Original Article

Evaluation of Use and Outcomes of Heparins in Acute Deep Venous Thrombosis Treatment at Khartoum State Hospitals: A Descriptive Retrospective Study

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Abstract

Background: Deep venous thrombosis (DVT) considered a common emergent condition with life-threatening complications that require rapid intervention with an effective antithrombotic drug regimen; for that, this study was conducted. The current study aimed to evaluate the use and outcomes of heparins in treating acute DVT at selected hospitals in Khartoum state. **Methods:** A descriptive retrospective, hospital-based study was conducted in different hospitals at Khartoum state from July 2016 to July 2017. The sample size was 147 participants. Data were collected using a well-designed data collection form and analyzed with the Statistical Package for the Social Sciences. **Results:** A total of 147 DVT patients were included, most of them (77.6%) were females, and 49.8% of them were old and aged more than 60 years. The patients with a past medical history of major surgery were represented 27.9%. Low-molecular-weight heparins (LMWHs) were the most prescribed drugs (74.1%), of which enoxaparin at a dose of 6000 IU twice per day is the most frequently prescribed in 32% of the patients. LMWHs were shown to achieve their therapeutic goal of activated partial thromboplastin time earlier compared with unfractionated heparin (UFH). Enoxaparin 6000 IU twice daily was the most suitable regimen, since it achieved its therapeutic goal within 3 days and maintained it for up to 5 days. 86.1% of the patients were discharged to their homes, whereas 12.9% were dead, and the percentage of death increased with advanced age. **Conclusions:** Past medical history of major surgery and advanced age were the major risk factors of DVT. LMWHs are the most frequently used drugs and were more effective than UFH, and enoxaparin 6000 IU twice per day was the most suitable regimen as a fixed dose for adults.

Keywords: Deep venous thrombosis, enoxaparin, heparin, Sudan, tinzaparin

Introduction

Deep venous thrombosis (DVT) is defined as the formation of blood clots in one of the large veins, mainly in the lower leg or calf.[1] It considers manifestations as venous thromboembolism (VTE) along with pulmonary embolism.[2,3] The most substantial risk factors for DVT are surgery and malignancies, in addition to immobilization, old age, estrogen treatment, cancer, obesity, and disorders of hypercoagulation.[4-6] The reported incidence of DVT in hospitalized patients from developed nations ranges from 48 to 124 per 100,000 populations.[7,8] It represents two-third of patients with symptomatic VTE. Despite anticoagulant therapy, some patients may suffer from DVT recurrence within a few months of therapy, with a recurrence rate of 7% at 6 months. Death occurs in approximately 6% of the cases within the 1st month of diagnosis.[9]

DVT is rare in children but exponentially increases in incidence between the ages of 20 and 80 years, and the rates increase sharply after around the age of 45 years.[10] The increase in the risk of DVT with advanced age is likely related to increases in body mass with the age of 46 years, and activity decreases, frailty increases, and the number of comorbidities tend to mount with age.[11,12] There are minor gender differences in a large population DVT study, with 50 DVT per 100,000 women

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and 47 DVT per 100,000 men. Furthermore, they noted that the incidence was somewhat higher among women of childbearing age. However, in older age groups, the incidence was generally higher among men.[10] Patients undergoing surgery are subject to a 6–22-fold increase in risk for DVT, especially those associated with a higher immobilization rate.[2] Other studies revealed a higher frequency of left-sided when compared to the right-sided DVT, which suggested the possibility of left common iliac vein compression by the right common iliac artery for this left-sided association, but the exact mechanism remains unclear.[13,14]

The treatment approach in patients with acute DVT started either with unfractionated or low-molecular-weight heparin (LMWH) for at least 5–10 days; an oral anticoagulant such as warfarin is started on day 1 with a goal international normalized ratio of 2–3 for 3–6 months. With this regimen, the 3-month thrombus recurrence rate is about 5%–7%.[15] Treatment with unfractionated heparin (UFH) is based on body weight 80 IU/kg bolus, followed by a continuous infusion at 18 IU/kg per hour, and the dosage is titrated based on the activated partial thromboplastin time (aPTT). An aPTT of 1.5–2.3 times control is a desirable range, usually defined as 60–90 s.[16,17] The treatment of DVT with LMWH is either with enoxaparin in a dosage of 100 IU/kg twice daily or 150 IU once daily, or tinzaparin, in a dosage of 175 IU/kg/day.[17,18] The therapeutic goal of aPTT for LMWH varied between 54s and 69s for enoxaparin and between 101s and 140s for tinzaparin.[19]

