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Comparative Analysis of Time to Achieve Target Blood Parameters in Patients with Venous Thromboembolism Receiving UFH and LMWH

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ABSTRACT

Venous Thromboembolism (VTE) is a serious and potentially life-threatening condition characterized by the formation of blood clots usually occuring in the deep veins of the legs causing deep vein thrombosis (DVT) and sometimes the clot may travel to the lungs and cause a pulmonary embolism (PE). It develops as a result of endothelial injury, hypercoagulable state or stagnant blood flow [(1).] The factors that contribute to VTE include prolonged immobility due to any major surgeries and in conditions like cancer, pregnancy, or inherited clotting disorders [(2).] The symptoms of DVT include leg pain, swelling, warmth, and redness, while PE commonly presents with sudden onset of chest pain, shortness of breath, tachycardia, and sometimes hemoptysis. The diagnosis of VTE includes a combination of clinical assessment, D-dimer values, Doppler tests, CT pulmonary angiography [(3).] Treatment include drugs like Unfractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH), oral anticoagulants, thrombolytics or procedures like thrombectomy [(4)]. This study aims to estimate the time taken for blood parameters like D-dimer, platelet APTT, INR and prothrombin time which are usually abnormal in VTE conditions to achieve desirable levels by using UFH and LMWH [(5).] In our study there were 96 VTE patients among which 36 patients were treated with UFH and 63 were treated with LMWH. The results obtained suggested that both heparins were equally effective in normalising the abnormal blood parameters.

KEYWORDS: Venous Thromboembolism (VTE), Deep Vein thrombosis (DVT), pulmonary embolism (PE), Unfractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH)

INTRODUCTION

Venous Thromboembolism (VTE) is a condition that occurs when a blood clot forms in the vein. It is of 3 types Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and Cerebral Venous Sinus Thrombosis (CVST) [(1)]. DVT is a condition in which a blood clot develops in a deep vein, typically in the lower leg or pelvis or veins of the arm. Most patients may be asymptomatic but, in some, it may present with swelling, pain, tenderness, warmth, and redness. If left untreated, DVT can lead to serious complications such as pulmonary embolism (PE), where the clot escapes from the wall of a vein, travels to the lungs and prevent blood flow to a lung. Symptoms include shortness of breath, chest pain and

cough.CVST is a condition in which a blood clot forms in the venous sinuses of the brain reducing the blood supply to the brain. Sometimes a hemorrhage may occur as a result of blood cells breaking and leaking blood into the brain's tissues [3]. Symptoms include headache, seizure, blurred vision, fainting and loss of control. DVT can be assessed using Well's criteria and Padua score [6]. The Caprini score is used to calculate VTE risk by adding up each risk factor and classifying patients into four groups based on the severity of risks [7].

The etiology of VTE involves hereditary causes like Factor V Leiden and mutations in the prothrombin G20210A gene. Other factors such as hyperhomocysteinemia, vitamin deficiencies, or chronic illnesses may increase the risk of DVT.Cerebral venous thrombosis (CVT) and antiphospholipid syndrome (APS) are multifactorial and can lead to serious complications, including fetal loss and stroke. [8] The pathophysiology of VTE includes the formation of a thrombus, composed of platelets, fibrin, and blood cells typically in deep veins due to hypercoagulability or obstruction. As the clot extends proximally, it can dislodge and embolize to the lungs, causing pulmonary embolism (PE), which disrupts gas exchange and increases pulmonary vascular resistance. Individuals over 40 years of age, obese patients, patients with a history of Varicose vein, and patients who underwent any surgeries are more prone to VTE. It is diagnosed by certain blood tests including D-dimer, imaging tests like Doppler studies, RI, Contrast venography, Pulmonary angiography, Computed tomographic pulmonary angiography (CTPA) etc. [4]

