if the patient is using enoxaparin for a long period of time”. Surgeon 7 said “monitoring would be important if the patient has a risk of bleeding, history of bleeding or have thrombosis at the time of enoxaparin use”. Surgeon 9 said “I think monitoring is important only if the patient is obese or has movement issues or the patient has multiple fractures that may need long period of immobility”. Surgeon 10 said “monitoring would be important if the patient will be immobile for a long time or the patient is very obese.

4.4.7. Awareness of HIT Risk Factors

Surgeons were asked in the sixth question if they think there are risk factors that can determine the incidence of thrombocytopenia with enoxaparin thromboprophylaxis: the majority of them (7) did not think there are any risk factors that can determine the incidence of thrombocytopenia. The minority (n=3) of them thought it might be, Surgeon 1 said “if the patient used unfractionated heparin for treatment in the past for long period of
time, this can be a risk factor to the incidence of thrombocytopenia”. Surgeon 5 stated that “the previous incidence of thrombosis in a patient can be a risk factor for thrombocytopenia”. Surgeon 6 said “it might occur if the patient has a risk for developing thrombocytopenia such as patients with genetic conditions or pregnant women or any other conditions that may predispose thrombocytopenia”.

4.4.8. Awareness of HIT Monitoring Protocols

Surgeons were asked in the seventh question about the appropriate timing for monitoring of platelet count if it is implemented. 4 of them thought that, there is no need for routine monitoring of platelet count as they indicated earlier to the safety of enoxaparin and other low molecular weight heparins. The other six surgeons gave different responses but only in the presence of risk factors: Surgeon 1 said” I think it should be performed every other day if there are risk factors”. Surgeon 4 said “in my opinion it should be performed daily if there is an obvious risk factor” .Surgeon 5 said “routine monitoring should be done every 2 weeks in the first follow up; because once the patient has become mechanically active there would be no need to continue enoxaparin, so there is no need for further monitoring”. Surgeon 6 said “in the presence of the risk factors, monitoring should be done every 3 days”. Surgeon 7 said “routine monitoring should be done as baseline and then every month unless something came up and then when the patient comes to refer clinic”. Surgeon 9 said “monitoring should be performed as baseline, then on discharge and later in the next follow up after 2 weeks”. Surgeon 10 said “monitoring should be performed every follow up which means every 2 weeks in the first 6 weeks postoperatively”.

4.4.9. Difficulties of HIT Monitoring

Surgeons were asked in the eighth question if the routine monitoring of platelet count would be difficult: the majority of them (8) thought that regular monitoring of platelet count for these patients would be difficult. The other two thought it would not be difficult. Regarding these two registrars who thought there would be no difficulties, Surgeon 7 said “the test of CBC is available like any other tests and patients perform X-rays after surgery
when they are asked to”. Surgeon 9 said “these patients when asked to perform any test, they do it such as diabetic patients, these diabetic patients when they are asked to perform blood glucose level test after discharge they do the test and bring the test results with them in the follow up”. The majority who thought there were difficulties gave to some extent similar difficulties or barriers which are outlined below.

4.4.10. Barrier of HIT Monitoring

Barriers of routine monitoring of platelet count in postoperative orthopedic patients according to the opinions of the 8 orthopedic surgeons were: surgeon 1 said” the barriers are financial: the health insurance of Gezira state is not available for all patients and covers only 33% of them, so for the rest of the patients who do not have health insurance, performance of regular platelet count investigations would be difficult because the price of complete blood count test (CBC) is not affordable for the patient with low income status”. Surgeon 2 said “the barrier in my opinion is being distant from the center, so it would be difficult to come regularly for these investigations”. Surgeon 3 said “I think the barriers are compliance of the patients: because not all the patients or the co-patients are well educated and aware of the importance of the investigations and regular monitoring in general, also the absence of the health insurance for these patients is a significant problem”. Surgeon 4 said “in my opinion, because most of the patients are located far away from the center and outside the Wad Medani, routine monitoring would be difficult because they can’t be able to come back regularly to the center to perform the investigations as 80% of these patients are from far rural areas and also the non availability of the tests for these patients who live in rural areas is a barrier as well”. Surgeon 5 said” most of the patients are discharged few days postoperatively from the center, so it would be difficult to control the regular performance of platelet count test as the compliance is very low which also affects the use of enoxaparin itself”. Surgeon 6 said “I think the compliance of patients after discharge, and cost of investigations are the most important barriers to routine monitoring”. Surgeon 8 said “because of the cost of investigations, patients will not be able to perform any routine investigation like CBC”. Surgeon 10 said “the residence of the patient which is far
from the center is the barrier to the regular investigation, sometimes this issue affects even the attendance for follow up after surgery”.

