“A ONE YEAR RANDOMIZED CONTROL TRIAL TO COMPARE LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN IN THE RATE OF REDUCTION OF LOWER LIMB GIRTH IN A CASE OF DEEP VEIN THROMBOSIS”

By

REG No. BH0115006

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY (M. S.)
in
GENERAL SURGERY

DEPARTMENT OF SURGERY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"A ONE YEAR RANDOMIZED CONTROL TRIAL STUDY TO COMPARE LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN IN THE RATE OF REDUCTION OF LOWER LIMB GIRTH IN A CASE OF DEEP VEIN THROMBOSIS"** is a bonafide research work done by **CANDIDATE REG. NO. BH0115006**.

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LIST OF ABBREVIATIONS USED

ABG	-	Arterial blood gas
aPTT	-	Activated partial thromboplastin time
B.W.	-	Body weight
BC	-	Before Christ
BD	-	Twice daily
BP	-	Blood pressure
CBC	-	Complete blood count
CDT	-	Catheter-directed thrombolysis
CHF	-	Congenital heart failure
cm	-	Centimeter
CNS	-	Central nervous system
CT	-	Computed tomography
cumm	-	Cubic millimeter
DVT	-	Deep vein thrombosis
ECG	-	Electrocardiogram
ELISA	-	Enzyme linked immunosorbent assay
EPCR	-	Endothelial protein C receptor
FXa	-	Fondaparinux
g/dL	-	Grams per deciliter
Ga	-	Calf girth after treatment
Gb	-	Calf girth before treatment
GCS	-	Graduated compression stocking
gm%	-	Gram percent
HIT	-	Heparin induced thrombocytopenia

i.v.	-	Intravenous
ICU	-	Intensive care unit
INR	-	International normalized ratio
IPC	-	Intermittent pneumatic compression
IVC	-	Inferior vena cava
LFT	-	Liver function test
LMWH	-	Low-molecular-weight heparin
mg	-	Milligram
mg/kg	-	Milligram per kilogram
MI	-	Myocardial infarction
mL	-	Milli litre
mm Hg	-	Millimeters of mercury
mol. wt.	-	Molecular weight
MR	-	Mini renal
MRI	-	Magnetic resonance imaging
NS	-	Normal saline
OD	-	Once a day
OPD	-	Out patient department
P/A	-	Per abdomen
PaO_2	-	Partial pressure of oxygen
PE	-	Pulmonary embolism
PIOPED	-	Prospective Investigation of Pulmonary Embolism Diagnosis
PREPIC	-	Prevention du Risque d'Embolie Pulmonaire par Interruption Cave

PT	-	Prothrombin time
PTS	-	Post-thrombotic syndrome
RE-COVER	-	Randomized Evaluation of Long-Term Anticoagulation Therapy trial
s.c.	-	Subcutaneous
SD	-	Standard deviation
SimpliRED	-	Red blood cell whole blood agglutination assay
THR	-	Total hip replacement
TKA	-	Total knee arthroplasty
TKR	-	Total knee replacement
TM	-	Thrombomodulin
UFH	-	Unfractionated heparin
V/Q	-	Ventilation/perfusion
viz.,	-	Namely
VKAs	-	Vitamin K antagonists
vs	-	Versus
VTE	-	Venous thromboembolism
vWF	-	Von Willebrand factor
µL	-	Micro litre

ABSTRACT

Background and objectives

Low Molecular Weight Heparin has emerged as a new generation of drug, which is reported to be as safe and efficacious as unfractionated heparins. This study was aimed to compare Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of deep vein thrombosis (DVT).

Methodology

This one year randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016. A total of 60 patients with lower limb swelling, and diagnosed to have DVT were divided into two groups of 30 each as group A (treatment with LMWH by subcutaneous route) and group B **(**Treatment with UFH by intravenous infusion).

Results

Majority of the patients (76.67%) males. The male to female ratio was 3.2:1. (p=1.000). The mean age in group A and group B was also comparable (44.43±15.12 vs 45.13±13.45 years;p=0.850). The other pre treatment characteristics of the study population were comparable (p> 0.050) in both the groups. In patients with group A, the mean calf girth before treatment was 35.34±2.98 cms which reduced to 30.91±2.07 cms after treatment. In group B, the mean calf girth before treatment was 34.55±4.48 cms which reduced to 30.28±3.69 cms after treatment. However, the mean calf girth at all the intervals

that is 6,12,24,48,72 and 96 as well as after treatment was comparable in group A and group B ($p>0.050$). The mean percentage rate of reduction in calf girth before and after treatment was slightly high in group A compared to group B (12.35±3.31 vs 12.16±3.13 percent; $p=0.817$) but same was not true statistically.

Conclusion and interpretation

The LMWH is as effective as UFH in the treatment of DVT as measured by rate of reduction in lower limb girth.

Key words

Deep vein thrombosis; Low Molecular Weight Heparin; Unfractionated Heparins;

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INTRODUCTION

The term thrombosis refers to the formation of an abnormal mass within the vascular system from constituents of blood. When this process occurs within the deep veins, it is referred to as deep vein thrombosis (DVT). It can lead to complications such as postphlebitic syndrome, pulmonary embolism and eventually death.[1]

Deep-vein thrombosis has an estimated annual incidence of 67 per 100,000 among the general populations.[2,3] Despite adequate therapy, 1% to 8% of patients in whom pulmonary embolism develops will die,[4] whereas others will experience long-term complications such as postphlebitic syndrome (40%)[5] and chronic thromboembolic pulmonary hypertension (4%).[6]

The condition is predisposed by transient and reversible clinical risk factors such as surgery or oestrogen exposure, or long term and permanent factors, such as hemiparesis from stroke.[7]

Clinical features are nonspecific; hence new strategies for diagnosing this condition have evolved.[1]

An accurate diagnosis of DVT is extremely important to prevent potentially fatal acute complication like pulmonary embolism (PE) and long-term complications like postphlebitis syndrome and pulmonary hypertension. It is also important to avoid unjustified therapy with anticoagulants with associated high risk of bleeding in patients misdiagnosed with the condition.[8]

Prevention of VTE requires a reliable tool for the stratification of the risk for developing VTE, screening strategies and effective prophylaxis to significantly reduce mortality in intensive care unit (ICU) patients. Common occurrences in VTE, including endothelial abnormality, stasis of blood flow and hypercoagulability, are typically observed in the critically ill.[9]

DVT is treatable and reversible in the earlier stages, so to choose the appropriate modality of treatment is important.

Therapeutic objectives are prevention of thrombus extension and embolization, and the prevention of recurrent episodes of venous thromboembolism (VTE) to reduce the risk of fatal pulmonary embolism. Despite the availability of different treatment strategies, the large majority of patients commonly receive anticoagulation.[10-12]

Patients need to be started on treatment as soon as the diagnosis is confirmed by objective testing, and because anticoagulant drugs with a rapid onset of action are needed in this phase, three parenteral therapeutic options are currently available for initial treatment: Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and fondaparinux.[13] Heparin anticoagulation is the standard of care for DVT treatment and is proven to significantly reduce the risk of PE, as well as recurrent DVT.[12] The choice between UFH and LMWH for the treatment of patients with PE or DVT is controversial. Data suggest that both classes of drugs have comparable efficacy and safety.[14]

Low-molecular-weight heparins, which are prepared by the depolymerization of standard heparin, have proved to be safe and effective in preventing

thromboembolism in patients at high risk[15] and to be at least as safe and effective as standard heparin for the treatment of acute proximal DVT, provided standard heparin administered by continuous intravenous infusion and dosage adjusted to keep the activated partial-thromboplastin time within a prescribed range. The low-molecular-weight heparins are administered by subcutaneous injection in doses adjusted for the patient's weight, without laboratory monitoring. This is more convenient method of administering the treatment which is possible as low-molecular weight heparins have a more predictable anticoagulant response than standard heparin, a longer plasma half life, and better bioavailability when administered subcutaneously. These properties of low-molecular-weight heparins offer a potential advantage of treating the patients with proved deep-vein thrombosis at home rather than in the hospital.[16-19]

Unfractionated Heparins (UFH) were used since many years, now Low Molecular Weight Heparin) LMWH have emerged as a new generation of drugs, which are as safe and efficacious as UFH. Each class of drug has its own set of benefits. So the treatment is individualized. Further there are limited numbers of studies that compare the Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of Deep Vein Thrombosis, especially in India.

Considering the above facts, this study was designed to compare Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of Deep Vein Thrombosis.

OBJECTIVES

The objectives of this study were to compare Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of Deep Vein Thrombosis.

REVIEW OF LITERATURE

DEEP VEIN THROMBOIS

Historical note

Deep vein thrombosis (DVT) is a common disease. However, unlike that of varicose veins, which have been depicted since ages in art and literature, its description was more recent in the history of medicine. The first well-documented case of DVT was reported during the Middle Ages: in 1271, Raoul developed a unilateral edema in the ankle, which then extended to the leg. The number of reported DVT cases steadily increased thereafter, particularly in pregnant and postpartum women. During the first half of the 20th century, well before the discovery of anticoagulants, many therapeutic approaches were used, and those approaches arose from the pathologic hypotheses that prevailed at their time.[20]

Despite the development of anticoagulants, and the fact that they were thought to dramatically decrease DVT mortality, numerous complementary treatments have also been developed in the last 50 years: these include vena cava clips and surgical thrombectomy, and are intended to decrease mortality or to prevent late complications. Most of these treatments have now been abandoned, or even forgotten. In this review, we also recall the discovery and the use of vitamin K antagonists and heparin, which have constituted the mainstay of treatment for decades. We also bring some perspective to historical aspects of this disease and its treatment, notably regarding elastic compression and early mobilization, and also abandoned and complementary treatments. In these times of change regarding DVT

treatment, mainly marked by the arrival of new oral anticoagulants, efforts of physicians through the ages to treat this common disease provide a beautiful example of the history of knowledge.[20]

Anatomy

Deep venous thrombosis (DVT) of the lower extremity is a prevalent disease, yet distressingly, little is known about the anatomy of the process.[21,22]

The venous system of lower limb can be divided into two major classes – superficial and deep venous system. Insufficiencies can present in any of these veins, and treatment can vary depending on the classification.

Deep Venous System

These are primary veins that drain venous blood from the lower extremity. They include:[23]

- Common Femoral
- Deep femoral
- External Iliac
- Femoral
- Popliteal
- Peroneal
- Tibial (Anterior and Posterior)

Deep veins are located within the muscle fascia which allows a high volume and pressure of blood to pass through the veins. They account for approximately 90-

95% of venous blood return to the heart. Formation of clot in Deep veins leads to deep vein thrombosis, or DVT.[23]

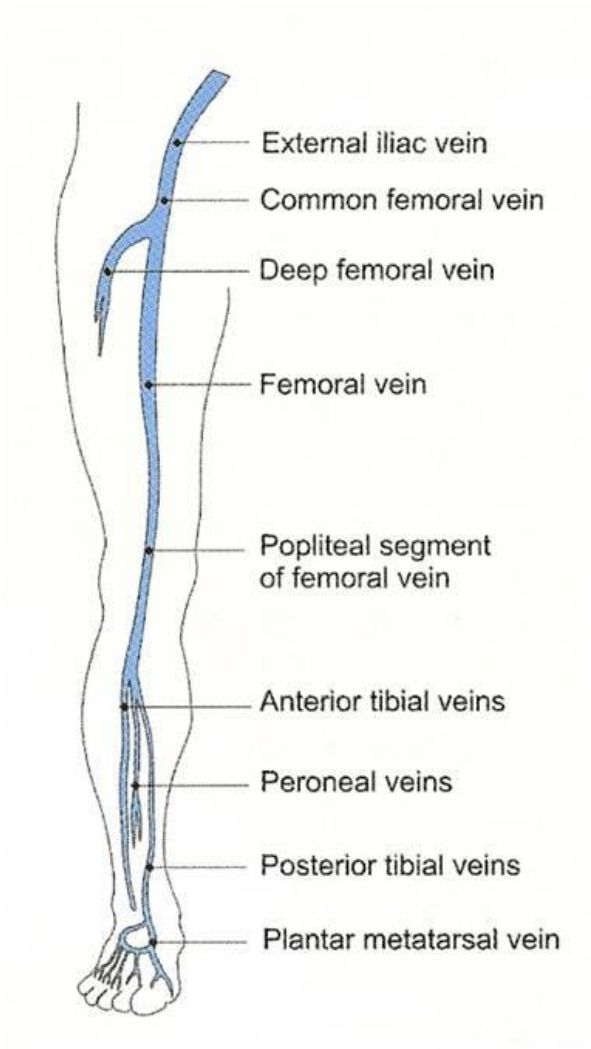


Figure 1. Deep venous system[23]

Deep veins are located within the muscle fascia which allows a high volume and pressure of blood to pass through the veins. They account for approximately 90-95% of venous blood return to the heart. Deep veins can form deep vein thrombosis, or DVT.[23]

The peripheral venous system functions both as a reservoir to hold extra blood and as a conduit to return blood from the periphery to the heart and lungs. Unlike arteries, which possess 3 well-defined layers (a thin intima, a well-developed muscular media, and a fibrous adventitia), most veins are composed of a single tissue layer. Only the largest veins possess internal elastic membranes, and this layer is thin and unevenly distributed, providing little buttress against high internal pressures. The correct functioning of the venous system depends on a complex series of valves and pumps that are individually frail and prone to malfunction, yet the system as a whole performs remarkably well under these extremely adverse conditions.[24]

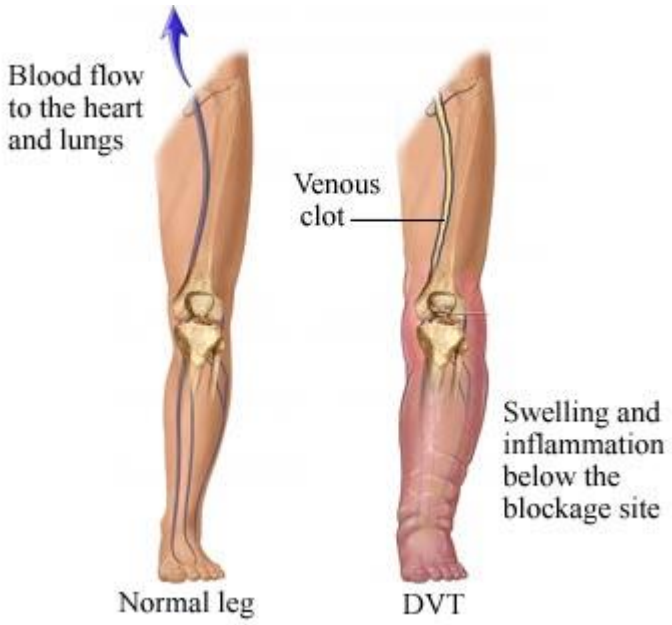


Figure 2. Deep Vein Thrombosis[25]

Primary collecting veins of the lower extremity are passive, thin-walled reservoirs that are tremendously distensible. Most are suprafascial, surrounded by loosely bound alveolar and fatty tissue that is easily displaced. These suprafascial collecting veins can dilate to accommodate large volumes of blood with little

increase in back pressure so that the volume of blood sequestered within the venous system at any moment can vary by a factor of 2 or more without interfering with the normal function of the veins. Suprafascial collecting veins belong to the superficial venous system.[24]

Outflow from collecting veins is via secondary conduit veins that have thicker walls and are less distensible. Most of these veins are subfascial and are surrounded by tissues that are dense and tightly bound. These subfascial veins belong to the deep venous system, through which all venous blood eventually passes through on its way back to the right atrium of the heart. The lower limb deep venous system is typically thought of as 2 separate systems, one below the knee and one above.[24]

The calf has 3 groups of paired deep veins: the anterior tibial veins, draining the dorsum of the foot; the posterior tibial veins, draining the sole of the foot; and the peroneal veins, draining the lateral aspect of the foot. Venous sinusoids within the calf muscle coalesce to form soleal and gastrocnemius intramuscular venous plexuses, which join the peroneal veins in the mid calf. These veins play an important role in the muscle pump function of the calf. Just below the knee, these tibial veins join to become the popliteal vein, which too can be paired on occasion.[24]