Several blood parameters play crucial roles in the diagnosis, management, and risk assessment of VTE.D-dimer is a key marker, elevated in the presence of active clot formation and breakdown, and is used to rule out VTE due to its high sensitivity. D-dimer levels > 500 ng/mL suggests active clotting [9]. Platelets help in the formation and stabilization of blood clots by supporting the coagulation process. High platelet counts (thrombocytosis) can increase VTE risk, especially in conditions like cancer, while low counts (thrombocytopenia) may indicate complications such as heparin-induced thrombocytopenia (HIT). Monitoring platelet levels during anticoagulant therapy is essential to detect HIT early [10]. PT and INR measure the function of the extrinsic and common coagulation pathways and are primarily used to monitoring anticoagulation therapy with warfarin and heparin [11]. A therapeutic INR range of 2.0–3.0 is typically targeted to prevent clot recurrence. APTT assesses intrinsic and common pathways and is used to monitor unfractionated heparin therapy, with varying therapeutic ranges. These coagulation tests helps to ensure effective anticoagulation by minimizing the risk of bleeding. Abnormal baseline values may also indicate underlying coagulation disorders that contribute to VTE risk or influence treatment choices.

Usually patients are administered either heparins or oral anticoagulants. In this study we are comparing the Unfractionated Heparin with Low Molecular weight Heparin (LMWH) in normalising the abnormal blood parameters [12].

OBJECTIVE

The objective of this study is to estimate the median time taken for various blood parameters to achieve desirable level for those on UF Heparin and LMW Heparin

MATERIALS AND METHODOLOGY

This was a Retrospective Cohort study conducted to determine the efficacy of UFH and LMWH in achieving desirable levels of blood parameters and was conducted among 96 VTE patients at a Tertiary care hospital in Kerala, India for six months from November 2023 to April 2024. Participants were all patients aged between 40- 80 with a confirmed diagnosis of VTE i.e. DVT, PE or CVT. The patients below

the age of 18 years, patients who took (DAMA) i.e. Discharge Against Medical Advice and those patients administering both UFH and LMWH together were excluded from the study. The data were obtained from medical records and patient drug charts. The medical records with incomplete information on drugs were excluded from the data collection.

Profile of the study population was described using mean and SD for quantitative variables and proportions for qualitative variables. Median time to event will be assessed using Kaplan Meier curves. Difference in probability of an even at any point in time will be tested using log rank test. All analysis was done using the SAS® software. Data were analyzed using Microsoft Excel-2019.The results were approved by the Institutional review Board of the Tertiary Care Hospital, Kerala, India.

SAMPLE SIZE:

Sample size of 96 patients. Statistical formula for calculating sample size:

[Z2 * p * (1-p)/e2] / [1 + (Z2 * p * (1-p)/e2 * N]