4.4.11. Suggested Solutions and Recommendations for HIT Monitoring

Surgeons were asked in the rest of the questions about solutions for routine monitoring difficulties and recommendations according to their opinions: the responses were similar, they thought it is important to increase patients’ awareness about the importance of investigations and the importance of follow up by educating these patients before discharge in order to increase patient compliance to medications and requested investigations after discharge. They also thought it is important to decrease the cost of the investigations if possible and make it affordable for patients with low income, at the same time, efforts should be taken to cover large numbers of patients by health insurance in order to ease routine monitoring investigations of platelet count and other investigations and also to prevent the skipping doses of medications because of health insurance policy about dispensing only the daily dose of enoxaparin.

Table1: Summary of Orthopedic Surgeons’ Awareness about HIT

<table>
<thead>
<tr>
<th>Concept</th>
<th>Themes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting ADRs</td>
<td>No one ever reported any adverse effect</td>
</tr>
<tr>
<td>Noticing thrombosis with enoxaparin use</td>
<td>6 of them noticed thrombosis cases</td>
</tr>
<tr>
<td></td>
<td>Prolonged bed ridden state</td>
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<tr>
<td></td>
<td>Being very obese</td>
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<tr>
<td></td>
<td>Immobile status of after the surgery</td>
</tr>
<tr>
<td></td>
<td>Non compliance to enoxaparin</td>
</tr>
<tr>
<td></td>
<td>Being old and obese</td>
</tr>
<tr>
<td>Reporting HIT</td>
<td>No one reported HIT</td>
</tr>
<tr>
<td>Opinions of importance of HIT monitoring</td>
<td>5 surgeons thought it is not important at all</td>
</tr>
<tr>
<td></td>
<td>5 surgeons thought it can be important only with risk factors</td>
</tr>
<tr>
<td>Opinions about who</td>
<td>History of thrombosis within the past period</td>
</tr>
<tr>
<td>needs monitoring</td>
<td>Being on blood medications</td>
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<tr>
<td>------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td></td>
<td>Having co-morbidities</td>
</tr>
<tr>
<td></td>
<td>Being old or obese</td>
</tr>
<tr>
<td></td>
<td>Having thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Using enoxaparin for a long time</td>
</tr>
<tr>
<td></td>
<td>Having risk of bleeding or thrombosis</td>
</tr>
<tr>
<td></td>
<td>Being obese</td>
</tr>
<tr>
<td></td>
<td>Having movement issues or multiple fractures</td>
</tr>
<tr>
<td></td>
<td>Being immobile for a long time</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Awareness of HIT risk factors</th>
<th>3 surgeons thought there are risk factors as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Previous long use of UFH,</td>
</tr>
<tr>
<td></td>
<td>Incidence of thrombosis</td>
</tr>
<tr>
<td></td>
<td>Risk for developing thrombocytopenia</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Awareness of HIT monitoring protocols</th>
<th>4 surgeons thought there is no need for monitoring</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Every 3 days</td>
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<tr>
<td></td>
<td>Every 2 weeks in first follow up</td>
</tr>
<tr>
<td></td>
<td>Baseline and then every month</td>
</tr>
<tr>
<td></td>
<td>Baseline on discharge and in follow up</td>
</tr>
<tr>
<td></td>
<td>Every follow up</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Difficulties of HIT monitoring</th>
<th>2 surgeons thought it would not be difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 surgeons thought it would difficult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barrier of HIT monitoring</th>
<th>High cost of the test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lack of health insurance</td>
</tr>
<tr>
<td></td>
<td>Far distance from the center</td>
</tr>
<tr>
<td>Non availability of test there</td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td></td>
</tr>
<tr>
<td>Non compliance of patients</td>
<td></td>
</tr>
<tr>
<td>Early discharge from the center</td>
<td></td>
</tr>
</tbody>
</table>

**Suggested solutions for HIT monitoring**

<table>
<thead>
<tr>
<th>Increasing patients’ awareness about importance of investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreasing the cost of the investigations if possible,</td>
</tr>
<tr>
<td>Covering large numbers of patients by health insurance.</td>
</tr>
</tbody>
</table>