LMWHs, compared with UFH, have fewer side effects such as bleeding, thrombocytopenia, and osteoporosis and more convenient for patients because of better bioavailability and longer biologic half-life and can be administered subcutaneously in the weight-adjusted dose for once or twice daily use.[15,20] Nevertheless, for certain groups of patients, including those with obese (body mass index >40 kg/m^2), underweight (<50 kg), high bleeding risk, or renal failure in whom the dosing of LMWH is unreliable, UFH may remain the preferred therapy of DVT.[15] In addition to that, UFH requires laboratory monitoring and dose adjustment. For these reasons, LMWHs are the parenteral treatment of choice.[21,22]

DVT is a health problem that can cause major complications for patients such as postthrombotic syndrome, pulmonary hypertension, pulmonary embolism, and major disability.[1,23] Moreover, their treatment requires restricted monitoring to avoid the side effects of drug and disease complications. Furthermore, there is no sufficient study to determine the epidemiology and treatment outcomes in Sudan; thus, this study was conducted to evaluate the risk factors for DVT and the outcomes of heparins at Khartoum state hospitals.

Methods

Study setting

A descriptive retrospective hospital-based study was conducted at Bahri Teaching Hospital, Ibrahim Malik Teaching Hospital, and Omdurman Maternity Hospital, Khartoum, Sudan. The study population was DVT patients admitted to these hospitals from July 2016 to July 2017.

Participants and study size

All patients who were diagnosed with DVT and received any type of heparin at the selected hospitals were included in this study. Eligibility criterion patients diagnosed with DVT received any type of heparin, whereas patients with liver disease were excluded from the study. Accordingly, Raosoft sample size calculator was undertaken using a 95% confidence interval, which indicated that the required sample size was 147 patient records from a total of 237.[24] A simple random sampling technique was used to select the patients' files in the department of statistics.

Data collection tool

Medical records for included participants were reviewed, and the following data were extracted using a well-designed check which contains patient demographic data (age, gender, and residence), clinical characteristics (site of DVT and risk factors), medication data (prescribing pattern and drug regimens), and the outcomes following treatment.

Statistical analysis

The data were entered for analysis using the Statistical Package for Social Sciences [SPSS] for Windows, Version 22.0 software [Armonk, NY: IBM Corp]. The results were presented in tabular form. The data were analyzed using descriptive statistics (frequency and percentages). Chi-square and ANOVA tests were applied to check the significant difference between categorical variables. $P < 0.05$ was considered statistically significant.

Ethical statement

The ethical clearance was obtained from Khartoum state Ministry of Health. The additional official agreement was obtained from the three hospitals to check the medical record; all medical records were coded with ensuring confidentiality throughout the study.

Results

147 DVT patients were enrolled in this study. Table 1 shows the sociodemographic and clinical characteristics of the participants. It was observed that the sample was distributed normally between the three hospitals, and the majority of patients were elderly within the age range above 60 years; a total of (n = 114, 77.6%) were female; and most of them (n = 113, 70.1%) came from urban areas. Clinically, the left leg was the most frequent site (n = 109, 74.1%) for DVT among patients who presented to the hospitals. It was also found that about 82.3% (n = 121) of the DVT patients had a family history of DVT [Table 1].

Regarding the treatment, the most frequently prescribed drug was enoxaparin (65.3%), followed by UFH (25.9%) and then tinzaparin (8.8%), as shown in Table 2. Moreover, enoxaparin 6000 IU given twice per day was the most

Table 1: Sociodemographic and clinical characteristics of the participants (*n*=147)

Variable	Frequency, *n* (%)
Hospitals	
Bahri Teaching Hospital	57 (38.8)
Ibrahim Malik Teaching Hospital	49 (33.3)
Omdurman Maternity Hospital	41 (27.9)
Gender	
Male	33 (22.4)
Female	114 (77.6)
Age (years)	
<20	4 (2.7)
21-40	43 (29.3)
41-60	37 (25.2)
>60	63 (49.8)
Residence	
Rural	44 (29.9)
Urban	103 (70.1)
Site of DVT	
Left leg	109 (74.1)
Right leg	30 (20.5)
Bilateral	8 (5.4)
Family history	
Yes	26 (17.7)
No	121 (82.3)
Past medical history	
None	65 (44.2)
Hypertension	15 (10.2)
Diabetes	9 (6.1)
Dyslipidemia	6 (4.1)
Major surgery	41 (27.9)
Hypertension + diabetes	5 (3.4)
Previous DVT	6 (4.1)

DVT: Deep venous thrombosis

prescribed regimen (*n* = 47, 32%) for DVT management, followed by heparin 10000 IU four times a day (*n* = 25, 17.0%). Following these treatments, 86.1% of the patients with DVT who presented to emergency departments were discharged, whereas 13.9% of them died within the 1st month of diagnosis.