Where,

P = Standard Deviation

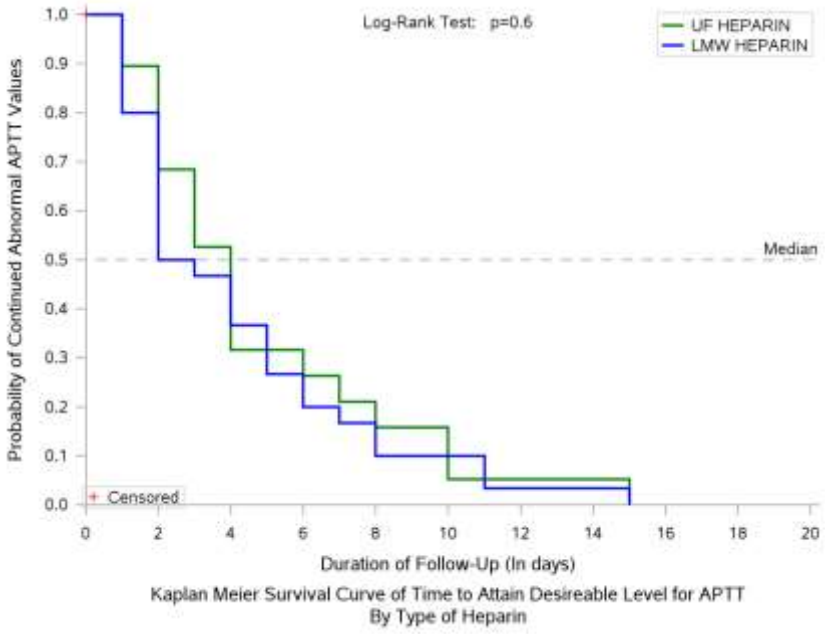
N = Population Size

e = Margin of error

Z = 95% Confidence interval of Z

RESULTS

FIGURE 1: TIME TAKEN BY BOTH HEPARINS TO ACHIEVE DESIRABLE APTT VALUES FROM INITIAL VALUES

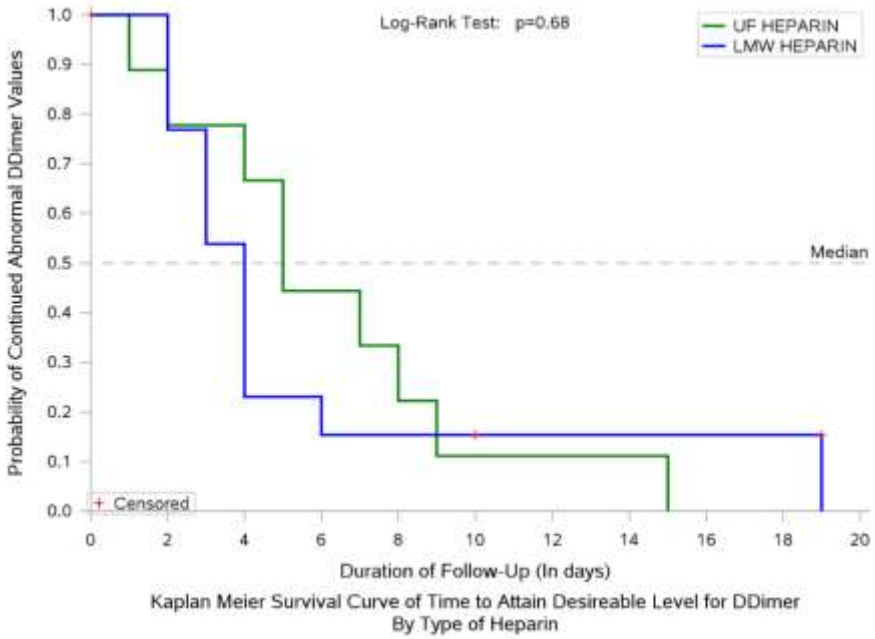


This KM curve indicates the time to attain a desirable APTT levels in patients receiving two heparins. Green line indicates UF heparin and blue indicates LMWH. X axis shows the duration of follow up in days ie how long it takes to achieve targeted APTT. Y axis shows the probability of continued abnormal APTT i.e. it starts from 1 indicating that initially all patients had abnormal APTT values. As the curve drops the proportion of patients whose APTT became normal increases. The stepwise drops reflect individual patient events (when their APTT becomes normal). Both groups reached normal APTT over 15

days. Log rank test p=0.6 indicates no significant difference between two heparin types. Dotted horizontal line at 0.5 represent median time for each group to normalise APTT. As both cross this line around the same day supports that no major difference.

Hence observed that there is no statistically significant difference between the survival curves of UF heparin and LWM heparin. This suggests that there is not enough evidence to conclude that one type of heparin is more effective than the other at normalising aPPT levels

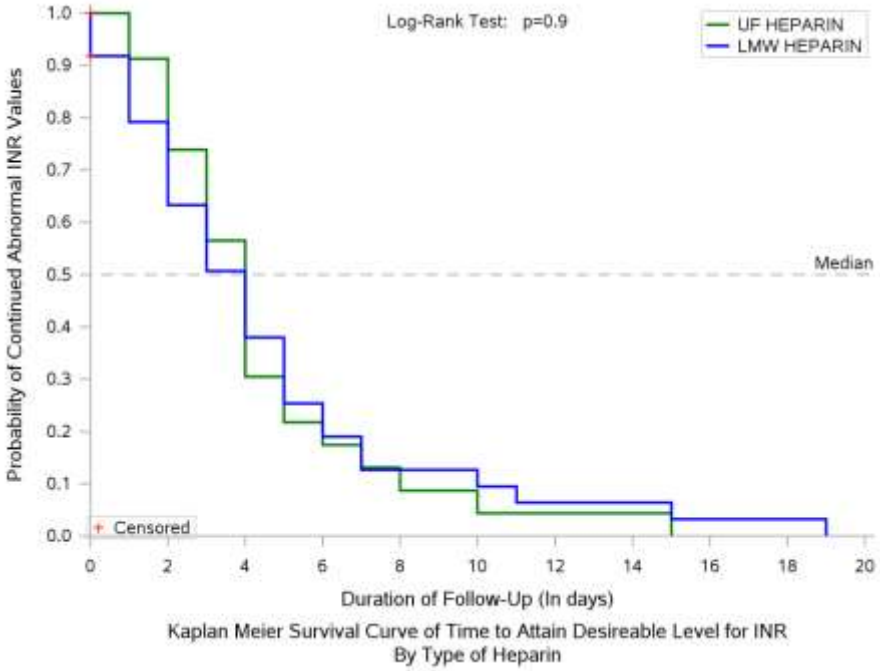
FIGURE 2: TIME TAKEN BY BOTH HEPARINS TO ACHIEVE DESIRABLE D-DIMER VALUES FROM INITIAL VALUES