Together, the calf's muscles and deep vein system form a complex array of valves and pumps, often referred to as the "peripheral heart," that function to push blood upward from the feet against gravity. The calf-muscle pump is analogous to the common hand-pump bulb of a sphygmomanometer filling a blood pressure cuff. Before pumping has started, the pressure is neutral and equal everywhere throughout

the system and the calf fills with blood, typically 100-150 mL. When the calf contracts, the feeding perforator vein valves are forced closed and the outflow valves are forced open driving the blood proximally. When the calf is allowed to relax, the veins and sinusoids refill from the superficial venous system via perforating veins, and the outflow valve is then forced shut, preventing retrograde flow. With each "contraction," 40-60% of the calf's venous volume is driven proximally.[24,26]

The deep veins of the thigh begin distally with the popliteal vein as it courses proximally behind the knee and then passes through the adductor canal, at which point its name changes to the femoral vein. (This important deep vein is sometimes incorrectly referred to as the superficial femoral vein in a misguided attempt to distinguish it from the profunda femoris, or deep femoral vein, a short, stubby vein that usually has its origin in terminal muscle tributaries within the deep muscles of the lateral thigh but may communicate with the popliteal vein in up to 10% of patients.)[24]

The term superficial femoral vein should never be used, because the femoral vein is in fact a deep vein and is not part of the superficial venous system. In the proximal thigh, the femoral vein and the deep femoral vein unite to form the common femoral vein, which passes upwards above the groin crease to become the iliac vein.[24]

The external iliac vein is the continuation of the femoral vein as it passes upward behind the inguinal ligament. At the level of the sacroiliac joint, it unites with the hypogastric vein to form the common iliac vein. The left common iliac is longer than the right and more oblique in its course, passing behind the right

common iliac artery. This anatomic asymmetry sometimes results in compression of the left common iliac vein by the right common iliac artery to produce May-Thurner syndrome, a left-sided iliac outflow obstruction with localized adventitial fibrosis and intimal proliferation, often with associated deep venous thrombosis. At the level of the fifth lumbar vertebra, the 2 common iliac veins come together at an acute angle to form the inferior vena cava.[24]

Epidemiology

Worldwide

DVT is a major and a common preventable cause of death worldwide. It affects approximately 0.1% of persons per year. The overall average age- and sex-adjusted annual incidence of venous thromboembolism (VTE) is 117 per 100,000 (DVT, 48 per 100,000; PE, 69 per 100,000), with higher age-adjusted rates among males than females (130 vs 110 per 100,000, respectively).[3] Both sexes are equally afflicted by a first VTE, men having a higher risk of recurrent thrombosis.[27,28] DVT is predominantly a disease of the elderly with an incidence that rises markedly with age.[3]

A study by Keenan and White[29] revealed that African-American patients are the highest risk group for first-time VTE. Hispanic patients' risk is about half that of Caucasians. The risk of recurrence in Caucasians is lower than that of African-Americans and Hispanics.

The incidence of VTE is low in children. Annual incidences of 0.07 to 0.14 per 10,000 children and 5.3 per 10,000 hospital admissions have been reported in Caucasian studies.[30,31] This low incidence may be due to decreased capacity to

generate thrombin, increased capacity of alpha-2-macroglobulin to inhibit thrombin, and enhanced antithrombin potential of vessel walls. The highest incidence in childhood is during the neonatal period, followed by another peak in adolescence.[32] The incidence rate is comparatively higher in adolescent females because of pregnancy and use of oral contraceptive agents.[33]

Pregnant women have a much higher risk of VTE than non pregnant women of similar age and the risk has been shown to be higher after cesarean section than after vaginal delivery.[34] The incidence appears to be the highest in the postpartum period.[35]

In a study conducted in an African population, the documented rate was 48 DVT per 100,000 births per year.[35]

The approximate risk for DVT following general surgery procedures is 15% to 40%. It nearly doubles after hip or knee replacement surgery or hip fracture surgery (40% to 60%).[36] Though regarded mainly as a surgical complication, most symptomatic VTE events and fatal PE occur in medical patients.[37]

India

Though the exact incidence of VTE in the Indian population is not known because of non-uniform reporting of such incidents, its incidence is not expected to be different from that in the western population.[38]

Natural Course

DVT in the lower extremity may arise in the calf veins or in the proximal veins. The thrombus may extend proximally to iliac veins and inferior vena cava.

The incidence of DVT in the upper extremity is also increasing because of widespread use of central venous catheters. DVT may occur in deep pelvic veins or renal veins. There may be formation of thrombus in the right side of the heart due to atrial fibrillation.[39]

The most clinically important and fatal, pulmonary embolism (PE) occurs from proximal more than distal DVT in the leg. PE occurs in 50% of patients with proximal DVT,[40] while asymptomatic thrombosis of the leg veins has been observed in 70% of patients with PE.[41]

On early ambulation, the thrombus in the deep veins may resolve completely. Post-thrombotic syndrome may develop in 25% of patients, 2 years after the initial diagnosis and proper treatment of DVT.[42] The damage to the venous valves causes chronic venous congestion.[39]

Inadequate treatment of DVT results in 20%-50% risk of recurrent VTE,[43] and collaterals develop parallel to the thrombosed segment of the vein.[39]

A chronic unresolved thrombus leads to chronic thromboembolic pulmonary hypertension and right heart failure in 3.8% of patients at 2 years after diagnosis and proper treatment.[44]

Pathogenesis/classification

Thrombus formation preferentially starts in the valve pockets of the veins of the calf and extends proximally. This is especially true for those that occur following surgery.[45] Though most thrombi begin intraoperatively, some start a few days, weeks, or months after surgery. Lending its support to the origin of thrombus in

valve pockets is a recent hypothesis of an increased expression of endothelial protein C receptor (EPCR) and thrombomodulin (TM) and a decreased expression of Von Willebrand factor (vWF) noted in valve sinus endothelium compared with vein luminal endothelium. This means an upregulation of anticoagulants (EPCR, TM) and a downregulation of procoagulant (vWF) properties of the valvular sinus endothelium.[46]

Thrombus is composed predominantly of fibrin and red cells (red or static thrombus). Venous thrombus must be differentiated from postmortem clot at autopsy. Postmortem clots are gelatinous and have a dark red dependent portion (formed by red cells that have settled by gravity and a yellow chicken fat supernatant resembling melted and clotted chicken fat). They are usually not attached to the underlying wall. This is in contrast to the venous thrombi which are firmer. They almost always have a point of attachment to the wall and transection reveals vague strands of pale gray fibrin.[47]

DVT in the lower limb can be classified as a) proximal, when the popliteal vein or thigh veins are involved or b) distal, when the calf veins are involved. Clinically, proximal vein thrombosis is of greater importance and is associated with serious chronic diseases such as active cancer, congestive cardiac failure, respiratory insufficiency, or age above 75 years, whereas distal thrombosis is more often associated with risk factors such as recent surgery and immobilization. Fatal PE is far more likely to result from proximal DVT. Post-thrombotic syndrome, a chronic, potentially disabling condition characterized by leg swelling, pain, venous ectasia, and skin induration, is established by 1 year after DVT in 17% to 50% of cases.[1,48]

Uncommon presentations of VTE are forms of acute massive venous thrombosis with obstruction of venous drainage to the extremity. These include phlegmasia alba dolens, phlegmasia cerulea dolens, and venous gangrene. In phlegmasia alba dolens, the thrombosis involves only the major deep venous channels of the extremity, sparing collateral veins. However, in phlegmasia cerulea dolens, the thrombosis extends to the collateral vein, resulting in massive fluid sequestration and more significant edema.[1]

Etiology

Rudolph Virchow in 1856 described the factors that predispose to DVT, which are relevant even today. Virchow's triad comprises of: venous stasis, damage to venous wall and hypercoagulability.[39]

Risk factors

Rudolph Virchow described three conditions that predispose to thrombus. This triad includes endothelial injury, stasis of blood flow, and blood hypercoagulability.[1]

Stasis and endothelial injury are important in DVT following trauma or surgery while hypercoagulability is responsible for most cases of spontaneous DVT. At least 96% of patients treated for VTE have been shown to have at least one risk factor.[49]

Risk can be classified as acquired or genetic. When genetic defects are combined with one or more acquired risk factors, or in combined genetic defects or

combination of two acquired defects, it results in a risk of VTE that exceeds the separate effects of a single factor.[50]

In adults, the clinical conditions that predispose to VTE are increasing age, cancer and its treatment, prolonged immobility, stroke or paralysis, previous VTE, congestive heart failure, acute infection, pregnancy or puerperium, dehydration, hormonal treatment, varicose veins, long air travel, acute inflammatory bowel disease, rheumatological disease, and nephrotic syndrome. Other acquired factors that have recently been associated with increased risk of VTE disorders include persistent elevation of D-dimer and atherosclerotic disease.[1,51]

Oral contraceptive pills, especially those that contain third-generation progestins increase the risk of VTE. Risk of DVT associated with long-duration air travel is called economy class syndrome. It is 3% to 12% in a long-haul flight with stasis, hypoxia, and dehydration being pathophysiological changes that increase the risk.[1] van Aken et al.[52] demonstrated that subjects with elevated levels of interleukin-8 have increased risk of venous thrombosis, supporting an important role of inflammation in etiopathogenesis of venous thrombosis.

Clayton et al.[53] have described a strong association between recent respiratory infection and VTE. They demonstrated an increased risk of DVT in the month following infection and PE in 3 months following infection, both persisting up to a year.

In the pediatric age group, the most important triggering risk factors for development of thromboembolism are the presence of central venous lines, cancer, and chemotherapy. Severe infection, sickle cell disease, trauma, and

antiphospholipid syndromes are clinical conditions associated with hypercoagulability states.[54]

Genetic risk factors can be divided into strong, moderate, and weak factors.[55] Strong factors are deficiencies of anti-thrombin, protein C and protein S. Moderately strong factors include factor V Leiden, prothrombin 20210A, non-O blood group, and fibrinogen 10034T. Weak genetic risk factors include fibrinogen, factor XIII and factor XI variants.[1]

Patient-specific risk factors

These are either acquired or inherited hypercoagulable states associated with a high incidence of DVT and PE.[39]

Inherited patient-specific factors[39]

- Factor V Leiden and Cambridge mutation (activated protein C resistance)
- Prothrombin gene mutation (20210A)
- Congenital deficiencies of Antithrombin III, Protein C, and Protein S
- Dysfibrogenaemia
- Hyperhomocysteinaemia
- An inherited abnormality may not be found in 40%-60% of patients with idiopathic VTE.

Acquired patient-specific factors

Past history of thromboembolism, malignancy; age>40 years; obesity; varicose veins; prolonged immobilization; dehydration; heart failure; nephrotic syndrome; stroke; myeloproliferative syndrome; pregnancy; puerperium; oral

contraceptives; hormone replacement therapy; and antiphospholipid antibody syndrome.[39]

The overall risk of thrombosis in cancer patients is sevenfold as compared to non-cancer patients. Drugs used in cancer may directly contribute to thrombosis[39]

Surgery-specific risk factors

Predisposing factors for the development of DVT after surgery[39,56,57]

Event	Low risk	Moderate risk	High risk
General surgery	< 40	> 40	> 40
Age (years)			
Duration of surgery (Minutes)	< 60	> 60	> 60
Othopaedic surgery			THR, TKR
Trauma			Extensive soft tissue injury, major fractures, multiple trauma sites
Medical condition	Pregnancy	Postpartum period MI, CHF	Stroke

Incidence of DVT and PE after surgery[39,56,57]

Event	Low risk %	Moderate risk %	High risk %
DVT without prophylaxia	2	10-40	40-80
Symptomatic PE	0.2	1-8	5-10
Fetal PE	0.002	0.1-0.4	1-5

There are some operative procedures and medical conditions associated with high incidence of postoperative DVT and PE. Depending on the clinical risk factors, patients may be categorized into low-, medium- and high-risk groups.[39,56,57]

Clinical features

History and clinical examination are not reliable ways of diagnosing DVT.[58] Lower extremity DVT can be symptomatic or asymptomatic. Patients with lower extremity DVT often do not present with erythema, pain, warmth, swelling, or tenderness. Symptomatic patients with proximal DVT may present with lower extremity pain, calf tenderness, and lower extremity swelling.[1,59,60] Homans' sign may be demonstrable in DVT. Most of these features lack specificity; hence clinical evaluation usually implies the need for further evaluation. The left leg is the commonest site for venous thrombosis in pregnancy[35] and in acute massive venous thrombosis. This may be due to compression of the left iliac vein by the right iliac artery (May–Thurner syndrome).[61]

Phlegmasia alba dolens is characterized by edema, pain, and blanching without cyanosis while phlegmasia cerulea dolens is characterized by these features in addition to cyanosis, which characteristically progresses from distal to proximal areas and bleb/bulla formation.[1]

Signs and Symptoms of DVT

The clinical diagnosis is difficult as the signs and symptoms are not specific. Some patients may complain of pain in the calf muscles and thighs and may present with swollen legs. There may be presence of tenderness, a palpable thickened vein, distended veins, discolouration or cyanosis.[39]

Clinical prediction rules

A commonly accepted evidence-based approach to diagnosis of VTE is the use of a clinical model that standardizes the clinical assessment (combining risk factors, signs and symptoms) and subsequently stratifies patients suspected of DVT.[1]

Though this model has been used for both primary care patients and secondary settings, there is no doubt that it does not guarantee accurate estimation of risk in primary care patients in whom DVT is suspected.[62]

The most commonly recommended model is that developed by Wells and colleagues. Based on clinical presentation and risk factors, an initial model was developed to group patients into low-, moderate-, and high-probability groups. The high-probability group has 85% risk of DVT, the moderate-probability group 33% risk, and the low-probability group 5% risk.[63] However, in a later study, Wells and colleagues[64] further streamlined the diagnostic process by stratifying patients into two risk categories: “DVT unlikely” if the clinical score is ≤1 and “DVT likely” if the clinical score is ≥2.

Pretest probability assessment (Wells score)[64]

	Points
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or major surgery within 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep veins	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema limited to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previous DVT	1
Alternative diagnosis as likely as or more likely than DVT	−2

Notes: DVT unlikely: ≤1; DVT likely: ≥2

D-dimer assay

D-dimer is a degradation product of cross-linked fibrin that is formed immediately after thrombin-generated fibrin clots are degraded by plasmin. It reflects a global activation of blood coagulation and fibrinolysis.[65] It is the best recognized biomarker for the initial assessment of suspected VTE. The combination of clinical risk stratification and a D-dimer test can exclude VTE in more than 25% of patients presenting with symptoms suggestive of VTE without the need for additional investigations.[66] Even in patients with clinically suspected recurrent DVT,

this combination (clinical evaluation and D-dimer) has proved to be useful for excluding DVT, especially in patients included in the lower clinical pretest probability group.[1]

Levels of D-dimer can be measured using three types of assay:[1]

- Enzyme linked immunosorbent assay (ELISA).
- Latex agglutination assay.
- Red blood cell whole blood agglutination assay (simpliRED).