### 4.5. Practice of HIT Monitoring in Gezira Center

The current study suggests that HIT monitoring of platelet count in the study area was low. Monitoring of platelet count was particularly low for the included patients who were considered to be at relatively increased risk for developing HIT. As venous thromboembolism (VTE) is very common in orthopedic patients who undergo hip fracture surgery in the absence of thromboprophylaxis (Kakkar *et al*., 2013), low molecular weight heparin (enoxaparin) was used in Gezira center for trauma and orthopedic surgery as a protocol measure for VTE thromboprophylaxis in the surgical orthopedic patients who are above 40 years of age and have trauma to their lower extremities. As LMWHs are successfully proven to be effective in the prevention of VTE in orthopaedic surgery and are recommended by ACCP clinical guidelines (Kalyani *et al*., 2011). Postoperative orthopedic patients exposed to heparin thromboprophylaxis are susceptible for developing HIT and HIT complications (Patel *et al*., 2007) as these included patients. Therefore, it’s recommended to monitor the platelet count of the LMWHs exposed patients to avoid the deleterious effect of HIT (ACCP, 2012).

It is recommended to monitor platelet count 2 to 3 times from day 4 till day 14 in which HIT is suspected to occur (Warkentin, 2002), and because the detection of HIT is often delayed; the platelet count should be monitored in patients on heparin (Sturtevant *et
Postoperative patients, who are considered at high or intermediate risk, should undergo regular platelet count with intervals assigned by clinical guidelines. (Warkentin, 2002), unfortunately, in the present study monitoring of platelet count was completely absent during enoxaparin use (the period after discharge and before follow up) and after attendance for the first follow up in referral clinics. Regarding performance of baseline platelet count which means performance of platelet count before administration of enoxaparin, it was absent in 34% of the patients (n=17) this was potentially risky for their safety. Neither HIT monitoring of platelet count was performed nor clinical guidelines were followed; although the guidelines’ recommendations for monitoring of platelet count and management of possible HIT in patients receiving LMWHs are published and available since 2004. Baseline complete blood count (CBC) was routinely done to monitor blood cell counts

4.6. HIT Monitoring Guidelines and Recommendations

American College of Chest Physicians (ACCP) guidelines was used in the current study to define compliance to platelet count monitoring for HIT. Consistent with these guidelines’ recommendations: in the current study orthopedic postoperative patients exposed to enoxaparin were evaluated for whom the risk for HIT was considered; this risk was mainly performance of orthopedic surgical operation. ACCP has published these guidelines on recognition, prevention, and treatment of HIT to prevent the devastating consequences of HIT in 2004 and then it had been updated in 2008 and 2012. The guidelines recommend routine monitoring for the patient receiving UFH or LMWHs depending on patient’s risk that is to be assessed by clinicians ACCP clinical recommendations are described below in table 2.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Clinical Situation</th>
<th>Recommendations</th>
</tr>
</thead>
</table>

Table 2: ACCP Recommendations for Platelet Count Monitoring Per Clinical Situation
<table>
<thead>
<tr>
<th></th>
<th><strong>Postoperative patients receiving prophylaxis with UFH</strong></th>
<th>Every other day</th>
</tr>
</thead>
</table>
| **High (> 1%)**    | * General/medicine/obstetric-gynecologic service patients receiving prophylaxis with UFH  
|                    | * postoperative patients receiving prophylaxis with LMWH | Every 2 or 3 days |
| **Moderate (0.1%–1%)** | * General/medicine/obstetric-gynecologic service patients receiving only LMWH  
|                    | or general medicine service patients receiving only intravascular catheter UFH flushes | No routine monitoring |
| **Low (< 0.1%)**   | * Postoperative patients receiving prophylaxis with UFH |               |