This KM curve indicates the time to attain a desirable D-Dimer levels in patients receiving two heparins. .X axis shows the duration of follow up in days ie how long it takes to achieve targeted D-Dimer values. Y axis shows the probability of continued abnormal D-Dimer i.e. it starts from 1 indicating that initially all patients had abnormal D-Dimer values. Both the lines show step wise decline indicting that patients are attaining normal D-Dimer levels. And the curves are closer together suggesting that both drugs had similar normalising effects. Log rank test p=0.68 indicates no significant difference between two heparin types. Dotted horizontal line at 0.5 represent median time for each group to normalise D-Dimer. As both roughly cross this line around the same time, again supports that no major difference.

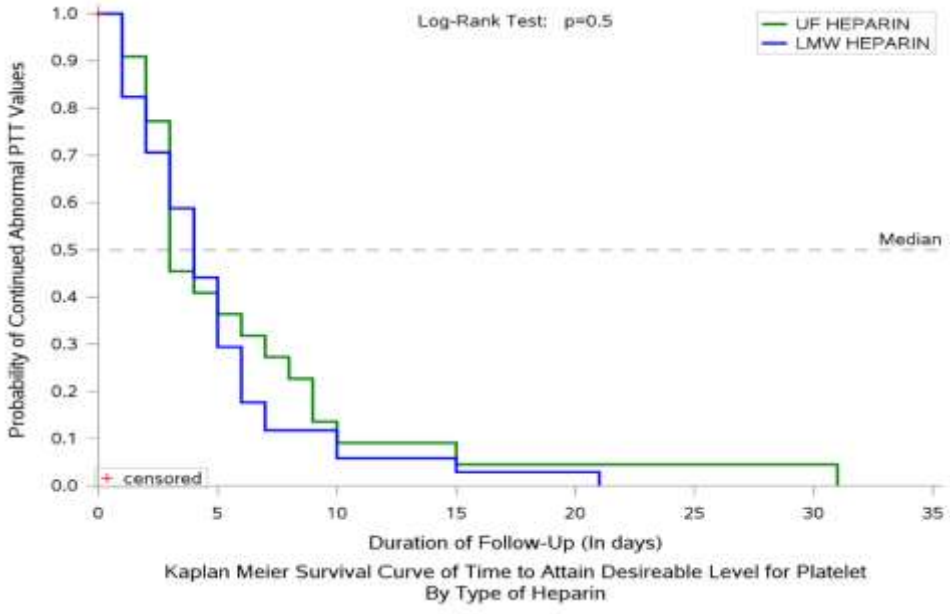
Overall, the graph shows that people who received UF Heparin were more likely to have their D Dimer values return to normal than people who received LMW Heparin, however this difference was not statistically not significant.