These assays differ in sensitivity, specificity, likelihood ratio, and variability among patients with suspected VTE. ELISAs dominate the comparative ranking among D-dimer assays for sensitivity and negative likelihood ratio.[1]

D-dimer assays are highly sensitive (values up to 95%), but have poor specificity to prove VTE. The negative predictive value for patients with a negative D-dimer blood test is nearly 100%. Hence a negative value of D-dimer may safely rule out both DVT and PE. False positive D-dimer results have been noted in inflammation, pregnancy, malignancy, and in the elderly. Clinical usefulness of the measurement of D-dimer has been shown to decrease with age. The use of age-dependent cut-off values of D-dimer assays is still a matter of controversy. Elevated D-dimer was found to be predictive of poor outcome (persistent thrombosis, recurrence or post-thrombotic syndrome) in children with an acute thrombotic event. False negative D-dimer results have been noted after heparin use; hence it has been recommended that D-dimer assay should be done prior to administering heparin to a

patient. Other causes of false negative D-dimer results are late presentation (symptoms longer than 2 weeks) and small below-knee DVT.[1]

Venous ultrasonography

Venous ultrasonography is the investigation of choice in patients stratified as DVT likely.[67] It is noninvasive, safe, available, and relatively inexpensive. There are three types of venous ultrasonography: compression ultrasound (B-mode imaging only), duplex ultrasound (B-mode imaging and Doppler waveform analysis), and color Doppler imaging alone. In duplex ultrasonography, blood flow in normal vein is spontaneous, phasic with respiration, and can be augmented by manual pressure. In color flow sonography, pulsed Doppler signal is used to produce images.[68] Compression ultrasound is typically performed on the proximal deep veins, specifically the common femoral, femoral, and popliteal veins, whereas a combination of duplex ultrasound and color duplex is more often used to investigate the calf and iliac veins.[69]

The major ultrasonographic criterion for detecting venous thrombosis is failure to compress the vein lumen under gentle probe pressure. Other criteria for ultrasonographic diagnosis of venous thrombosis include loss of phasic pattern in which flow is defined as continuous, response to valsava or augmentation (Duplex ultrasound), and complete absence of spectral or color Doppler signals from the vein lumen.[70]

The other advantages of venous ultrasound are its ability to diagnose other pathologies (Baker's cysts, superficial or intramuscular hematomas, lymphadenopathy, femoral aneurysm, superficial thrombophlebitis, and abscess),

and the fact that there is no risk of exposure to irradiation, while its major limitation is its reduced ability to diagnose distal thrombus.[60] Venous compressibility may be limited by a patient's characteristics such as obesity, edema, and tenderness as well as by casts or immobilization devices that limit access to the extremity. Compression B-mode ultrasonography with or without color Duplex imaging has a sensitivity of 95% and a specificity of 96% for diagnosing symptomatic, proximal DVT.[71] For DVT in the calf vein, the sensitivity of venous ultrasound is only 73%.[72]

Repeat or serial venous ultrasound examination is indicated for initial negative examination in symptomatic patients who are highly suspicious for DVT and in whom an alternative form of imaging is contraindicated or not available. Serial testing has been found unnecessary for those in whom DVT is unlikely by Wells score and has a negative D-dimer test.[1]

Contrast venography

Venography is the definitive diagnostic test for DVT, but it is rarely done because the noninvasive tests (D-dimer and venous ultrasound) are more appropriate and accurate to perform in acute DVT episodes. It involves cannulation of a pedal vein with injection of a contrast medium, usually noniodinated, eg, Omnipaque. A large volume of Omnipaque diluted with normal saline results in better deep venous filling and improved image quality.[73]

The most reliable cardinal sign for the diagnosis of phlebothrombosis using venogram is a constant intraluminal filling defect evident in two or more views.[73] Another reliable criterion is an abrupt cutoff of a deep vein, a sign difficult to

interpret in patients with previous DVT.[59] It is highly sensitive especially in identifying the location, extent and attachment of a clot and also highly specific.[1]

Being invasive and painful remains its major setback. The patient is exposed to irradiation and there is also an additional risk of allergic reaction and renal dysfunction. Occasionally a new DVT may be induced by venography,[74] probably due to venous wall irritation and endothelial damage. The use of nonionic contrast medium has reduced considerably risks of anaphylactic reaction and thrombogenecity or may have even eliminated them.[1]

Impedance plethysmography

The technique is based on measurement of the rate of change in impedance between two electrodes on the calf when a venous occlusion cuff is deflated. Free outflow of venous blood produces a rapid change in impedance while delay in outflow, in the presence of a DVT, leads to a more gradual change.[75] It is portable, safe, and noninvasive but its main drawback remains an apparent insensitivity to calf thrombi and small, nonobstructing proximal vein thrombi.[1]

Magnetic resonance imaging (MRI)

This investigative modality has high sensitivity in detecting calf and pelvic DVTs,[76] and upper extremity venous thromboses.[77] It is also relevant in ruling out differential diagnoses in patients suspected of DVT. MRI is the diagnostic test of choice for suspected iliac vein or inferior vena caval thrombosis when computed tomography venography is contraindicated or technically inadequate. There is no risk of ionizing radiation but it is costly, scarce, and reader expertise is required.

Diagnosis of DVT[39]

1. Compression/duplex ultrasonography of femoral and popliteal veins has both sensitivity and specificity of 97% in detecting DVT in a symptomatic patient. It is sensitive for proximal vein thrombosis but less sensitive for calf vein thrombosis.
2. Impedance plethysmography records the electrical impedance of the calf region following a temporary occlusion of proximal veins. The sensitivity of this method is 96%, 50% and 38% for the diagnosis of acute DVT of the proximal, popliteal and distal veins, respectively.
3. Contrast venography remains the gold standard for the diagnosis of DVT. It is able to detect all clinical forms of DVT, including thrombosis in calf veins, pelvis and inferior vena cava.
4. Radionuclide ascending venography assesses the "thrombus burden" in the femoral, iliac, caval and pulmonary circulation.[78] It has a sensitivity of 90% and specificity of 92% in detecting DVT in the proximal leg veins.
5. Plasma D-dimer - A negative D-dimer result can exclude DVT and PE in a patient with suspected VTE.

Once VTE is diagnosed, further tests may be done:[39]

1. To have baseline tests - prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count, before starting anticoagulants.

2. To identify inherited risk factors as the cause of VTE, as these patients require lifelong or extended period of management. In acute life-saving situations, this may not be possible.

Pulmonary Embolism

The clinical diagnosis of acute pulmonary embolism is not very accurate as signs and symptoms of PE are not very specific. Based on the clinical presentation, Well's Diagnostic Scoring System has been used for the diagnosis of PE. A high probability score, viz., >6 out of a maximum score of 12.5, represents high probability (58%) of PE. The diagnosis becomes more difficult in patients with coexisting cardiac or pulmonary disease. The most frequent clinical manifestations in patients with PE are dyspnoea, tachypnoea, pleuritic pain, one or more of which occur in 97% of patients with PE.[39,79]

Diagnosis of PE

Certain diagnostic tests are performed to confirm the diagnosis of PE.[39]

1. ECG - An S wave in lead I, a Q wave in lead III, an inverted T wave in lead III are some of the characteristic changes in acute PE (S_1 , Q_3 , T_3 pattern). Arrhythmias, right ventricular strain, P pulmonale, right ventricular hypertrophy, and right bundle branch block may be present in some cases. Non-specific abnormalities of the ST segment or T wave may occur in more than 49% of cases.[79]
2. X-ray chest - Atelectasis or pulmonary parenchymal abnormality may occur in 68% of patients. An elevated haemidiaphragm, pleural effusion or pulmonary oedema may be present.[39]

3. Arterial blood gas analysis (ABG) analysis - PaO_2 of ≤80 mm Hg may be present in 26% of patients.[39,79]

4. Ventilation/perfusion scan (V/Q scan) - Interpretation of V/Q scan, using PIOPED criteria (National Collaborative Study of the Prospective Investigation of Pulmonary Embolism Diagnosis) showed high-probability results indicative of PE in 87% of patients. A normal V/Q scan entirely excluded PE.[39]

5. Pulmonary angiography is a gold standard test, but less frequently performed due to the availability of CT/MRI/spiral CT angiography. A diagnostic strategy that includes clinical evaluation, V/Q scan and evaluation for DVT would decrease the number of patients who require pulmonary angiography from 72% to 33%.[39]

6. CT/MRI/spiral CT angiography has a high specificity for the identification of main and lobar emboli and can exclude other pulmonary diseases.

7. Plasma D-dimer - A negative D-dimer result can exclude DVT and PE in a patient with suspected VTE.[39]

Algorithm for the diagnosis of DVT

The first step is the pretest probability assessment using an established model such as the Wells score (Figure 1). If score is ≤1 (DVT unlikely), D-dimer assay is done. If assay is negative, DVT is excluded and the patient can be discharged without further investigations. If assay is positive, a venous ultrasound is indicated. Negative venous ultrasound scan excludes the diagnosis of DVT. Diagnosis of DVT is made if venous ultrasonography is positive.[1]

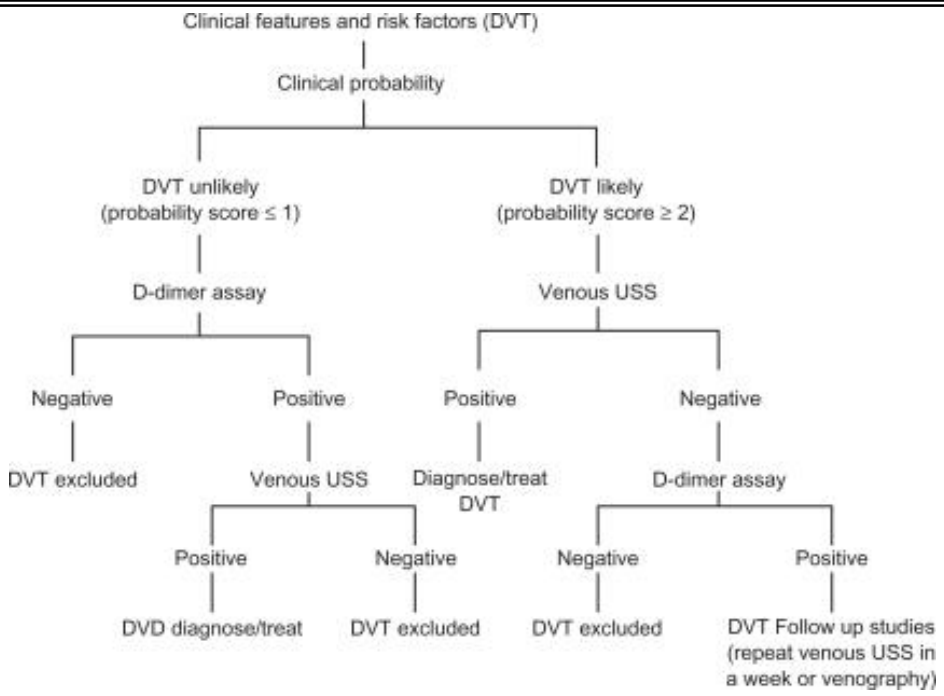


Figure 3. Algorithm for diagnosing DVT using clinical assessment, D-dimer testing, and venous ultrasonography[1]

If the DVT is likely (probability score ≥2), venous ultrasonography is indicated. DVT is diagnosed and treated if venous ultrasound is positive. If negative, D-dimer assay should be done. Negative D-dimer excludes the diagnosis of DVT while a positive result is an indication for follow-up studies; repeat ultrasound in 6 to 8 days or do venography. This algorithm is not used in pregnancy because D-dimer is falsely elevated.[1]

Treatment

The history of DVT treatment started more than 700 years ago, and has involved medical and surgical treatments. All major breakthroughs have been made during the last 100 years. During the first half of the last century, anticoagulants were discovered, shifting the issue from the fear of death to less severe and less frequent complications: VTE recurrence and major bleeding. The second half of the

century was characterized by the simplification of anticoagulant treatment, which allowed ambulatory treatment of the disease and the end of the bed-rest dogma. Complementary treatments were developed, but have not provided sufficiently good results to justify their use in routine practice. The next steps in the improvement of DVT treatment will probably focus on decreasing DVT morbidity, such as PTS, for which therapeutic options are currently limited.[1] New oral anticoagulants might have the potential to decrease this morbidity through safer and longer duration of treatment. Another option under development is the use of microbubbles for safe early thrombus removal. Finally, the main treatments for atherothrombosis, antiplatelet agents and statins, could be used to reinforce the DVT therapeutic arsenal in the coming years. Indeed, both drugs have recently been demonstrated to prevent VTE effectively. This is a therapeutic confirmation of the suspected pathophysiologic link between VTE and atherothombotic diseases. The numerous ongoing therapeutic trials assessing various promising potential treatments for DVT are clear evidence of the dynamism of venous thrombosis research.[1]

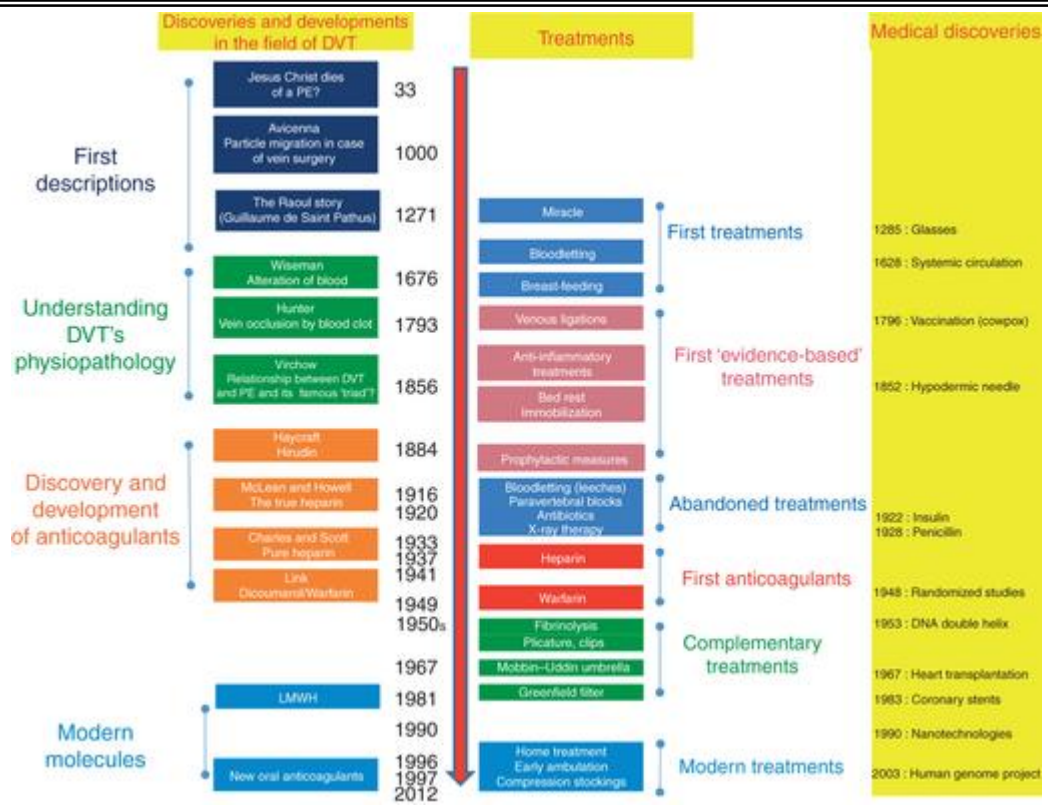


Figure 4. Brief summary of deep vein thrombosis (DVT) history and treatment. LMWH, low molecular weight heparin; PE, pulmonary embolism[20]

Heparin

The first isolated anticoagulant was hirudin, obtained in 1884 by Haycraft.[80] It was extracted from the saliva of leeches. However, it could not be used as a potent anticoagulant agent until its production by genetic engineering in 1986. Thus, the first anticoagulant that could be effectively used for the treatment of DVT was heparin. It was discovered in 1916 by McLean[20]

McLean noticed that these extracts, and more particularly heparphosphatide, became anticoagulant agents after long-term exposure to air. In 1918, Howell renamed heparphosphatide, which was a mixture of phospholipids, 'heparin'.[20]

Four years later, he discovered true heparin, a water-soluble mucopolysaccharide from dog liver. A dispute over the paternity of the discovery started between the two scientists. However, this dispute might well have been vain, as it emerged later that the anticoagulant isolated years earlier in 1911 by Doyon after peptone shock was, in fact, heparin.[20]

In 1933, Charles and Scott succeeded in producing pure crystalline heparin, allowing its use in humans, which began in 1935. The severity of DVT and the absence of convincing effective treatment were probably the main reasons for the rapid spread of this innovative drug. As was the case for today's modern anticoagulants, the first indication for heparin was thromboprophylaxis in surgical patients: in 1937, Murray and Crafoord published the first series of patients, and this was followed in the next year by a series of patients treated for acute venous thromboembolism (VTE).[20]

Despite the absence of randomized placebo-controlled trials, the effectiveness of heparin was almost immediately considered to be unquestionable: in Bauer's comparative historical series of patients (1929–1938 vs. 1940–1949), mortality from PE among inpatients with symptomatic DVT dropped from 18% to 0.4% after the introduction of anticoagulants.[81]

Therefore, in the early 1940s, heparin was already widely used, when available. The duration of heparin treatment varied between centers, but was usually 7–10 days.[81,82] The introduction of oral vitamin K antagonists (VKAs) for this indication in 1941 allowed treatments to be prolonged.[20]

Vitamin K antagonists (VKAs)