Furthermore, the results of aPTT were taken before using the drug, and after 3 and 5 days from using the drug, we compare these three readings of aPTT, as demonstrated in Table 3. Regarding these, the effect of heparin 10000 IU on aPTT value regarding the frequency of dosing, both twice and four times a day regimen, will show a significant effect at 3 and 5 days compared with initial reading. However, there is no significant difference between the two regimens at 3 and 5 days. For enoxaparin, most of the regimens were raised the aPTT value, with significant effect after 3 and 5 days when compared with initial readings [Table 3], whereas tinzaparin 4500 IU with a regimen of twice daily used was raised the aPTT value, with minor significant effect at 3 and 5 days compared with initial [Table 3].

Discussion

The study revealed that DVT disease was affected both genders, with a higher rate in females (77.6%), and this may be due to that one of the three hospitals in which the study was conducted specified for maternity health that increases the frequency of female gender; this is in line with Heit 2015[10] who noted that the incidence was somewhat higher among women of childbearing age. The frequency of disease was increased as age increased with a higher frequency percentage (49.8%) at the age category of more than 60 years; this may be because of decreased mobilization rate and the rate of comorbidities with advanced age, which are considered as the major risk factors for DVT. This agrees with Bulger *et al*., who reported that the annual rate of DVT increased from 1.8 per 1000 at the age of 65–69 years to 3.1 by the age of 85–99 years which is likely related to multiple age-associated factors including an increased number of major thrombotic risk factors.[11] Our findings indicated that a higher frequency of patients came from urban areas due to the differences in lifestyle.

Regarding the risk factors, only 17.7% of the patients showed to have a family history of DVT disease, which suggested a weak association between family history and disease. These findings are in contrast to that from The Netherlands, in which the family history of VTE is considered a risk indicator, and a positive family history increases the risk of DVT more than twofold.[25] This contradiction is possibly due to the genetic differences between the European and Sudanese populations. On the other hand, past medical history of the patients with DVT revealed that major surgery was the predominant history among these patients (27.9%); this may be due to the immobilization associated with major surgery, and this is in accordance with Bulger *et al*., 2004, who reported that patients undergoing surgery are subject to a 6–22-fold increase in risk for DVT, especially those associated with higher immobilization rate, in which the surgery has been associated with activated coagulation and transient depression of fibrinolysis.[11] An increase in thrombin activation and elevated levels of plasminogen activator inhibitor-1 during the perioperative period have been described.[11]

Concerning DVT treatment, the study indicated that LMWHs were the most prescribed parenteral anticoagulant drugs; this may be due to their many advantages compared with UFH, which includes long biologic half-life, better bioavailability, and predictable anticoagulant effect.[15,26] Among LMWHs, enoxaparin was the most prescribed drug (65.3%) for treating acute DVT due to its rapid onset of action and high bioavailability compared with tinzaparin. This was in accordance with previous studies that indicated enoxaparin as a first approved LMWH with the broadest range of indications, and tinzaparin has the fewest indications, whereas dalteparin is approved for prophylaxis from VTE.[17,18]

Furthermore, the current study demonstrated that enoxaparin was given as a subcutaneous injection in different doses and frequencies, but the dose 6000 IU given twice daily was the

Table 2: Medication used to treat deep venous thrombosis among the participants (*n*=147)

Variable	Frequency, *n* (%)
Medications	
Heparin	38 (25.9)
Enoxaparin	96 (65.3)
Tinzaparin	13 (8.8)
Prescribing pattern	
Heparin 10,000 IU BID	13 (8.8)
Heparin 10,000 IU QID	25 (17.0)
Enoxaparin 4000 IU BID	13 (8.8)
Enoxaparin 6000 IU OD	14 (9.5)
Enoxaparin 6000 IU BID	47 (32.0)
Enoxaparin 8000 IU BID	22 (15.0)
Tinzaparin 4500 IU OD	13 (8.8)