According to these clinical guidelines, monitoring of platelet counts in heparin thromboprophylaxis vary based on performance of surgical operation. In the current study; all included patients underwent surgical operations. The clinical guidelines recommend routine platelet count monitoring for specific patient populations: the guidelines do not recommend routine monitoring of platelet count in all types of patients who receive LMWHs, but only in patients who are considered to be at increased risk for HIT, for example: surgical patients who receive prophylactic doses of LMWHs. So any patient who received enoxaparin without undergoing surgical operation in Gezira center was excluded from the study. The difference between UFH and LMWHs preparations affects the incidence of HIT which in turn leads to the difference of monitoring recommendations (Shantsila et al., 2009); this was obvious in ACCP recommendations as not all patients exposed to LMWHs need to be monitored. Any decrease in platelet count by 50% for at least 5 days after the start of heparin therapy is considered significant suspicion for HIT (ACCP, 2012) which did not influence surgeons’ behaviors when dealing with surgical orthopedic patients who receive prophylactic enoxaparin at Gezira center. In postoperative
patients, drop in platelet count is normally occurs after day 5 till day 14 of heparin administration, therefore it had been selected to be at least five consecutive days for an episode of monitoring of platelet count for LMWH exposed patients (Greinacher et al., 2005). A drop in platelet count of at least 50% after surgery is considered HIT and monitoring for HIT is performing at least one platelet count at the day of start of treatment and performance of platelet count on at least two different following days during LMWHs treatment (Warkentin, 2002). However, in the current study, a single platelet count measurement within the suspected days of HIT (5 to 10), when the risk for HIT is highest, is considered awareness about platelet count monitoring. It has been found that in all surgical patients with prophylactic doses of enoxaparin, no platelet count monitoring protocol was followed; only one platelet count was obtained before administration of enoxaparin (baseline). Despite the high incidence of HIT in orthopedic surgical patients (4% - 7%), monitoring of platelet count is generally low (Arepally et al., 2006). This low monitoring is documented in the current study., which suggests that awareness for the importance of platelet count monitoring with LMWHs is low, which may put the patients at higher risk for the potential harm of enoxaparin adverse effect of enoxaparin.

4.7. Studies of HIT in Sudan

This area of study is underrecognized in Sudan: there is only a single study that was published in 2014 Hemadi and Mahdi that was conducted at AL-Dayat labor hospital in Omdurman. The study highlighted the incidence of HIT among pregnant women (10.3%, n = 165). The study pointed out the importance of routine monitoring of platelet count and investigations for HIT antibodies whenever there is a suspicion of HIT among such group in Sudan. Evaluation of compliance with UFH and LMWHs platelet count monitoring of HIT is very essential in patient safety practice (Spinler, 2009). The researcher is not aware of any other study conducted on evaluation of monitoring of HIT or reporting on compliance with recommendations for platelet count monitoring for possible HIT in patients receiving heparin products in Sudan.

4.8. Studies of Compliance with Recommendation worldwide
Several studies investigated the compliance with recommendations of clinical guidelines for laboratory monitoring in different drug treatment and showed that compliance is low in general (Raebel et al., 2005). While in the area of monitoring of HIT, studies are generally few. Compliance with guidelines of platelet count monitoring in patients who received prophylactic doses of two types of LMWHs, was reported to be 23% and considered low (Berg et al., 2009). Compliance by physicians and unrelated compliance to ACCP recommendations of platelet count monitoring during heparin thromboprophylaxis was reported to be 78% (Kim et al., 2012). The evaluation of the compliance with heparin thromboprophylaxis for platelet count monitoring is important from patient safety prospective (Spinler, 2009). The current study found that platelet counts of all included patients were not monitored during enoxaparin use. The absence of compliance in the study was determined when patients’ platelet count was not tested over the period recommended by clinical guidelines. In fact the absence of monitoring was strongly associated with primary service in all orthopedic surgery patients. Thus, the current study reported that platelet count monitoring is lower than those previously reported in the previously mentioned studies.

4.9. Patient’s Demographics and Risk Factors for Developing HIT

Included patients who their platelet count was not monitored as recommended, they were considered to be at increased risk for developing HIT.

4.9.1. Performance of Surgery

Risk of developing HIT is higher for postoperative patients than non operative (medical) patients (Shantsila et al., 2009; Arepally et al., 2006), with 3-fold greater risk among surgical than medical patients (Warkentin et al., 2006), this the most important risk factor addressed in the current study as all patients who received enoxaparin without undergoing surgical operation were excluded from the study such as patients who were under 40 years of age and patients who had trauma in upper extremities.