The story of VKAs begins in the in the prairies of North Dakota and Alberta at the beginning of the 20th century. A mysterious hemorrhagic disease decimated cattle in the area, ruining numerous farmers. In 1921, Schoefield, a Canadian veterinary pathologist, showed that the disease was caused by spoiled sweet clover. It could be prevented by withdrawal of the spoiled clover from food, and could be treated by blood transfusion. In 1939, Link and his co-workers provided evidence that coumarin, a non-pathogenic agent, was oxidized to dicoumarol in moldy bay, and they demonstrated that the effects of both dicumarol and spoiled clover could be reversed by vitamin K. Two years later, dicoumarol was used for the first time to treat DVTs.[20]

The proliferation of rats was a public health concern; rodent behavior, and particularly their habit of eating small pieces of foodstuff and the presence of tasters among them, made eradication by fast-acting poisons ineffective. Link decided to test the anticoagulant power of all coumarins that had been synthesized in his laboratory between 1940 and 1944 to develop the optimal rodenticide. Here started the story of warfarin, initially launched in 1948 as the ideal rat poison and considered to be too toxic for human use.[20]

However, the unsuccessful suicide attempt of a navy inductee with 567 mg of warfarin (absorbed in 5 days) demonstrated that this molecule was not as toxic as initially believed. This opened the way to its commercialization as a therapeutic agent in 1954.[20]

Interestingly, heparin and VKAs never really competed with each other for the treatment of VTE. Physicians quickly realized that the two drugs were complementary: heparin is parenteral and immediately effective, whereas VKAs are taken orally, allowing longer courses of treatment.[83] Thus, only a few years after the first use of VKAs to treat VTE, the classic sequential use of heparin followed by VKAs was already prescribed: in the Jorpes series of 445 cases of DVT managed in Sweden from 1945 to 1948, most patients benefited from this type of therapeutic scheme; at the same time, in the absence of contraindications to anticoagulants (bleeding, or renal or hepatic insufficiency), 31 of 37 patients hospitalized for DVT at Cleveland university hospital were prescribed heparin followed by dicoumarol.[20,81,83]

The modern era: ambulatory management of DVT and the development of complementary treatments (since 1950)

Unlike the previous period, the last 60 years have been characterized by major progress in the field of diagnostics rather than therapeutic management. This has dramatically modified DVT presentation and management. Venography, which, although developed by Berberich and Hirsch in 1923, has been widely used only since the 1970s after the standardization of the procedure. Physicians no longer treated clinically suspected DVT but objectively confirmed DVT. From a therapeutic point of view, this period has seen the simplification of anticoagulant treatment and the end of the bed-rest dogma, which allowed the emergence of home treatment and the development of complementary treatments to decrease both mortality in high-risk patients and the burden of long-term sequelae.[20]

LMWH, early ambulation, and home treatment of DVT

Before the anticoagulant era, bed rest was usually prescribed for 6 weeks for cases of DVT. This attitude was based on pathophysiologic data. Indeed, during the first 6 weeks, namely the 'acute phase' of DVT, the thrombus was considered non-adherent to the vessel wall and therefore at high risk of migration. The duration of bed rest was also based on more practical considerations: as diagnosis of DVT was clinical, only the most symptomatic/proximal cases were recognized, and bed rest was the most effective analgesic available. However, prolonged immobilization was often associated with serious adverse consequences, including ankle or knee ankylosis, and amyotrophia.[20]

To prevent such outcomes, Dagron, in 1905, suggested reducing strict bed rest in a splint to the first 10 days. In the 1930s, a growing number of authors started to raise serious doubts about this management, and told in favor of early ambulation and the use of compression stockings to fix the thrombus in place. Since then, bed rest has been shortened, being recommended only during heparin treatment (~ 10 days) or even only as long as the pain lasts.[20]

However, in the absence of clear evidence of its harmlessness, most physicians remained reluctant to recommend immediate mobilization, for fear of thrombus migration. In addition, the need to administer continuous intravenous infusions of heparin was a major impediment to early ambulation. This explains why bed rest, lasting for 5–7 days, was still included in DVT treatment as late as the beginning of the 1990s.[20]

The most significant step in the simplification of anticoagulant treatment was the development of LMWH, which, in most cases, does not require laboratory monitoring. Those molecules were introduced in Europe at the beginning of the 1980s, and their use was widespread within 10 years.[20] In 1996, Levine demonstrated that LMWH given at home was as safe and effective as unfractionated heparin administered in the hospital to treat proximal DVT.[84] This was confirmed by Boccalon in the Vascular Midi-Pyrenees study, in which home treatment with LMWH was as effective as inpatient treatment with LMWH.[85] In the same year, Partsch's small randomized trial provided evidence that, relative to bed rest, early ambulation with compression stockings improved pain and counteracted swelling without increasing the risk of PE.[86] These studies were rapidly followed by widespread implementation of early ambulation with compression stockings in outpatient settings, which has now become the standard and, indeed, recommended management.[20,87]

Complementary treatments

Compression therapy

The use of compression therapy was reported during ancient times: Hippocrates, in his *Corpus Hippocraticum* (450–350 BC), prescribed compression bandages to treat leg ulcers. In his treatise entitled *Chirurgica Magna*, which remained a standard reference in Europe for almost four centuries, Guy de Chauliac, a French surgeon, recommended treating varicose veins with bandages.[20]

It is only from the late 19th century, after observing that superficial vein thromboses disappeared rapidly after application of compression bandages, that

Fischer and Lasker, two German phlebologists, started prescribing compression bandages to their patients with DVT. However, the prolonged bed rest imposed on patients with DVT at that time prevented the diffusion of this approach to DVT treatment. Compression bandages started to be more widely used when anticoagulants became available. They were usually prescribed at the end of heparin treatment, once ambulation was authorized.[20] A demonstration of their usefulness in preventing post-thrombotic syndrome (PTS) was provided by Brandjes in 1997.[88]

Surgical and endovascular treatments

Heparin was the treatment of choice for DVT in the 1950s, but surgery was still used, notably in cases of severe VTE. The surgical procedure was mainly bilateral, femoral or IVC ligation; IVC ligation was associated with a high fatality rate (14%). To reduce surgery-related adverse outcomes, various devices were proposed from the mid-1950s onwards for temporary or partial interruption of the IVC: temporary exclusion of the IVC with removable metal or plastic clips; temporary ligation of the IVC with absorbable catgut; and plication or compartmentalization of the IVC with a mechanical stapler, dividing it into multiple small channels.[20]

However, these devices did not provide substantial clinical improvement, and were associated with a rate of IVC thrombosis narrowing of 30%.[20]

In 1958, De Weese constructed the first intraluminal ‘harpgrip’ filter, which could block the transit of emboli without significantly disturbing the function or dynamics of the venous system.[89] It showed promising results in preventing PE, but its placement still required major surgery and general anesthesia. This problem was

solved with the Mobin–Uddin umbrella (1967, and released for general clinical use in 1970), which could be installed with a simple catheter under local anesthesia. In addition to potential migration, one of the major and most frequent complications of this filter was gradual obstruction of the IVC. This was finally partially prevented by coating the device with heparin.[20]

In 1981, Greenfield developed the first true percutaneous filter, which did not necessitate any venotomy;[90] this was followed by a rapid increase in the indications for and number of implantations of IVC filters.[20] In 1998, the PREPIC trial showed no clear benefit of additional IVC filters in patients with DVT and without contraindications to anticoagulants, largely because of high late thrombosis rates in the filter group.[91] From that moment, the indications for, and interest in, IVC filters decreased, at least in Europe. Temporary caval filtration in the acute phase of DVT is a possible alternative to permanent IVC filters. Indeed, it has the potential to decrease short-term VTE mortality in high-risk DVT patients without increasing the risk of long-term adverse outcomes (VTE recurrence and PTS). The concept was first developed by Eichelter in 1968, with his removable, umbrella-tipped catheter tied to the femoral vein. However, truly retrievable filters (without a catheter and without persisting venous access) became available for clinical use only two decades ago. Therapeutic trials are currently underway.[20]

From thrombectomy to thrombolysis to decrease the PTS burden

Other treatments complementary to anticoagulants have been developed, with the aim of preventing long-term morbidity – thanks to early thrombus removal – rather than of lowering mortality. The first venous thrombectomy, without ligation

of the upper extremity of the thrombosed venous segment, was performed by Läwen in 1938. Twenty years later, Mahorner and Fontaine improved the technique, following the surgical procedure with a course of anticoagulant treatment to prevent rethrombosis. Thrombi were removed at the iliac level by abdominal pressure and by the passage of tubes through the femoral venotomy, and at the calf level by massaging or by elevating and compressing the leg. However, thrombectomy was rarely performed, owing to the persistent risk of fatal intraoperative embolism and a high re-thrombosis rate. Despite subsequent progress, such as the use of Fogarty balloons (1963) or the creation of a transient arteriovenous fistula (1974) to prevent early re-thrombosis, surgical thrombectomy is now not recommended for the routine treatment of proximal DVT.[20]

In current practice, early thrombus removal mainly relies on the use of pharmacologic thrombolytic agents. Recently, a randomized study suggested that thrombolysis was slightly superior to anticoagulants and compression stockings alone in preventing PTS. However, confirmatory studies are still ongoing.[20]

Current Treatment options

The goal of therapy for DVT is to prevent the extension of thrombus, acute PE, recurrence of thrombosis, and the development of late complications such as pulmonary hypertension and post-thrombotic syndrome. The initial treatment usually involves achieving a therapeutic dose of UFH or LMWH, or with fondaparinux.

Studies have shown that the efficacy of treatment with heparin largely depends on the ability to achieve a critical therapeutic ratio within the first 24 hours

of treatment,[92,93] i.e. achieving an activated partial thromboplastin time (aPTT) that is 1.5 times the mean of control value or the upper limit of normal aPTT range (aPTT ratio) of 1.5 to 2.5. This level corresponds to a heparin blood level of 0.3 to 0.7 U/mL by amidolytic antifactor Xa assays.[94]

Because of the advantages of LMWH, it is recommended over unfractionated UFH for treatment of acute DVT. UFH is, however, preferred in patients with severe renal failure as LMWH is mainly excreted via the kidneys. Heparin is initially given with warfarin and stopped after a minimum of 4 to 5 days, at which time the international normalized ratio (INR) should be within 2.0 to 3.0 (therapeutic range). This overlap with warfarin is essential because factors II, IX, X will not be affected until after 5 days, hence the intrinsic clotting pathway is intact. The initial prolongation of INR is mainly due to the effect of depression of factor VII which has a half-life of 5 to 7 hours.[1]

Warfarin remains the drug of choice for long-term therapy to prevent clot formation once acute anticoagulation is achieved. LMWH is, however, preferred after long-term therapy of DVT in pregnancy as warfarin therapy is contraindicated,[95] and in patients with cancer. Long-term anticoagulant therapy with LMWH is more effective than warfarin at preventing recurrent venous thrombosis in cancer patients without a statistically significant bleeding risk.[96]

The duration of anticoagulation depends on whether the patient has a first episode of DVT, ongoing risk factors for VTE disease, and known thrombophlebitis.[97] In patients with first proximal DVT occurring in the context of a transient risk factor such as surgery or trauma, the risk of recurrence is very low and

a limited duration of treatment (3 months) is adequate.[98,99] Long-term anticoagulation therapy should be considered for recurrent thromboses, patients with ongoing risk such as active cancer and a first unprovoked proximal DVT or PE where no risk factors for bleeding are present, and where, the anticoagulation control is good. This may be particularly the case if D-dimer is raised after discontinuing anticoagulation, in males, in those with post-thrombotic syndrome, and in those with antiphospholipid antibodies.[100,101]

Thrombolytic therapy

This is rarely indicated. The risk of major bleeding, including intracranial hemorrhage, should be weighed against the benefits of a complete and rapid lysis of thrombi. It is indicated in massive DVT which leads to phlegmasia cerulean dolens and threatened limb loss. The available thrombolytic agents include tissue plasminogen activator, streptokinase, and urokinase.[1]

Endovascular thrombolytic methods have evolved considerably in recent years. Catheter-directed thrombolysis (CDT) can be used to treat DVTs as an adjunct to medical therapy.[102] Current evidence suggests that CDT can reduce clot burden and DVT recurrence and consequently prevent the formation of post-thrombotic syndrome compared with systemic anticoagulation.[102] Pharmacomechanical CDT is now routinely used in some centers for the treatment of acute iliofemoral DVT.[103]

Appropriate indications may include younger individuals with acute proximal thromboses, a long life expectancy, and relatively few comorbidities. Limb-threatening thromboses may also be treated with CDT, although the

subsequent mortality remains high.[102] A number of randomized controlled trials are currently underway comparing the longer-term outcomes of CDT compared with anticoagulation alone.[1]

Vena cava filters

Vena cava filters are indicated in very few circumstances. They include absolute contraindication to anticoagulation, life-threatening hemorrhage on anticoagulation, and the failure of adequate anticoagulation.[104] Absolute contraindications to anticoagulation include central nervous system (CNS) hemorrhage, overt gastrointestinal bleeding, retroperitoneal hemorrhage, massive hemoptysis, cerebral metastases, massive cerebrovascular accident, CNS trauma, and significant thrombocytopenia (<50,000/μL).[104] They may be retrievable or non-retrievable, most of the newly developed ones being retrievable.

Studies to assess the effectiveness of filters revealed significantly fewer patients suffering PE in the short term, but no significant effect on PE. There was a higher rate of recurrent DVT in the long term.[105] Complications of inferior vena cava filters include hematoma over the insertion site, DVT at the site of insertion, filter migration, filter erosion through the inferior vena cava wall, filter embolization, and inferior vena cava thrombosis/obstruction.[106]

Prophylaxis

Mechanical

Mechanical methods of prophylaxis against DVT include intermittent pneumatic compression (IPC) device, graduated compression stocking (GCS), and

the venous foot pump. Intermittent pneumatic compression enhances blood flow in the deep veins of the leg, preventing venous stasis and hence preventing venous thrombosis.[1] Agu et al.[107] have shown that these mechanical methods reduce postoperative venous thrombosis. A Cochrane review[108] showed a reduction of VTE by about 50% with the use of graduated compression stockings. Intermittent pneumatic compression, in addition to preventing venous thrombosis, has been shown to reduce plasminogen activator inhibitor-1, thereby increasing endogenous fibrinolytic activity.[1]

Compared with compression alone, combined prophylactic modalities decrease significantly the incidence of VTE. Compared with pharmacological prophylaxis alone, combined modalities reduce significantly the incidence of DVT, but the effect on PE is unknown. This is recommended especially for high-risk patients.[109]

A mechanical method of DVT prophylaxis is indicated in patients at high risk of bleeding with anticoagulation prophylaxis. These includes patients with active or recent gastrointestinal bleeding, patients with hemorrhagic stroke, and those with hemostatic defects such as severe thrombocytopenia. It is contraindicated in patients with evidence of leg ischemia due to peripheral vascular disease. There is a theoretical risk of fibrinolysis and clot dislodgement. Leg wrappings and stockings with no pressure gradient are ineffective in the prevention of DVT.[1]

Hilleren-Listerud demonstrated that knee-length GCS and IPC devices are as effective as thigh-length GCS and IPC devices. They are also more comfortable, cheaper and more user-friendly for the patient.[110]

Chin et al.[111] compared the efficacy and safety of different modes of thromboembolic prophylaxis (IPC, GCS, and enoxaparin) for elective total knee arthroplasty (TKA) in Asian patient and recommended IPC as the preferred method of thromboprophylaxis for TKA. However no meaningful difference in performance between GCS and IPC was demonstrated by Morris and Woodcock.[1]

Daily use of elastic compression stockings after proximal DVT reduced the incidence of postphlebitis syndrome by 50%.[1]

Other mechanical means in both medical and surgical patients include ambulation and exercises involving foot extension. They improve venous flow and should be encouraged.[1]

Pharmacological

Unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), fondaparinux, and the new oral direct selective thrombin inhibitors and factor Xa inhibitors are effective pharmacological agents for prophylaxis of DVT. Studies have shown that the incidence of all DVTs, proximal DVT, and all PE including fatal PE has been reduced by low-dose UFH.[112,113]

Unfractionated heparin

There is an increased incidence of major bleeding in 5% of cases. A prothrombotic immune-mediated, heparin-induced thrombocytopenia (HIT) occurs in 0.5% to 5% of patients treated for at least 5 days with UFH. Antibodies to heparin-PF4 complex are formed. HIT is characterized by an unexplained 50% or

more decrease in the platelet count, often to<150 × 10^{9} /L. Heparin should be discontinued in such situation.[39]

Low-molecular weight heparins (LMWH)

LMWHs have demonstrated their efficacy and safety as drugs of choice in the prophylaxis of thromboembolism. LMWHs produce therapeutic effect within 2 hours, and peak plasma level is achieved within 4 hours. This decreases to 50% of peak values 12 hours after subcutaneous injection.[114] LMWHs cause antithrombin-mediated inactivation, mainly of FXa and less of FIIa. Lab assessment of anti-Xa is routinely not required. Therapeutic range of anti-Xa is 0.5-1.0 units/mL. APTT may be prolonged when anti-Xa is >1.0 units/mL.[39]

Mean molecular weight and anti-Xa to anti-IIa activity of unfractionated heparin with different LMWHs[39]

Type of heparin	Mean mol.wt. (Daltons)	Anti-Xa to lla-ratio
Unfractionated heparin	13000	1.0
Tinzaparin	5500	1.5
Parnapairn	4500	2.4
Delteparin	5000	2.5
Nadroparin	4500	3.2
Enxoparin	4400	3.9
Reviparin	3900	4.1

There are three prophylactic LMWH regimens in use in patients undergoing high-risk surgeries:[39]

1. Prophylaxis started 12 hours before surgery (followed in European countries).
2. Prophylaxis started 12-24 hours after surgery (followed in North America).