FIGURE 3: TIME TAKEN BY BOTH HEPARINS TO ACHIEVE DESIRABLE INR VALUES FROM INITIAL VALUES



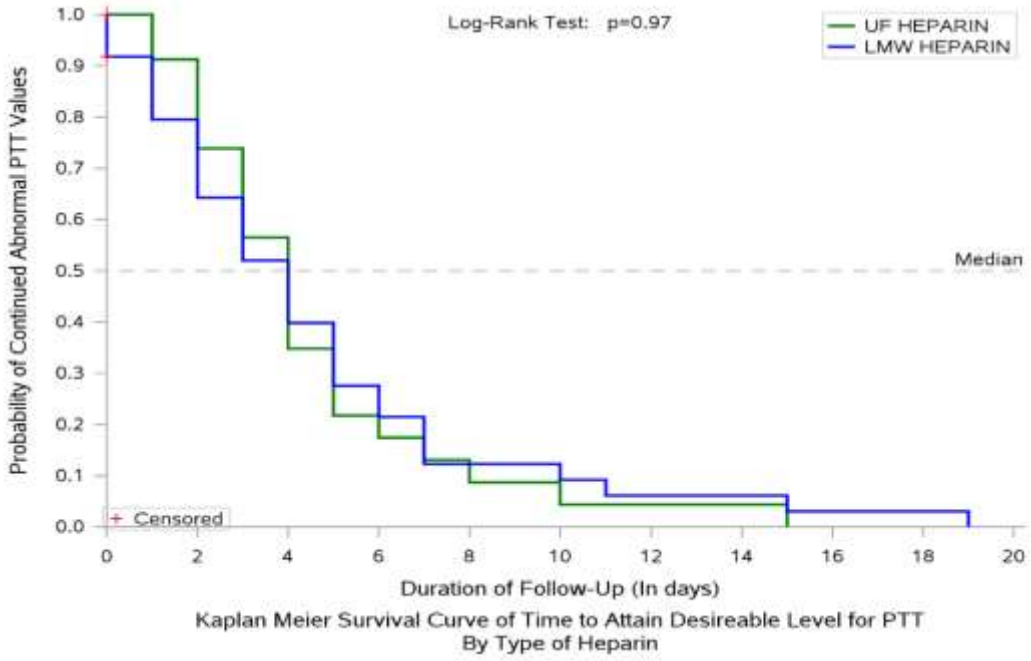
This KM curve indicates the time to attain a desirable INR levels in patients treated with two heparins. .X axis shows the duration of follow up in days i.e. how long it takes to achieve targeted INR values Y axis shows the probability of continued abnormal INR i.e. it starts from 1 indicating that initially all patients had abnormal INR values. Both the lines show gradual decline indicting that patients are attaining normal INR levels. Log rank value=0.9 indicates that there is no statistically difference between the groups in achieving target INR.

FIGURE 4: TIME TAKEN BY BOTH HEPARINS TO ACHIEVE DESIRABLE PLATELET VALUES FROM INITIAL VALUES



This KM curve indicates the time to attain a desirable platelet levels in patients treated with two heparins. .X axis shows the duration of follow up in days i.e. how long it takes to achieve targeted platelet values Y axis shows the probability of continued abnormal platelet i.e. it starts from 1 indicating that initially all patients had abnormal platelet values. Both the lines show gradual decline indicting that patients are attaining normal INR levels. Both the curves reach the 50 % in same time. Log rank value=0.5 indicates that there is no statistically difference between the groups in achieving target INR. This suggests that there is not enough evidence to conclude that one type of heparin is more effective than the other at increasing platelet levels.

FIGURE 5: TIME TAKEN BY BOTH HEPARINS TO ACHIEVE DESIRABLE PROTHROMBIN TIME VALUES FROM INITIAL VALUES



This KM curve indicates the time to attain a desirable prothrombin levels in patients treated with two heparins. .X axis shows how long it takes to achieve targeted prothrombin values Y axis shows the probability of continued abnormal prothrombin i.e. it starts from 1 indicating that initially all patients had abnormal platelet values. Both the lines show gradual decline indicting that patients are attaining normal prothrombin levels. Both the curves are closely overlapping suggests that both drugs have same effect in normalising prothrombin level Log rank value=0.97 indicates that there is no statistically difference between the groups in achieving target prothrombin. This suggests that there is not enough evidence to conclude that one type of heparin is more effective than the other at increasing prothrombin levels.