4.9.2. Orthopedic Surgery
Trauma and Orthopedic surgery are the most important risk factors for developing thrombocytopenia and thrombosis (Happe et al., 2008; Greinacher et al., 2005; Mumoli et al., 2008)), this related thrombosis manifests as DVT in the lower extremities and PE. (Davoren et al., 2006). All included patients were orthopedic ones as they may have high rates of incidence according to several studies. Generally, the incidence of HIT is more frequent in orthopaedic patients than it is currently believed (Lilikakis et al., 2007). Postoperative orthopedic patients with LMWH appear to be at higher risk for HIT, with an incidence of 0.9% (LaMuraglia et al., 2011), 1.7% after major orthopaedic surgeries (Happe et al., 2008) and 4% - 7% (Arepally et al., 2006). HIT was associated in 75% of cases in orthopedic patients which was manifested within 5 days to 10 days after the initiation of heparin therapy (Warkentin et al., 2003). HIT and its life threatening complications are unrecognized after major orthopedic surgery with mortality rate of 30% and amputation rate of 20% (Picker et al., 2004).These previous reported rates of HIT with orthopedic surgical patients pinpointed the great risk for HIT incidence with included patients in the current study.

4.9.3. Duration of Enoxaparin Use

Incidence of thrombocytopenia is strongly increased in patients with prolonged heparin therapy (LaMuraglia et al., 2011; Oliveira et al., 2008). It indicated that patients receiving thromboprophylaxis with heparins for 6 days or more have a higher probability of HIT than those receiving them for shorter periods (Martel et al., 2005). Similarly, patients who receive heparin for more than 5 consecutive days are more likely to develop HIT (Kato et al., 2011).Therefore its recommended to perform regular platelet count monitoring for patients receiving heparin treatment (ACCP, 2012). Accordingly, in the present study, patients (n = 40) have received enoxaparin thromboprophylaxis for more than 5 consecutive days, the duration of use ranged from 16 till 36 days with an average of 24 days, this long duration may be a risk factor for developing HIT for those patients.

4.9.4. Age

Older age is a significant risk factor for developing HIT and a significant risk factor addressed in the present study. The incidence of HIT is significantly increased at older age
(Oliveira et al., 2008) and to be more specific, the incidence of HIT is high in patients over 40 years of age (Stein et al., 2009). As the age being an essential determinant in the likelihood of HIT incidence, in the present study sample, the majority of patients (n=29, 58%) were from 60 to 80 years old with a median age of 70 years. The second largest group of patients (n= 9, 18%) was in the age group 80-89 years. Comparatively, 66% of HIT patients were 60 years or older and 57.3% of HIT patients was within the age group of 60–79 years (Greinacher et al., 2005). This older age may put this type of patients for risk of developing HIT.

4.9.5. Sex

The sex of the patients is also a significant risk factor for the likelihood of HIT: frequency of HIT had been more frequently reported in females (Mumoli et al., 2008) at approximately twice the risk for HIT as males (Warkentin et al., 2006). In the current study; the females (n= 29) were more common than males (n= 21) with a percentage of 58% of the overall sample, with similar documented rates in other studies: females constituted 56.4% of HIT patients (Warkentin et al., 2001) and constituted 58.9% of overall HIT population (Greinacher et al., 2005).

4.9.6. Severity of Trauma

As well as, severity of trauma and the need for major surgery can strongly affect the incidence of HIT; patients who undergo major surgical procedures are at greater risk of devolving HIT than those who undergo minor surgical procedures (Lubenow et al., 2009). In the current study, most of the patients were diagnosed with hip fractures and all of them underwent major surgical operations of dynamic hip screw and Austin Moore for fixation. Lower extremity surgical patients are at risk for the development of both HIT and HIT induced thrombosis (Bibbo et al., 2011). All included patients in the current study had lower extremities trauma as the policy of Gezira center for administering enoxaparin thromboprophylaxis is restricted to such patients.

4.9.7. Type of Heparin Used (LMWH)

The incidence of HIT is more common in UFH exposed patients than LMWHs exposed patients (Junqueira et al., 2012; Gray et al., 2008; Warkentin et al., 2006; Martel
et al., 2005). Although the incidence of HIT with LMWH it is less common, it can occur (Giuliani et al., 2015; Mumoli et al., 2008), with more severe thrombocytopenia and a long time observation (Walenga et al., 2005; Gruel et al., 2003) and with the same risk of thrombosis and death (Walenga et al., 2005). Due to the previous documented incidence: platelet count monitoring is highly recommended whenever LMWH is administered (Tian et al., 2009; Gruel et al., 2003). In the current study enoxaparin was the only heparin used for prophylaxis during the entire period of study. In general, LMWHs are considered to be safer that UFH in clinical practice. This issue obviously affected the opinions of the orthopedic surgeons in the present study in not considering the importance of monitoring for HIT with use of LMWHs that influenced their behaviors and practices of monitoring of HIT with platelet count.