3. Prophylaxis is started more than 12 hours before or 12 hours after surgery (followed by physicians who do not follow above regimens).

For indication and dosage, the physician should refer to the hospital's policies for the prevention of VTE and product inserts for further details.[39]

LMWH has additional advantages over unfractionated heparin. It can be given once or twice daily without laboratory monitoring. Other advantages are predictability, dose-dependent plasma levels, a longer half-life, less bleeding for a given antithrombotic effect, and a lower incidence of heparin-induced thrombocytopenia than with UFH.[115]

Advantages of low-molecular-weight heparin over unfractionated heparin[1]

- Greater bioavailability
- Predictability and dose-dependent plasma level
- Less risk of bleeding
- Lower incidence of heparin-induced thrombocytopenia
- Lower risk of heparin-induced osteoporosis
- No need for laboratory monitoring
- Can be safely administered in outpatient
- Duration of anticoagulant effect is longer, permitting once- or twice-daily administration

The risk of heparin-induced osteoporosis is lower with LMWH than with UFH as it does not increase osteoclast number and activity. It has a far greater effect on inhibition of factor Xa and a lesser effect on antithrombin III by inhibiting

thrombin to a lesser extent than UFH. Current contraindications to the early initiation of LMWH thromboprophylaxis include the presence of intracranial bleeding, ongoing and uncontrolled bleeding elsewhere, and incomplete spinal cord injury associated with suspected or proven spinal hematoma.[1]

Fondaparinux, a synthetic pentasaccharide, has been approved for prophylaxis of DVT. It is an indirect selective inhibitor of factor Xa which binds to antithrombin with high affinity in a reversible manner. Heparin-induced thrombocytopenia has not been reported with fondaparinux as it does not interact with platelet function and aggregation, and has a predictable response. Monitoring of prothrombin time or partial thromboplastin time is also not required. In summary, it has an equal or better effectiveness than currently available agents, a low bleeding risk, no need for laboratory monitoring, and once daily administration.[1]

Dabigatran is a new oral univalent direct thrombin inhibitor. Dabigatran etexilate is the prodrug of dabigatran. It is rapidly absorbed from the gastrointestinal tract with a bioavailability of 5% to 6%. It has a half-life of 8 hours after single-dose administration and up to 17 hours after multiple doses with plasma levels that peak at 2 hours. The drug is excreted largely unchanged via the kidneys. It has a low bioavailability (6%), produces a predictable anticoagulant effect, and requires no coagulation monitoring.[116] Dabigatran has been approved in Canada and Europe for VTE prevention after orthopedic surgery.[1]

The RE-COVER trial compared dabigatran etexilate with warfarin for 6 months in patients with acute VTE; dabigatran was as effective as warfarin in preventing recurrent VTE, with comparable major bleeding and significantly lower

total bleeding rates.[117,118] Another study (The RE-NOVATE II trial) compared the efficacy and safety of oral dabigatran with subcutaneous enoxaparin for extended thromboprophylaxis in patients undergoing total hip arthroplasty.[117] Extended prophylaxis with oral dabigatran 220 mg once daily was as effective as subcutaneous enoxaparin 40 mg once daily in reducing the risk of VTE after total hip arthroplasty, and superior to enoxaparin for reducing the risk of major VTE. The risk of bleeding and safety profiles were similar.[1]

Rivaroxaban is a potent and selective oral factor Xa inhibitor. It has a rapid onset of action, a high bioavailability (80%), and a half-life of 4 to 12 hours.[116] EINSTIEN-DVT trial has shown that oral rivaroxaban is as effective in preventing recurrence of symptomatic VTE as the current standard therapy of injectable LMWH, enoxaparin, or fondaparinux, and an oral vitamin K antagonist in well-managed patients.[119] The results of RECORD phase III trials have also shown that rivaroxaban 10 mg once daily is superior to the LMWH enoxaparin, when used for prophylaxis of VTE in orthopedic surgeries.[120] The drug also has the major advantages of once daily oral dosing and no required laboratory monitoring. Other drugs in this group such as apixaban and edoxaban are currently undergoing clinical trials.[1]

Oral anticoagulation with vitamin K antagonists such as warfarin can be commenced preoperatively, at the time of surgery, or postoperatively for the prevention of VTE. Warfarin is contraindicated in antepartum thromboprophylaxis because it crosses the placenta and can result in unwanted teratogenicity and bleeding in the fetus. However the drug is safe during lactation as it does not

accumulate in the breast milk to a substantial extent. Unlike warfarin, heparin is safe and it is recommended both in pregnancy and lactation.[1]

The use of aspirin alone is not recommended for thromboprophylaxis against VTE for any patient group. Some studies on the use of aspirin as prophylactic agent for DVT have shown some degree of protection against VTE in hospitalized patients, while other studies have either shown no benefit, or have proven to be less effective to other thromboprophylactic agents.[1]

Studies have been conducted to show that regular measurement of lower limb girth in patients of DVT is a reliable and sensitive technique and has been effective in early diagnosis and the response to treatment.[121] However, very few studies have been done pertaining to the lower limb girth reduction with UFH/LMWH.

In a study[122] conducted in Brazil, designed to compare the efficacy and safety of these two regimens i.e. UFH and LMWH for the treatment of patients with proximal lower limb DVT. 201 patients with proximal lower limb DVT from 13 centers in Brazil were randomized in an open manner to receive either enoxaparin [1.5 mg/kg subcutaneous (s.c.) OD] or intravenous (i.v.) UFH (adjusted to aPTT 1.5--2.5 times control) for 5--10 days. All patients also received warfarin (INR 2--3) for at least 3 months. The primary efficacy endpoint was recurrent DVT (confirmed by venography or ultrasonography), and safety endpoints included bleeding and serious adverse events. Baseline patient characteristics were comparable between groups. There was a nonsignificant trend toward a reduction in the rate of recurrent DVT with enoxaparin versus UFH, and similar safety. A once-daily regimen of

enoxaparin 1.5 mg/kg subcutaneous is at least as effective and safe as conventional treatment with a continuous intravenous infusion of UFH. However, the once daily enoxaparin regimen is easier to administer (subcutaneous versus intravenous), does not require aPTT monitoring, and leads to both a reduced number of hospital admissions and an average 4-day-shorter hospital stay.

Wan B et al.[124] in 2015 hypothesized that physiotherapy prophylaxis with intermittent pneumatic compression (IPC) would be safe and effective for patients unable to receive low-molecular-weight heparin (LMWH). In addition, this study investigated whether a combined therapy of IPC with LMWH would be more effective for the prophylaxis of deep vein thrombosis (DVT) in critical patients. A total of 500 patients were divided into four groups according to the prophylaxis of DVT. The IPC group consisted of 95 patients with heparin contraindication that received IPC treatment; the LMWH group consisted of 185 patients that received an LMWH injection; the LMWH + IPC group consisted of 75 patients that received IPC treatment and LMWH injection; and the control group consisted of 145 patients that received no IPC treatment or injection of LMWH. Each patient was evaluated clinically for development of DVT and the diagnosis was confirmed by Doppler study. Venous thromboembolism was a common complication among the trauma patients with severe injuries. Patients responded positively to the treatment used in the intervention groups. Patients exhibited an improved response to LMWH + ICP compared with IPC or LMWH alone, while no significant difference was detected between the IPC and LMWH groups. These results were applicable to patients that had a Wells score of ≥3; however, no significant differences in DVT incidence were observed among the patients who had a Wells score of <3. In this observational

study, LMWH + ICP appeared to be more effective than either treatment alone in treating critically ill trauma patients with severe injuries that are at high risk for VTE and bleeding simultaneously.

METHODOLOGY

The present study was done in the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016.

Study design and duration

The study design was a randomized controlled trial.

Study duration and period

This study was done for the period of one year from January 2016 to December 2016.

Place

This study was carried out in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi a tertiary care teaching hospital attached to KLE University's Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Patients attending General Surgery OPD with lower limb swelling, and diagnosed to have DVT, confirmed by a Colour Doppler of affected lower limb, and getting admitted to KLES Dr. Prabhakar Kore Hospital and MRC, Belagavi for the treatment.

Sample size

The study sample was comprised of 60 patients divided into two groups of 30 each.

Sampling procedure

Since no similar studies have been reported in the literature on comparison of low molecular weight heparin (LMWH) and unfractionated heparins (UFH) in the rate of reduction in lower limb girth in a case of Deep Vein Thrombosis applying thumb rule 60 cases were included.

Selection criteria

Inclusion

- Patients with Lower limb DVT (confirmed by Color Doppler study)
- Patients aged 18 years and above.
- Patients of either sex.
- Patients with weight >30 kg and <120 kg

Exclusion

- Pregnant woman
- History of allergy to heparin
- Hemorrhagic diathesis
- Symptoms of pulmonary embolism
- Survival prognosis <6 months
- Hepatic or renal failure

- Indication for thrombolysis or venous thrombectomy

Ethical clearance

Prior to the commencement, the Ethical Clearance was obtained from the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

Patients fulfilling selection criteria were detailed about the nature of study and a written informed consent was obtained (Annexure I).

Method of collection of data

The selected patients were interviewed and demographic data such as age and sex, past medical history, personal history of smoking, side affected, pain in affected limb, symptoms of chest pain or dyspnoea on minor excertion, bedridden for more than three days due to major surgery, and recent plaster immobilization of lower extremity were noted. The patients were subjected to clinical examination and evaluated for ability to walk, and signs of pitting oedema. Also vitals and weight were noted. These findings were recorded on a predesigned proforma (Annexure II).

Investigation

All the selected patients underwent following investigations

- Complete blood count (CBC)
- Prothrombin time (PT)
- International normalized ratio (INR)
- Activated prothrombin Time (aPTT)

- Liver function test (LFT)
- Mini renal profile (MR)
- Electrocardiogram (ECG)
- Chest X-ray P/A VIEW
- Colour doppler of affected lower limb

Randomization

Patients were divided into two groups of 30 each as group A and B based on computer generated random numbers on the basis of treatment administration.

Procedure

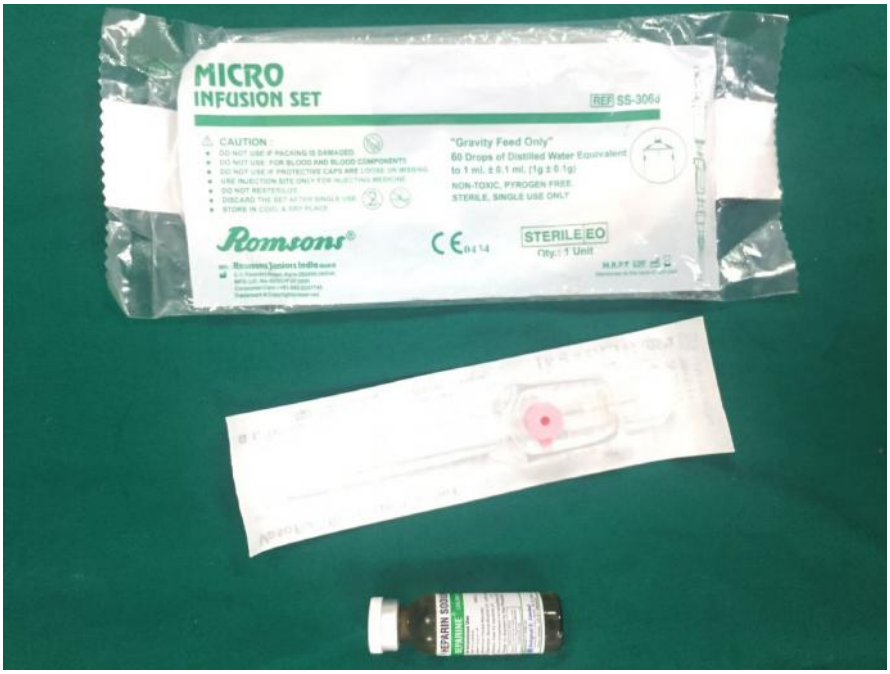
The patients were treated with either LMWH or UFH as below.

Group A: Patients in this group received LMWH (Enoxaparin) 1 mg/Kg B.W. by subcutaneous route.

Group B: Patients in this group received UFH according to the aPTT values by intravenous infusion.

All patients received oral Acitrom for three months after the completion of LMWH/UFH treatment to maintain PT INR between 2 to 3.

Photograph 1. Injection Enoxaperin with syringe used in its administration



Photograph 2. Unfractionated heparin injection along with IV set.

Outcome variables

The primary end point of the study was rate of reduction in calf girth circumference.

Measurement of calf girth circumference

The calf circumference was measured at the level of 10 cm below the tibial tuberosity with measuring tape. It was measured at the following intervals

- Time of admission.
- Before starting the treatment.
- Post treatment
    - Six hours
    - 12 hours
    - 24 hours
    - 48 hours
    - 72 hours
    - 96 hours
- After the treatment

Statistical analysis

The data was entered into the Microsoft Excel Spreadsheet (Annexure III). The data was analyzed using SPSS statistical software version 21.0. The categorical data was expressed as rates, ratios and percentages and comparison was done using Fishers exact test or chi-square test. Continuous data was expressed as mean ± standard deviation and the comparison was done using independent sample t test. iN

order to evaluate the effectiveness Percentage reduction in calf girth was calculated and it was expressed as mean±standard deviation and the comparison was done using independent sample t test. A probability (‘p’ value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

This one year randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016. A total of 60 patients with lower limb swelling, and diagnosed to have DVT were divided into two groups of 30 each as below.

Group A: Patients in this group received LMWH (Enoxaparin) by subcutaneous route.