Table 3: Effect of different treatment on activated partial thromboplastin time

Type of treatment	aPTT (s)		
	Initial	After 3 days	After 5 days
Heparin 1000 IU, BID	35.9±2.0	45.9±7.4**	66.1±5.4***
Heparin 1000 IU, Q6	36.3±3.0	52.6±6.4**	72.4±7.4***
Enoxaparin 4000 IU, BID	33.3±3.5	46.9±4.6***	57.2±3.7***
Enoxaparin 6000 IU, OD	34.8±1.7	49.9±4.5***	60.7±5.2***
Enoxaparin 6000 IU, BD	34.8±3.1	54.1±2.7***	65.7±5.6***
Enoxaparin 8000 IU, BD	38.3±2.6	55.1±3.9***	71.1±6.1***
Tinzaparin 4500 IU, OD	34.1±0.3	47.2±4.1*	62.7±6.2*

*P<0.05, **P<0.01, ***P<0.001 significance difference between 3 and 5 days reading versus initial aPTT reading. aPTT: Activated partial thromboplastin time

most prescribed, whereas previous reports demonstrated that the dose of enoxaparin must be according to the body weight at a dose of 100 IU/kg twice daily or 150 IU/kg once daily rather than the fixed dose.[17,26]

UFH raised the aPTT value when compared with initial regarding the frequency of dosing, although twice and four times a day regimen will show the significant effect at 3 and 5 days compared with initial, but there is no significant difference between two regimens at 3 and 5 days. This means that there was no difference in anticoagulant effects from the use of fixed dose of heparin at twice and four times a day regimen. UFH and LMWHs increased the patients' aPTT value in different proportions regarding the type of heparin, dose, and frequency of dosing. As the degree of aPTT increased, the anticoagulant and antithrombotic effects will increase. UFH has a higher effect on aPTT when compared with LMWHs at different dose regimens; this is in line with Hirsh and Raschke, who noted that compared to UFH, enoxaparin has lower anti-IIa activity relative to anti-Xa, and this translates into a reduced effect on the aPTT. The increase in the aPTT observed with UFH is mainly due to its anti-IIa activity.[27]

Enoxaparin will achieve their therapeutic goal of aPTT earlier than that of UFH, and this is due to their rapid anticoagulant effect and higher bioavailability of enoxaparin; this is in accordance with Mazzolai *et al*., 2018, who report that LMWHs have longer biologic half-life when compared with UFH.[21] Enoxaparin at a dosage regimen of 6000 IU used twice per day was the most appropriate one that achieved the therapeutic goal of aPTT at 54–69 s earlier at 3 days and maintained it at day 5 when compared with 4000 IU once-daily regimen. This will not achieve therapeutic goals until 5 days and when compared with an 8000 IU twice-daily regimen that exceeded therapeutic range at 5 days. These findings are in line with East and Wakefield, 2010[17] noted that the weight-adjusted dose of enoxaparin is 100 IU/kg twice per day. Moreover, the bodyweight of patients has an impact on dose determination, as previously shown in a study done by Walpole *et al*., 2012. They found that the average weight of adults in Africa is about 60.7 kg for that the enoxaparin regimen of 6000 IU twice per day is the most suitable regimen that produces a therapeutic effect with minimum side effects. On the other hand, Tinzaparin has a minor effect on aPTT when compared with UFH and enoxaparin. This is maybe due to the small number of DVT cases with tinzaparin in this study; this is in contradict with Thomas *et al*., 2015,[19] who report that tinzaparin increases aPTT and decreases thrombin generation more than enoxaparin. The outcomes following treatments revealed that the majority of patients with DVT were discharged 86.1%, whereas about 12.9% were dead. While, Wogan 2001,[9] in his study, reports that only about 8% of the cases were dead within one the 1st month of diagnosis.

Conclusions

Most of the patients with DVT enrolled in this study were female. Past medical history of major surgery and advanced age were considered the major risk factors for DVT. LMWHs were the most prescribed drug class compared with UFH, in which enoxaparin 6000 IU twice daily used regimen was the most prescribed. LMWHs achieved their therapeutic range earlier, and thus, they are more effective when compared with UFH. Furthermore, enoxaparin 6000 IU twice per day was the most suitable and effective regimen as a fixed daily dose, as it produced a maximum therapeutic effect with minimum side effects.

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Conflicts of interest

There are no conflicts of interest.

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