4.10. Enoxaparin use related practice

4.10.1. Duration of Hospitalization after Surgery

Patients in Gezira center are normally discharged within 3-4 days after surgical operations and based on their medical conditions. Included patients were discharged 2 days to 18 days postoperatively with a median of almost 4 days. This short period of hospitalization after surgery affect the routine monitoring for HIT because these patients would not be available to perform platelet count test every 2 to 3 days as recommended by the clinical guidelines. This was a major barrier to routine measurement of platelet count for HIT monitoring that was stated by most of the surgeons during in-depth interviews.

4.10.2. Patients’ Compliance to Enoxaparin

Compliance with medications improves patient safety, prevents re-hospitalization and reduces the increased health care cost (Kalogianni, 2011). A secondary finding of the present study revealed that among the study population (n=50), 10 patients (20%) did not receive the post discharge dose of enoxaparin regularly. This failure of compliance was attributed to tow main reasons: the policy of the health insurance in Gezira state for the discharged patient is to dispense only the daily dose of enoxaparin and not for the entire duration of use, this was the most significant problem because many patients as mentioned
earlier (62%) are located outside Wad Medani (n= 17, 34%) and sometimes in another state (n= 14, 28%) which makes the daily dispensing of enoxaparin very difficult for them. The other reason was the cost of enoxaparin which was also a problem for the non compliance of the patients who do not have health insurance as the cost of the enoxaparin is not affordable.

4.10.3. Patient’s Platelet Count value and Enoxaparin Use

Another secondary finding is that among the study population (n = 50), it was surprisingly found that complete blood count test that include platelet count test was a routine test for screening blood and not targeting the platelet count in particular ;this was obvious in the 4 cases mentioned earlier with the abnormal platelet count values which were: 3 patients had a low platelet count and still receive enoxaparin, and one patient had a high platelet count value and still received the same prophylactic dose, this may put these patients at great risk for bleeding and in case of the latter put the patient in failure to control thrombosis.

4.11. Awareness about HIT Monitoring among Orthopedic Surgeons

The primary findings of the current study reflected a lack of awareness towards HIT and its thrombotic consequences in general. These findings suggested that clinically recommended routine platelet count monitoring remains either undiscovered or ignored by orthopedic surgeons at the Gezira center for trauma and orthopedic surgery, because it did not appear to influence their behavior when dealing with surgical patients during the whole period of enoxaparin thromboprophylaxis. For further evaluation, in-depth interviews were carried out and investigated orthopedic surgeons’ awareness about HIT which has demonstrated a considerable lack of awareness of HIT and its monitoring. In many cases, HIT awareness and HIT practice in the emergency department is less known (Levine et al., 2004). Also a lack of awareness towards HIT was detected among physicians (36%) (Tafur et al, 2012). Another lack of awareness was documented by international survey (Rogers et al, 2010). These previous studies correspondingly with the present study findings
suggested that the awareness of HIT is low as the international guidelines (ACCP) was first published in 2004.

4.11.1. Surgeons’ Demographics

The age of the surgeons was not a significant factor in awareness of HIT monitoring in the present study, although the consultants were older and have more years of experience in practice. It also has been found that gender was also not a significant factor in their awareness; as similar barriers to monitoring were identified by both gender and at all age.

4.11.2. Noticing Thrombosis and Reporting HIT

The cases of thrombosis in surgical patients during enoxaparin use that were noticed by the 6 surgeons in the center could be a possibility of HIT. They attributed the causes to many factors such as: prolonged bid ridden state of the patient at the hospital after the surgery, non compliance of the patient to enoxaparin during the period of use, being old and obese; all of these could be possible but the suspicion for HIT risk should be considered. Regarding the knowledge about HIT, all of them never reported a thrombocytopenia with enoxaparin prophylaxis which cannot be noticed without performing a regular platelet count to observe the drop of platelet count related to heparins. Hence, these surgeons were not familiar with HIT knowledge during their practice except for one surgeon who was somewhat familiar with the condition in textbooks but not during practice.