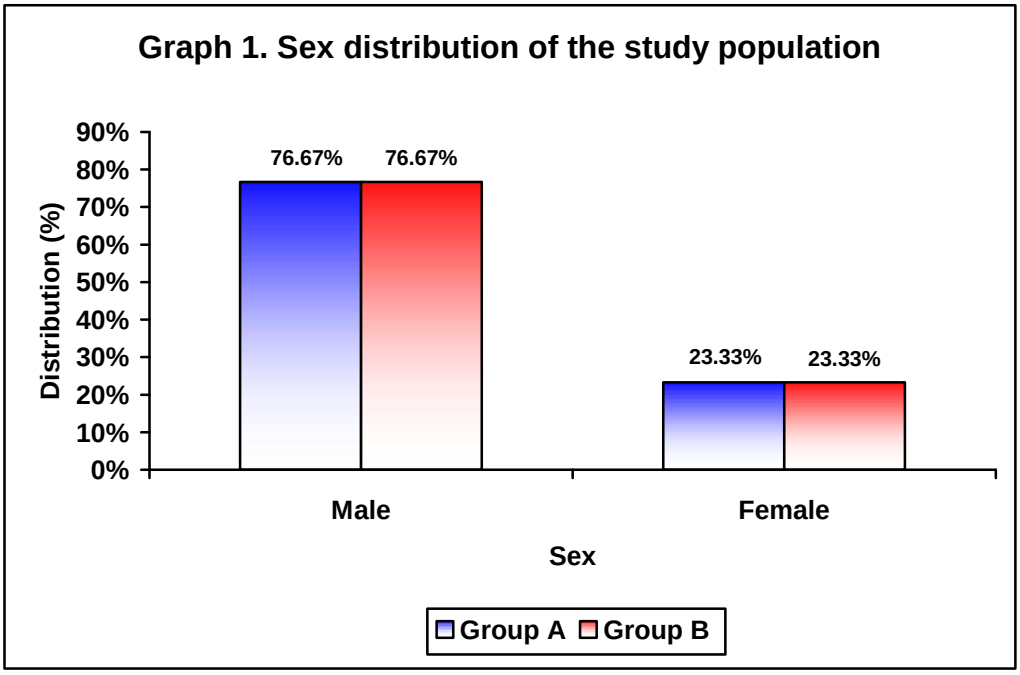
Group B: Patients in this group received UFH by intravenous infusion.

The data obtained was analysed and the final results were tabulated and interpreted as below.

Table 1. Sex distribution of the study population

Sex	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Male	23	76.67	23	76.67
Female	7	23.33	7	23.33
Total	**30**	**100.00**	**30**	**100.00**

p = 1.000

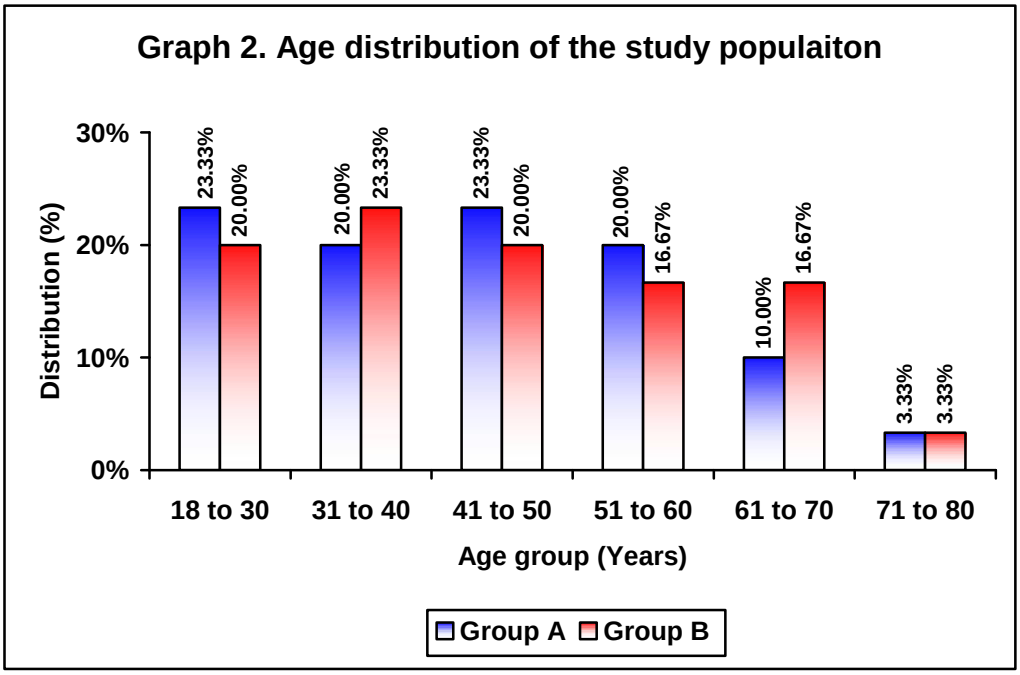


In the present study, 76.67% of the patients were males and 23.33% of the patients were females in group A as well as group B. The male to female ratio was 3.2:1. However the sex distribution in both the groups was statistically equal (p=1.000).

Table 2. Age distribution of the study population

Age group (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
18 to 30	7	23.33	6	20.00
31 to 40	6	20.00	7	23.33
41 to 50	7	23.33	6	20.00
51 to 60	6	20.00	5	16.67
61 to 70	3	10.00	5	16.67
71 to 80	1	3.33	1	3.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.983

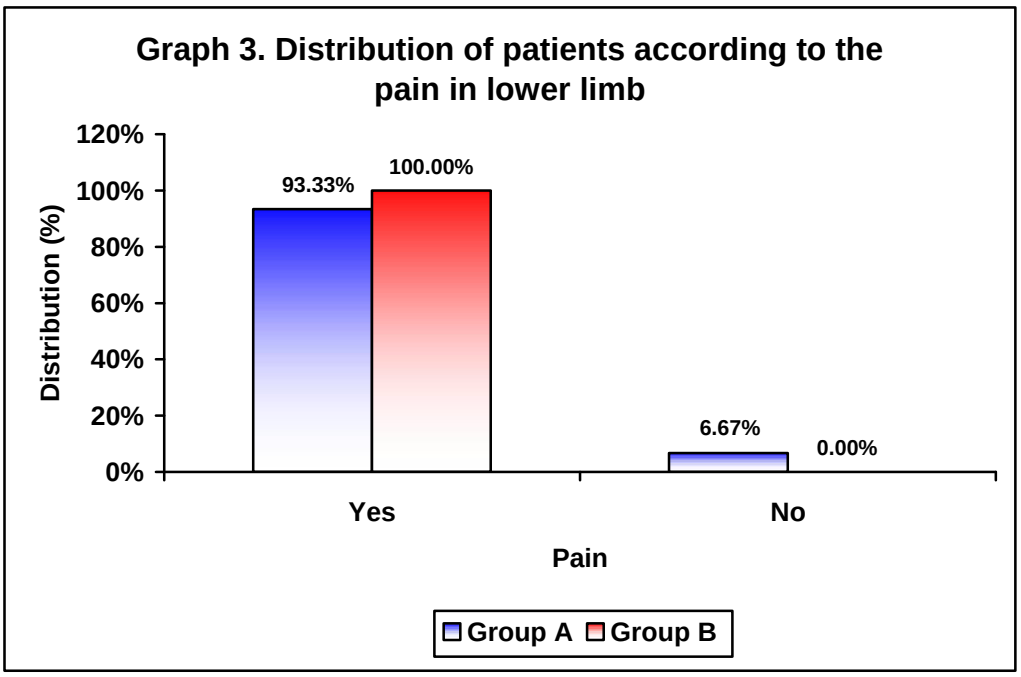


In this study most of the patients in group A (23.33%) were aged between 18 to 30 years and 41 to 50 years while in group B, 23.33% of the patients were aged 31 to 40 years. But, this difference was statistically not significant (p=0.983).

Table 3. Distribution of patients according to the pain in lower limb

Pain	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	28	93.33	30	100.00
No	2	6.67	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.246

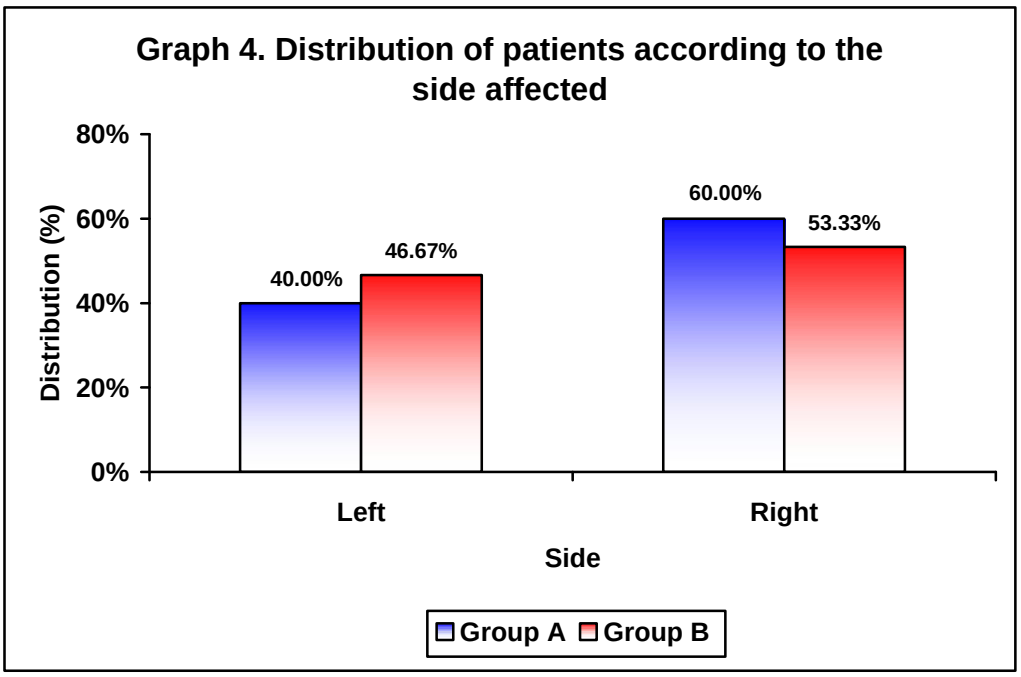


In the present study majority (93.33%) of the patients in group A and all the patients in group B (100.00%) had pain in lower limb (p=0.246).

Table 4. Distribution of patients according to the side affected

Side	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Left	12	40.00	14	46.67
Right	18	60.00	16	53.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.602

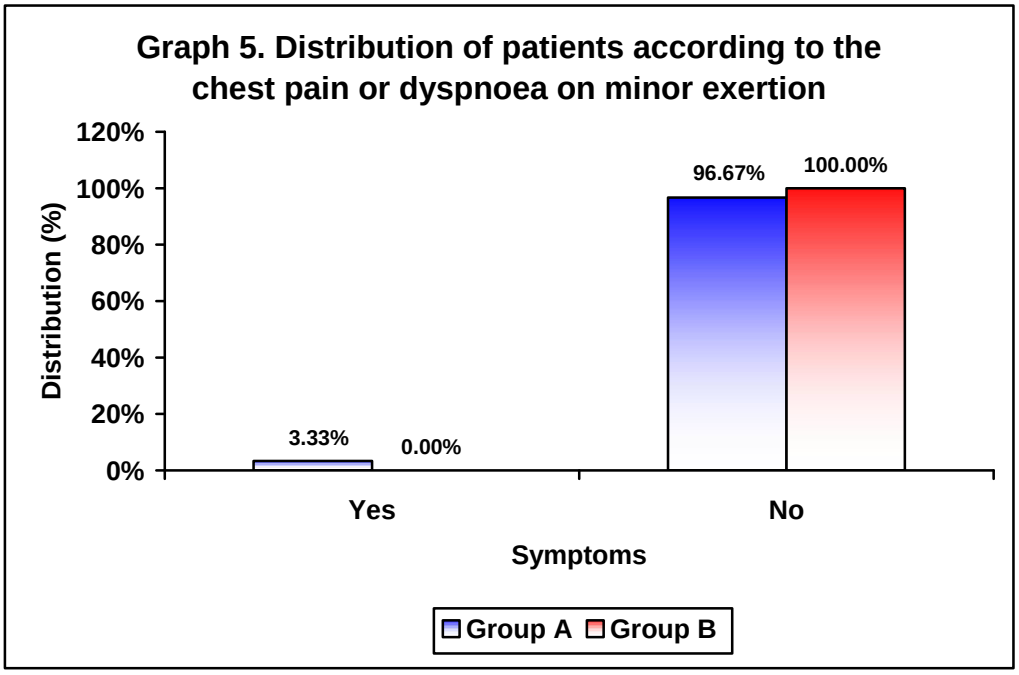


In this study right side was affected among 60.00% of the patients in group A compared to 53.33% of the patients in group B. However this difference was statistically not significant (p = 0.602).

Table 5. Distribution of patients according to the chest pain or dyspnoea on minor exertion

Symptoms	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
Yes	1	3.33	0	0.00
No	29	96.67	30	100.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.500

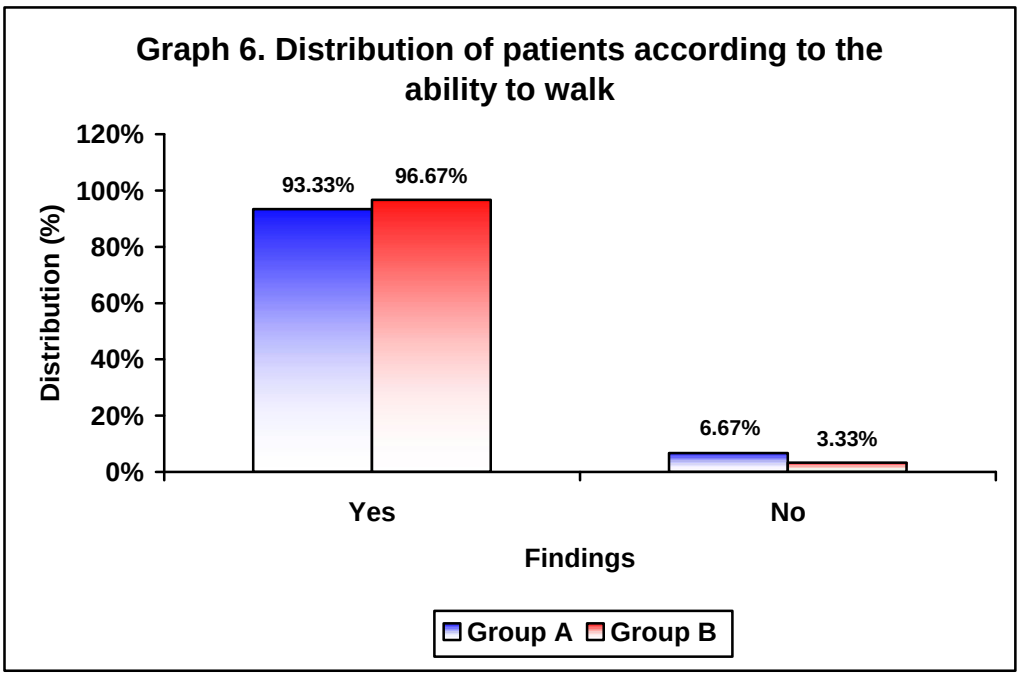


In the present study symptoms of chest pain / dyspnoea / minor exertion were noted among 3.33% of the patients in group A whereas none of the patients in group B had these symptoms (p=0.500).

Table 6. Distribution of patients according to the ability to walk

Findings	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	28	93.33	29	96.67
No	2	6.67	1	3.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.500

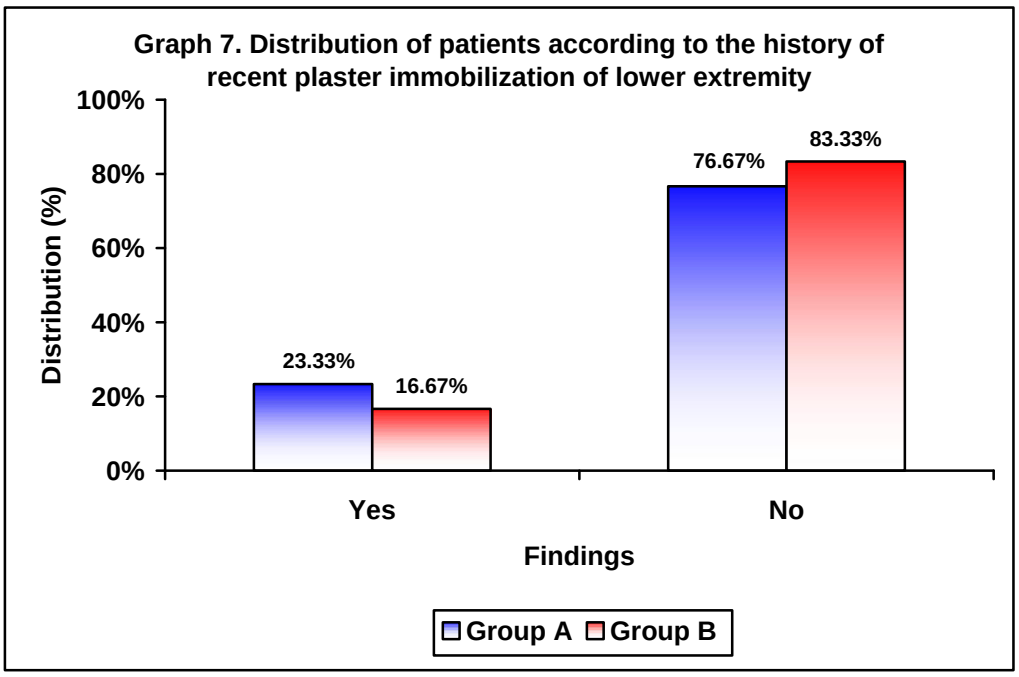


In this present study 93.33% of the patients who belonged to group A were able to walk compared to 96.67% of the patients in group B. However, this difference was statistically not significant (p=0.500).