TABLE 1: COMPARISON OF TIME FOR BLOOD PARAMETERS TO ATTAIN DESIRABLE VALUE BY BOTH HEPARINS

PARAMETER	MEDIAN TIME TO NORMALISATION	CURVE PATTERN	P VALUE	INTERPRETATION
APTT	~ 7-8 days (both groups)	Nearly overlapping curves	0.6	No significant difference

D DIMER	~6-8 days	Slight earlier with UFH	0.68	No significant difference
INR	~5-6 days	Overlapping curves	0.9	No significant difference
PLATELET	~9-10 days	Overlapping	0.5	No significant difference
PROTHROMBIN TIME	~6-7 days	Identical curves	0.9	No significant difference

DISCUSSION

Venous thromboembolism is a serious coagulation disorder involving the formation of blood clots in veins. The condition is detected by the elevation of blood parameters like D-dimers. The level of platelets may be normal or slight elevated. The treatment involves UFH, LMWH, noval oral anticoagulants and warfarin with each having its own therapeutic benefits and side effects. The APTT, INR,,prothrombin time may be prolonged after the initiation of the treatment[13]

The time taken for the five key coagulation parameters – APTT ,D-dimer, INR,platelet count and prothrombin time to achieve desirable levels from the initial values were analysed by using Kapler-Meier curve which revealed that there is no statistically significant difference between the UFH and LMWH.The survival curves for each blood parameters were nearly overlapping indicating that both drugs have similar effect in normalising the abnormal levels and log rank p values all exceeding 0.05(range: 0.5-0.97).But some studies highlighted that LMWH is effective and safe with reduced risk of heparin induced thrombocytopenia and with predictable pharmacokinetics [14]

It has been found from our study that both LMWH and UF Heparin are equally effective to achieve desirable APTT levels from initial values which were similar to the study conducted by Hull R D and et.al which was **a** randomized, open-label, noninferiority trial involving 703 patients with acute venous thromboembolism, comparing fixed-dose subcutaneous low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH)**;** the result observed is that UFH was as effective and safe as LMWH, with similar rates of recurrent VTE and major bleeding[15].

In case of D-dimer levels it has been found that both UF heparin and LMWH equally reduces D Dimer levels. The results were similar to the published by Earl U Esseboon which was a randomized, nonblinded comparative study involving 37 patients with acute pulmonary embolism; the result observed is that dalteparin is at least as effective as unfractionated heparin in reducing coagulation activity and perfusion abnormalities during early treatment [16]

Our study showed both LMWH and UF Heparin have no significant difference in achieving desirable INR and platelets levels from initial values which were contrast contrast to the results from the studies by Nicolaides et al both showed that LMWH may have a faster INR and platelet normalization compared to UFH. [17] Study suggested that both LMWH and UF Heparin have no significant difference in achieving desirable PTT levels from initial values. which were similar to the study conducted by Jack Hirsh et al "which states that Both UF Heparin and LMWH have little effect on prothrombin time [18]

UFH is preferred in renal impaired patients as it has shorter half life but It requires frequent APTT monitoring and it is usually administered within hospital settings' LMWH on the other hand has predictable pharmacokinetics, and available in fixed dose administration without the need for routine monitoring but it is expensive when compared to UFH.Hence the choice between UFH and LMWH may

be guided by factors like patient specific characteristics including comorbidities , cost , ease of administration and resource availability.

CONCLUSION

In conclusion, our study identified that both Low Molecular Weight Heparin (LMWH) and Unfractionated Heparin (UFH) exhibit similar efficiency in achieving critical coagulation parameters like APTT, D dimer, INR,platelets and prothrombin time. Our data does not reveal any significant differences between the both heparins with only conclusion that Heparin had been associated with more bleeding risk when compared to LMWH and require frequent monitoring. On the other hand LMWH has less bleeding risk. However certain studies also describe about the slight benefits of LMWH in faster INR or platelet normalisation.The coagulation tests thus play a significant role in monitoring and assessing the clotting status of patients with VTE thereby help in making prognosis and guide clinical decisions. This study enforces that the selection of anticoagulant must be based on patient specific characteristics and resource availability. Overall, in tertiary care setting both LMWH and UFH are reliable options for the management of venous thromboembolism.

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