4.11.3. Opinions about Importance of HIT Monitoring

The awareness of monitoring importance was also poor as they thought that routine monitoring is not necessary. Generally they think LMWHs are generally safe and have no serious related problems. Despite the fact that the incidence of HIT is less frequent with the use of LMWHs, HIT can occur with the same severity of HIT induced by UFH and cause potentially serious complications (Walenga et al., 2005; Gruel et al., 2003). The incidence of HIT in patients who undergone major surgeries is similar in UFH and LWWHs, and this can affect the platelet count monitoring recommendations for heparin thromboprophylaxis (Junqueira et al., 2012), but they thought this routine monitoring can be important only in the presence of the risk factors.
4.11.4. Awareness of HIT Monitoring Protocols

They were not familiar with the clinical guidelines for platelet count monitoring that recommend platelet counts tested every 2-3 days according to ACCP; they thought that monitoring of platelet count can be performed only in presence of risk factors. This clearly indicated a lack of awareness for any guidelines recommendations for HIT monitoring that necessitate the performance of platelet count monitoring in short intervals according to the timing of HIT which is suspected to occur between day 4 till day 14 (Warkentin, 2002).

4.11.5. Difficulties of HIT Monitoring and Barrier of HIT Monitoring

The majority of them thought that implementation of routine monitoring is very difficult: these difficulties of routine monitoring are investigated during data collection period. The early discharge of the patients after surgery affect routine monitoring as mentioned earlier: majority of the patients (n=46) were discharged within 2-4 days, this makes monitoring during the suspected period of HIT (4-15 days) not doable. The far distance of patients’ residence from Gezira center prevents regular platelet count as 62% of them were outside Wad Medan. Compliance of the patients is also an important factor in ensuring regular monitoring as 20% of the patients were not compliant to enoxaparin itself not to mention the compliance for routine monitoring, this is due to not having health insurance in patients and due to the cost of the drug and the investigations as it was addressed by the surgeons as a barrier.

Furthermore, HIT is considered under-diagnosed condition which reflects a lack of awareness about this condition among orthopaedic surgeons (Lilikakis et al., 2007) as observed in the current study. There is a gap that exists between HIT guidelines and clinical practice for heparin exposed and hospitalized patients which it indicated a lack of awareness about the serious adverse effect of HIT (Crespo et al., 2009). In the current study, the knowledge of HIT among orthopedic surgeons contained gaps: those gaps exist between their awareness of HIT and the clinical practice in the center. None of orthopedic surgeons were familiar or even somewhat familiar with the guidelines and with the importance of monitoring of HIT. They also indicated that it is often for the clinical guidelines to be followed in their clinical settings when treating patients. Although HIT is
considered a fatal condition but it can be prevented by early recognition and increased awareness towards the condition (Tafur et al., 2012). Therefore prompt and early diagnosis of HIT as recommended by the evidence-based guidelines facilitates the significant reduction of the thromboembolic outcomes (ACCP, 2012: Lubenow et al., 2005). A significant improvement in HIT diagnosis when the guidelines were implemented was documented by 2-56% (Rogers et al., 2010). So the lack of awareness that was detected in Gezira center about HIT and its monitoring may contribute in increasing the risk for HIT and HIT complications for such patients. Clinicians’ awareness about HIT was lower before these guidelines; therefore, the evaluation of compliance with UFH and LMWHs platelet count monitoring and management of HIT is very essential in patient safety practice (Spinler, 2009). Lack of awareness about HIT necessitates clinical alertness and laboratory confirmation in order to prevent its serious complications (Lilikakis et al., 2007). Increasing the awareness about HIT is essential in early recognition and in preventing the delayed and improper diagnosis of HIT, which can be achieved by developing clinical approaches to facilitate efficient and accurate HIT risk assessment (Levine et al., 2010). Implementation of guidelines for routine monitoring of HIT with platelet count in all postoperative patients who were at risk and received LMWH improves the diagnosis of HIT (Rogers et al., 2010). Also developing tools for improving platelet count monitoring and monitoring awareness may be helpful in decreasing the problems associated with HIT (Tafur et al., 2012). In the current study, educating the surgeons about the benefits of early detection of adverse drug reactions of enoxaparin and implementing routine monitoring of HIT are essential for improving the safe use of enoxaparin and prevent its serious adverse effects. As the occurrence of HIT life threatening complications and increased mortality rates is associated with the delayed detection and diagnosis of HIT (Sturtevant et al., 2006).