Table 7. Distribution of patients according to the history of recent plaster immobilization of lower extremity

Findings	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
Yes	7	23.33	5	16.67
No	23	76.67	25	83.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.519

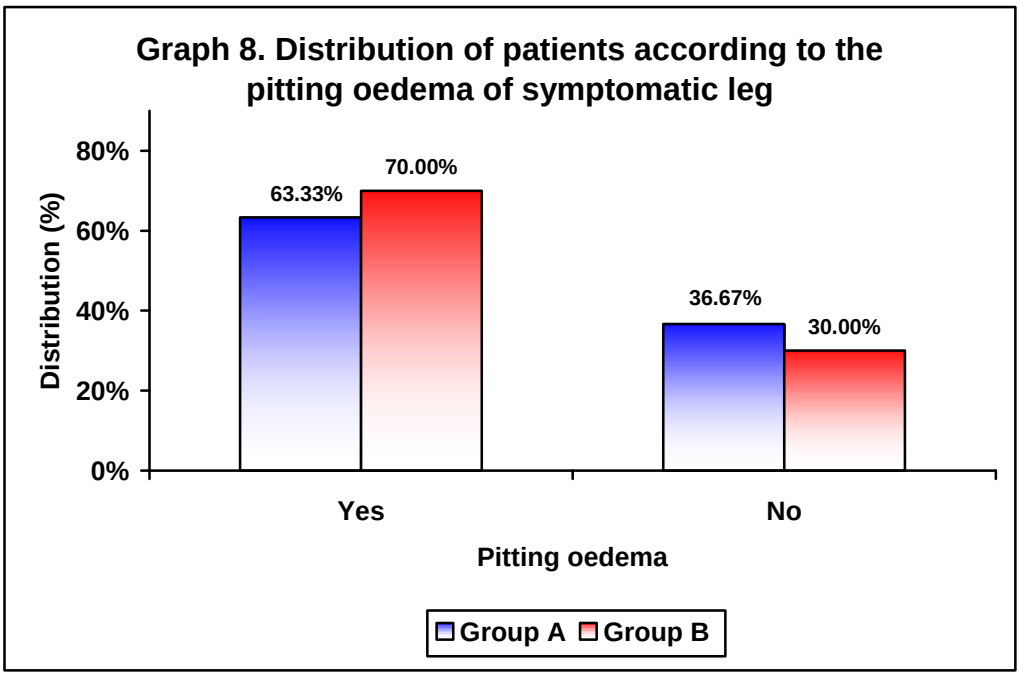


In the present study 23.33% of the patients in group A and 16.67% of the patients in group B reported the history of recent plaster immobilization of lower extremity. But this difference was statistically not significant (p =0.519).

Table 8. Distribution of patients according to the pitting oedema of symptomatic leg

Pitting oedema	Group A (n=30)		Group B (n=30)	
	Number	Percentage	Number	Percentage
Yes	19	63.33	21	70.00
No	11	36.67	9	30.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.584

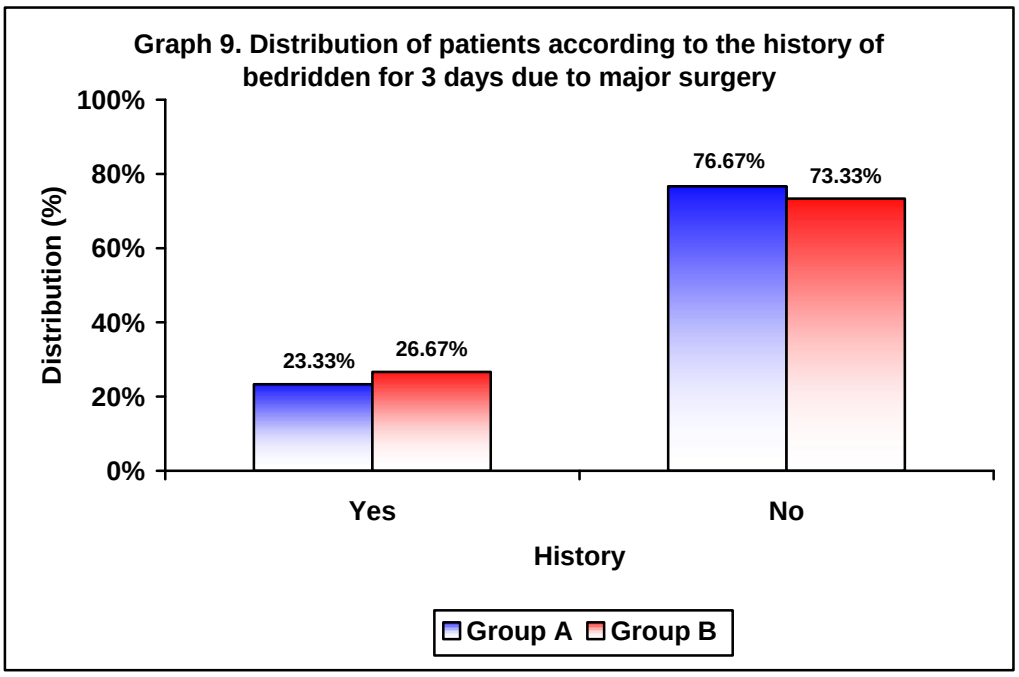


In this study pitting oedema was observed in 63.33% of the patients in group A compared to 70% of the patients in group B but the difference observed was statistically not significant (p =0.584).

Table 9. Distribution of patients according to the history of bedridden for 3 days due to major surgery

History	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	7	23.33	8	26.67
No	23	76.67	22	73.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.766

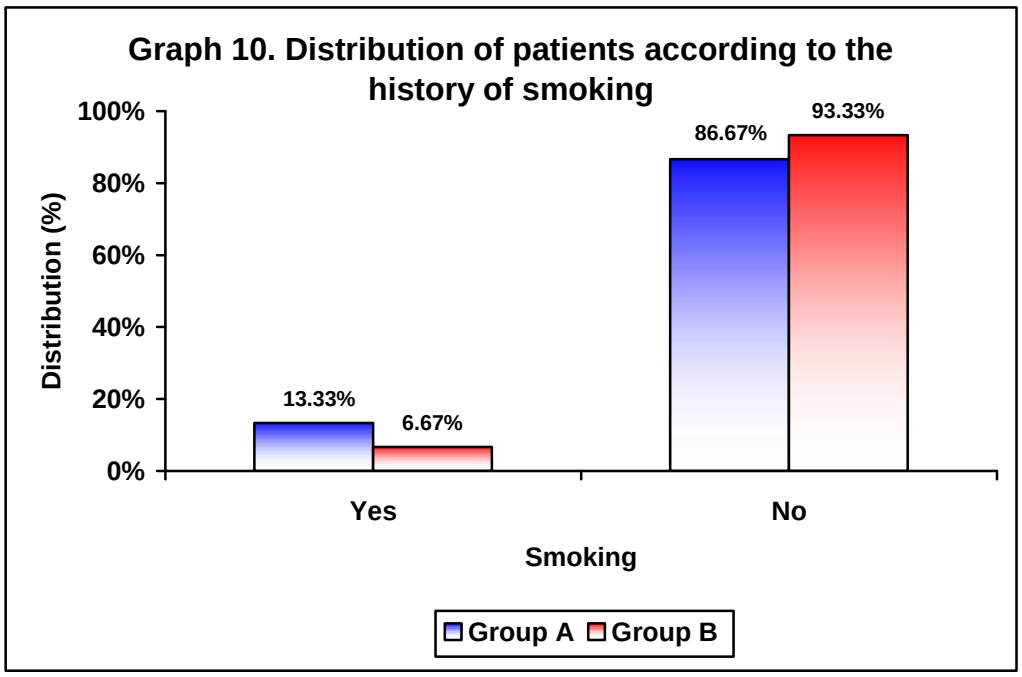


In the present study 23.33% of the patients in group A and 26.67% of the patients in group B were bedridden for three days due to major surgery (p=0.766).

Table 10. Distribution of patients according to the history of smoking

Smoking	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Yes	4	13.33	2	6.67
No	26	86.67	28	93.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.335

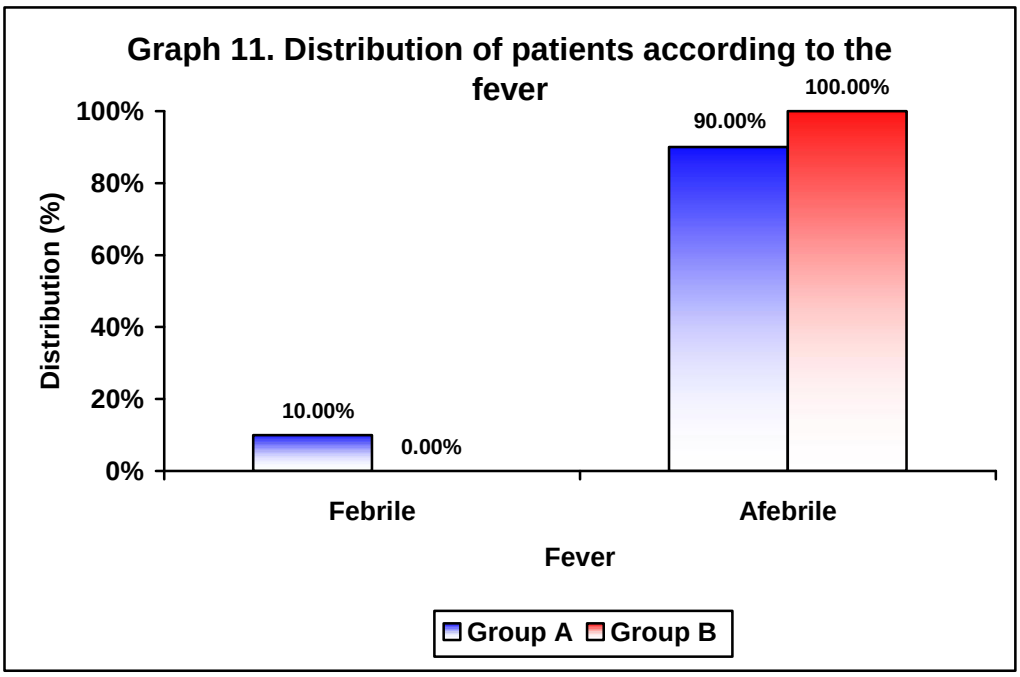


In this study 13.33% of the patients in group A and 6.67% of the patients in group B reported the history of smoking (p=0.335).

Table 11. Distribution of patients according to the fever

Fever	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Febrile	3	10.00	0	0.00
Afebrile	27	90.00	30	100.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.119



In the present study 10% of the patients in group A had fever while none of the patient in group B had fever (p=0.119).

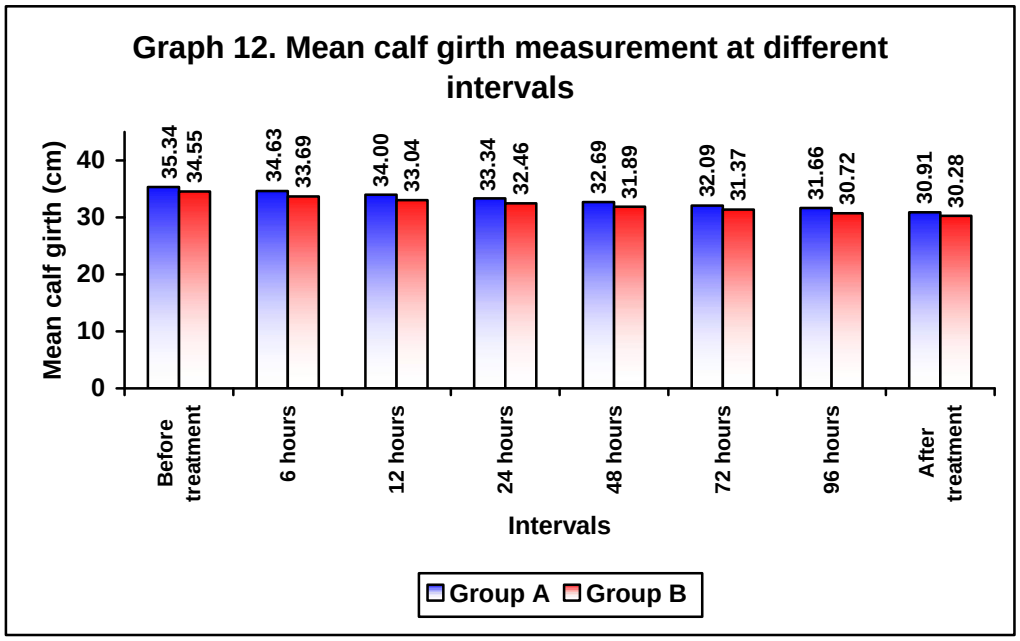
Table 12. Clinical and biochemical profile of study population

Parameters	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	44.43	15.12	45.13	13.45	0.850
Duration of swelling in leg (Days)	8.13	7.05	5.63	4.49	0.108
Calf girth at the time of admission (cm)	35.32	2.98	34.55	4.48	0.435
Weight (Kgs)	64.60	11.84	59.23	14.16	0.117
Pulse (/minute)	81.87	11.17	77.20	11.75	0.120
Systolic BP (mmHg)	126.87	10.10	122.60	12.35	0.149
Diastolic BP (mmHg)	79.37	11.39	77.87	6.39	0.533
Respiratory rate (/Minute)	16.63	2.14	16.10	2.37	0.364
Haemoglobin (gm%)	13.52	1.53	13.11	2.15	0.406
Random blood sugar (mg/dL)	141.00	25.53	131.93	14.97	0.100
Blood urea (mg/dL)	42.73	11.40	47.93	15.93	0.152
Serum creatinine (mg/dL)	0.87	0.33	0.89	0.36	0.882
Platelet count (lacks per cumm)	3.05	0.78	3.22	0.78	0.393
TLC (thousand per cumm)	8.43	2.57	7.79	2.17	0.299
PT control (sec)	11.20	0.00	11.20	0.00	1.000
PT test (sec)	23.81	16.38	21.25	13.33	0.509
INR	2.10	1.46	1.90	1.19	0.548
aPTT control (sec)	28.80	0.00	28.80	0.00	1.000
aPTT test (sec)	49.09	22.55	43.21	16.73	0.256
Ratio	1.71	0.79	1.53	0.62	0.323

The clinical and biochemical profile is as depicted in table 12. No statistically significant difference was observed between group A and group B.