In summary, both platelet count monitoring and HIT awareness among orthopedic surgeons are low at Gezira center for trauma and orthopedic surgery. Thus, the current findings suggest tools for increasing awareness of orthopedic surgeons about HIT and providing protocols for implementation of monitoring of platelet count in low molecular weight heparin exposed patients, to facilitate accurate and efficient monitoring of HIT, in
order to prevent the possible life threatening thrombotic consequences. So, the center should have policies that address baseline and ongoing laboratory tests which are required for low molecular weight heparin therapy. Together with significance of monitoring, continuous medical education for patients and co-patients to improve patient compliance should be introduced. Finally, the results representation of this study may be limited, because the data are obtained from one setting. Also, the study evaluated surgeons’ practices in a single center, which may not be generalizable to other facilities.
Chapter Five

5. Conclusion and Recommendations
5.1. Conclusion

- Platelet count monitoring for heparin-induced thrombocytopenia at Gezira center for trauma and orthopedic surgery was low for postoperative orthopedic patients. This was despite the fact that, patients who received enoxaparin for venous thromboembolism prophylaxis were considered to be at increased risk.
- Monitoring of heparin-induced thrombocytopenia was low before the administration of enoxaparin (66%) and was completely absent during the period of enoxaparin use post discharge and after attending referral clinics for follow up.
- Practice of HIT monitoring appeared to be unrelated to any guidelines’ recommendations about HIT recognition and prevention.
- The associated development of thrombocytopenia with heparin use is an under recognized and underreported in Sudan.
- Awareness about heparin-induced thrombocytopenia and its monitoring was considerably poor among orthopedic surgeons who work at the Gezira center for trauma and orthopedic surgery.
- Lack of awareness about heparin-induced thrombocytopenia and poor understanding of the importance of monitoring may contribute to a delayed recognition of the adverse effects and could negatively impact patients’ lives.
5.2. Recommendations

- A key recommendation for practitioners when using enoxaparin and other low molecular weight heparin in postoperative patients is to perform routine monitoring which is essential for patient safety.
- Policies should be developed to ensure the safe use of heparin and low molecular weight heparins to avoid serious adverse effect like HIT.
- There is a need to establish nationwide educational and monitoring programs to facilitate implementation of HIT monitoring in Sudan.
- There is a need for improvement of knowledge and awareness regarding HIT among surgeons in Gezira Center for Trauma and Orthopedic surgery.
- Further research is needed to elucidate the reasons behind the lack of awareness about HIT and determine the factors that may account in not following guidelines for monitoring of HIT.
- Future research is needed in other similar settings to address the issue of HIT related practice and demonstrate whether these findings can be generalized.
References


Appendices

Appendix 1: Ethical approval

Ref. study and ethical approval

This is to certify that the ethical committee have looked into the proposal of "Incidence of heparin-Induced Thrombocytopenia (HIT) among post-surgical orthopedic patients in Wad Medani orthopedics Hospital.

And it is found to confirm with the good medical ethics.

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FRCP, (Edin), SMSB
Chairman of the Ethical Committee
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Appendix 2: Data collection form

Patient Data

File No:

Unit:

Name:

Age:

Gender:

Residency:

D.O.A:

D.O.D:

Diagnosis:

Enoxaparin Dose and date of start:

D.O.O:

Type of Surgery:

CBC investigations:

Baseline Platelet counts:

D.O.F:

Regular use of Enoxaparin after discharge:

Platelet counts test s during & after discharge:

Platelet counts test after attending the follow up:
Appendix 3: Interview Questions

1- In your practice experience, have you ever noticed an adverse effect of a patient who used Enoxaparin? If yes: Would you give me an example?

2- Have you ever examined a patient with thrombosis who used or had been using Enoxaparin? If so, please explain?

3- Enoxaparin can cause thrombocytopenia, have you ever reported such a condition? If so, would you explain that further?

4- How important do you think is the monitoring of patients who use enoxaparin? Can you elaborate on that idea?

5- What types of patients do you think that monitoring should be performed on? Please explain?

6- In your opinion, do you think there are risk factors that can determine the incidence of the thrombocytopenia? Can you elaborate?

7- Regarding the monitoring; how regular do you think it should be performed?

8- In your opinion, do you think that monitoring could be difficult? And why?

9- What factors can influence the regular monitoring of platelet count? And what barriers can be the most challenging?

10- Do you have any solutions for monitoring difficulty?

11- What recommendations do you have regarding this monitoring?

12- Is there anything else you would like to add?