Table 13. Mean calf girth measurement at different intervals

Intervals	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Calf girth before treatment	35.34	2.98	34.55	4.48	0.424
6 hours	34.63	2.81	33.69	4.38	0.326
12 hours	34.00	2.71	33.04	4.30	0.310
24 hours	33.34	2.71	32.46	4.21	0.341
48 hours	32.69	2.66	31.89	4.10	0.372
72 hours	32.09	2.60	31.37	4.00	0.410
96 hours	31.66	2.57	30.72	3.85	0.271
Calf girth after treatment	30.91	2.07	30.28	3.69	0.417

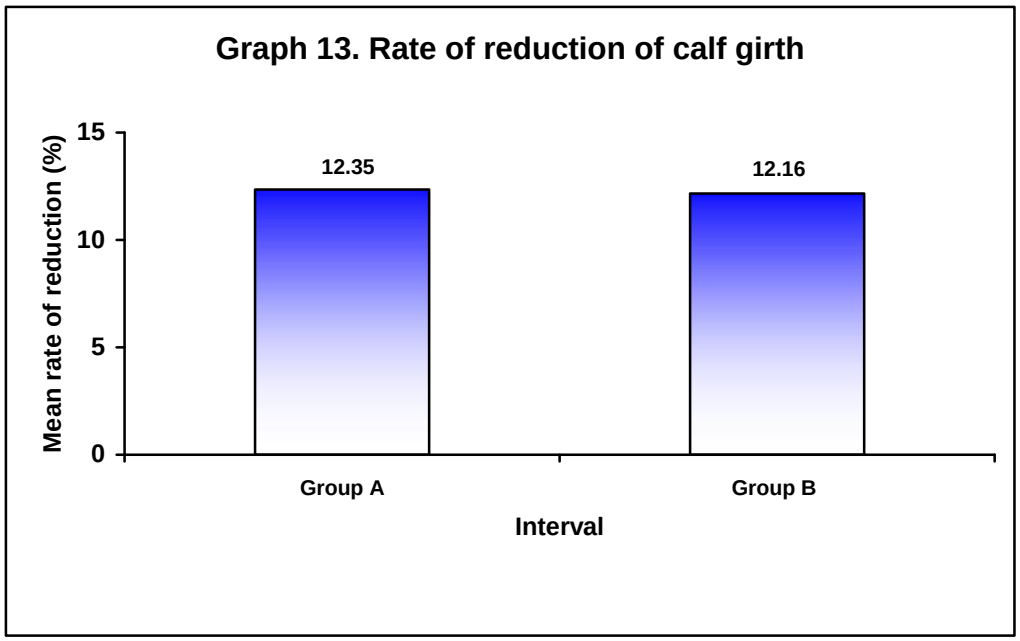


In this study among the patients with group A, the mean calf girth before treatment was 35.34±2.98 cms which reduced to 30.91±2.07 cms after treatment. In group B, the mean calf girth before treatment was 34.55±4.48 cms which reduced to 30.28±3.69 cms after treatment. However, the mean calf girth at all the intervals that is, 6 hours (34.63±2.81 vs 33.69±4.38 cms; p=0.326), 12 hours (34.00±2.71 vs 33.04±4.30 cms; p=0.310), 24 hours (33.34±2.71 vs 32.46±4.21 cms; p=0.341), 48

hours (32.69±2.66 vs 31.89±4.10 cms; p=0.372), 72 hours (32.09±2.60 vs 31.37±4.00 cms; p=0.410), 96 hours (31.66±2.57 vs 30.72±3.85 cms; p=0.271) and after treatment was comparable in group A and group B (p>0.050).

Table 14. Rate of reduction of calf girth

Parameter	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Rate of reduction (%)	12.35	3.31	12.16	3.13	0.817



In the present study the mean rate of reduction in calf girth before to after treatment was slightly high in group A compared to group B (12.35±3.31 vs 12.16±3.13 percent; p=0.817). But the difference was statistically not significant.

DISCUSSION

Venous Thrombotic Disease, which includes deep vein thrombosis, represents the third most common cardio vascular disorders. Deep Vein Thrombosis (DVT) occurs commonly in bedridden patients, post-operative patients and its disastrous sequel – pulmonary embolism which if not treated may prove to be fatal. The condition is treatable and reversible in the earlier stages, so to choose the appropriate modality of treatment is important.[1]

Unfractionated Heparins (UFH) were used since many years, now Low Molecular Weight Heparin (LMWH) has emerged as a new generation of drugs, which are as safe and efficacious as UFH.[20] Each class of drug has its own set of benefits. So the treatment is individualized. This study was aimed to compare Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of deep vein thrombosis.

This one year randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016. A total of 60 patients with lower limb swelling, and diagnosed to have DVT were divided into two groups of 30 each as group A (Patients in this group treated with LMWH (Enoxaparin) by subcutaneous route) and group B **(**Patients in this group treated with UFH by intravenous infusion). Both the groups were evaluated for reduction in calf girth before and after the treatment.

Epidemiological data suggests that, DVT is more frequently observed in males.[125] Same was true in the present study that is, majority of the patients in group A as well as group B were males that is 76.67% and 23.33% of the patients were females in group A as well as group B. In both the groups, the male to female ratio was 3.2:1. The sex distribution in both the groups was statistically equal. (p=1.000).

Epidemiological data suggests that, advanced age (more than 75 year) is the strong risk factor for DVT.[125] However, in this study the most of common age group was 18 to 30 years and 41 to 50 years (23.33%) in group A while in group B the most common age group was 31 to 40 years (23.33%). But, this difference was statistically not significant (p=0.983). The mean age in group A and group B was also comparable (44.43±15.12 vs 45.13±13.45 years; p=0.850).

The clinical picture of DVT has not been thoroughly specified yet, and symptoms such as pain or swelling of limbs are often found in many other diseases. The signs and symptoms are divided into two groups of DVT- and PE-related manifestations. In most cases, the first manifestations of DVT are leg swelling and limb pain and tenderness.[125] In the present study with regard to clinical presentation, majority 93.33% of the patients in group A and all the patients in group B (100.00%) had pain in lower limb (p=0.246). Right leg was affected in most of the patients in group A as well as group B (60.00% vs 53.33%; p=0.602). Symptoms of chest pain/dyspnoea on minor exertion were noted among few patients of group A (3.33%) while none of the patient in group B (0%) had symptoms of chest pain/dyspnoea on minor exertion (p=0.500). Majority of the patients in group A as well as group B were able to walk (93.33% vs 96.67%; p=0.500). Features of pitting oedema were observed in majority of the patients in group A as well as group B

(63.33% vs 70%; p=0.584). In group A, 10% of the patients in group A had fever while none of the patient in group B had fever (p=0.119). The mean duration of swelling in affected leg among the patients with group A and group B was comparable (8.13±7.05 vs 5.63±4.49; p=0.108). The other clinical characteristics including weight (64.60±11.84 vs 59.23±14.16 Kg; p=0.117), Pulse rate (81.87±11.17 vs 77.20±11.75 beats/minute; p=0.120), systolic blood pressure (126.87±10.10 vs 122.60±12.35 mm Hg; p=0.149), diastolic blood pressure (79.37±11.39 vs 77.87±6.39 m Hg; p=0.533), respiratory rate (16.63±2.14 vs 16.10±2.37 per minute; p=0.364) in group A and group B were statistically comparable. Also the mean haemoglobin levels (13.52±1.53 vs 13.11±2.15 g/dL; p=0.406), random blood sugar (141.00±25.53 vs 131.93±14. mg/dL; p=0.100), blood urea nitrogen (42.73±11.40 vs 47.93±15.93 mg/dL; p=0.152), serum creatinine (0.87±0.33 vs 0.89±0.36 mg/dL; p=0.882), platelet count (3.05±0.78 vs 3.22±0.78 Lakhs/cumm; p=0.393), total leukocyte count (8.43±2.57 vs 7.79±2.17 /cumm; p=0.299) did not differ significantly in group A and Group B. Further, coagulation profile that is mean prothrombin time control (11.20±0. vs 11.20±0.00 sec; p=1.000), prothrombin time test (23.81±16.38 vs 21.25±13.33 sec; p=0.509), international normalized ratio (2.10±1.46 vs 1.90±1.19; p=0.548), aPTT control (28.80±0.00 vs 28.80±00 sec; p=1.000) aPTT test (49.09±22.55 vs 43.21±16.73 sec; p=0.256) and aPTT ratio (1.71±0.79 vs 1.53±0.62 g/dL; p=0.323) was also comparable in both the groups.

In this study with regard to medical history, history of recent plaster immobilization of lower extremity was noted in 23.33% of the patients in group A compared to 16.67% of the patients in group B. But this difference was statistically

not significant (p =0.519). 23.33% of the patients in group A and 26.67% of the patients in group B reported history of bedridden for three days due to major surgery But the difference observed was statistically not significant (p=0.766). The history of smoking was noted in few patient of group A and group B (13.33% vs 6.67%; p=0.335).

In this study, the mean calf girth before treatment in patients in group A was 35.34±2.98 cms compared to 34.55±4.48 cms in group B (p=0.424).

These findings suggest that the pre treatment characteristics of the study population in group A and group B in terms of demographic characteristics, clinical examination findings, medical history, investigations including complete blood count, mini renal profile, coagulation profile and calf girth (p> 0.050) before treatment were comparable ruling out the possible bias in the study results.

In the present study the mean calf girth before treatment in patients in group A was 35.34±2.98 cms which reduced to 30.91±2.07 cms after treatment. In group B, the mean calf girth before treatment was 34.55±4.48 cms which reduced to 30.28±3.69 cms after treatment. However, the mean calf girth at all the intervals that is, 6 hours (34.63±2.81 vs 33.69±4.38 cms; p=0.326), 12 hours (34.00±2.71 vs 33.04±4.30 cms; p=0.310), 24 hours (33.34±2.71 vs 32.46±4.21 cms; p=0.341) 48 hours (32.69±2.66 vs 31.89±4.10 cms; p=0.372), 72 hours (32.09±2.60 vs 31.37±4.00 cms; p=0.410), 96 hours (31.66±2.57 vs 30.72±3.85 cms; p=0.271) and after treatment (30.91±2.07 vs 30.28±3.69 cms; p=0.417) were comparable in group A and group B (p>0.050). Also the mean percentage rate of reduction in calf girth from before to after treatment was slightly high in group A (12.35± 3.31) compared

to group B (12.16±3.13 percent; p=0.817) However the difference was statistically not significant.

These findings hypothesize that, a low-molecular-weight heparin can be effectively used to treat the patients with DVT at home as reduction of calf girth after the treatment with low-molecular-weight heparin was at par with unfractionated heparin. Though there is no added effect using low-molecular-weight heparin compared to unfractionated heparin, it has several advantages that is, the low-molecular-weight heparins were administered by subcutaneous injection in doses adjusted for the patient's weight, without laboratory monitoring. This is much convenient method of administering the treatment and it is possible because low-molecular-weight heparins have a more predictable anticoagulant response than standard heparin, a longer plasma half-life, and better bioavailability when administered subcutaneously.[17-19] Because of these properties, low-molecular-weight heparins have the potential advantage of allowing patients with deep-vein thrombosis to be treated at home rather than in the hospital.[84]

In the early trials comparing standard heparin with low-molecular-weight heparin in hospitalized patients, venography was performed at entry into the study and approximately one week later.[15,126,127] The primary outcome measure in these trials was a change in the size of the thrombus, a surrogate for clinically recurrent thrombosis. The primary outcome measure in the more recent larger trials in hospitalized patients was symptomatic recurrent venous thromboembolism.[128,129] We did not routinely screen our patients by ultrasonography or venography at specified times.

In a multicenter trial from France by Simonneau G. et al.[129] compared fixed-dose subcutaneous enoxaparin, given twice daily, with adjusted-dose intravenous unfractionated heparin (UFH) given by continuous intravenous infusion for the initial 10 days of treatment of patients with proximal vein thrombosis. The primary efficacy outcome was the change of the size of the thrombus assessed by repeated venograms between day 0 and day 10. The primary analysis of safety was based on the incidence of major bleeding during 10 days of treatment. There were 67 patients in each group. Venographic assessment of clot size evolution between day 0 and day 10 showed a statistically significant superiority ($p<0.002$) of enoxaparin over the reference treatment with UFH. Moreover, the incidence of overall recurrent thromboembolic events during 10 days of treatment was significantly higher ($P<0.002$) in the UFH group (seven of 67) than in the enoxaparin group (one of 67). There were no serious bleeding complications in either group. Study concluded that, Enoxaparin is at least as effective and safe as UFH and it is more comfortable for patients and less time-consuming for nurses and laboratories. Thus, study by Simonneau G. et al. confirmed that the use of low-molecular-weight heparin provides a real therapeutic advance in the treatment of deep vein thrombosis.

Another study by Merli G. et al.[130] in their Randomized, controlled, partially blinded equivalence trial to determine whether subcutaneous enoxaparin administered once or twice daily is as effective as continuously infused unfractionated heparin in acute symptomatic venous thromboembolic disease among 900 patients with symptomatic lower-extremity deep venous thrombosis, including 287 (32%) with confirmed pulmonary embolism from 74 hospitals in 16 countries showed that, subcutaneous enoxaparin once or twice daily is as effective and safe as

dose-adjusted, continuously infused unfractionated heparin in the prevention of recurrent symptomatic venous thromboembolic disease.

Earlier Livine M. et al.[16] in 1996 compared intravenous standard heparin and low-molecular-weight heparin in patients with acute proximal deep-vein thrombosis. They showed that, low-molecular-weight heparin can be used safely and effectively to treat patients with proximal deep-vein thrombosis at home.

Similarly Hull RD et al.[128] in a multicenter, double-blind clinical trial compared fixed-dose subcutaneous low-molecular-weight heparin given once daily with adjusted-dose intravenous heparin given by continuous infusion for the initial treatment of patients with proximal-vein thrombosis, using objective documentation of clinical outcomes. they opined that, low-molecular-weight heparin is at least as effective and as safe as classic intravenous heparin therapy under the conditions of their study and more convenient to administer. The simplified therapy provided by low-molecular-weight heparin may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting.

Despite the methodological differences the results of the present study are in agreement with the observations made by Simonneau G. et al.,[129] Merli G. et al.,[130] Levine M. et al.[16] Hull RD et al.[128]

Overall the present study shows that, subcutaneous low-molecular-weight heparin is as effective as unfractionated heparin given by continuous intravenous infusion. However the advantages of subcutaneous low-molecular-weight heparin administration make it as a better option as the need for intravenous infusion and for monitoring is eliminated and a single subcutaneous injection is given daily in an

outpatient setting for patients with deep vein thrombosis. However, these findings require further validation due to potential limitations of the study that is, smaller sample size, single centre design, economic constraints were not taken into the consideration also the primary outcome in this study was reduction in calf girth alone and We did not routinely screen our patients by ultrasonography or venography at specified times. Although increasing lower limb circumference might be the first sign of DVT, most physicians believe that it is not an accurate indicator.[125] Clinical examination of DVT is usually neglected in critically ill patients and DVT is diagnosed when presented as PE complications, which might increase patients' risk of mortality and morbidity.[131] On the other hand, the accuracy of such index is crucial. Lower limb circumference measurement is proposed for early diagnosis of DVT. And in some studies unilateral enlargement of limbs with difference of more than 3 cm was reported to predict DVT.[121] Hence, further multicentric studies with large sample size covering economic constraints and confirmation with ultrasonography or venography would provide insights of low-molecular-weight heparin in the treatment of DVT.

CONCLUSION

Based on the findings of this study it may be concluded that, low molecular weight heparin is as effective as unfractionated heparins in the treatment of deep vein thrombosis as measured by rate of reduction in lower limb girth. Treatment with LMWH is much convenient method of administering as it allows the patients with deep-vein thrombosis to be treated at home rather than in the hospital and avoids regular laboratory monitoring.

SUMMARY

Venous Thromboembolism (VTE), a disease that includes both Deep Vein Thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular disease after myocardial infarction and ischemic stroke. Low Molecular Weight Heparin has emerged as a new generation of drug, which is reported to be as safe and efficacious as UFH.. This study was aimed to compare Low Molecular Weight Heparin (LMWH) and Unfractionated Heparins (UFH) in the rate of reduction in lower limb girth in a case of deep vein thrombosis.

This one year randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2016 to December 2016. A total of 60 patients with lower limb swelling, and diagnosed to have DVT were divided into two groups of 30 each as group A (treatment with LMWH (Enoxaparin) by subcutaneous route) and group B **(**Treatment with UFH by intravenous infusion). The salient findings of the study are as summarized below.

- Majority of the patients (76.67%) males and 23.33% of the patients were females in group A as well as group B. The male to female ratio was 3.2:1. (p=1.000).

- The most of common age group was 18 to 30 years (23.33%) in group A while in group B the most common age group was 31 to 40 years (23.33%) (p=0.983). The mean age in group A and group B was also comparable (44.43±15.12 vs 45.13±13.45 years; p=0.850).

- The other pre treatment characteristics of the study population that is, demographic characteristics, clinical examination findings, medical history, investigations including complete blood count, mini renal profile, coagulation profile and calf girth before treatment were comparable (p> 0.050).

- In patients with group A, the mean calf girth before treatment was 35.34±2.98 cms which reduced to 30.91±2.07 cms after treatment. In group B, the mean calf girth before treatment was 34.55±4.48 cms which reduced to 30.28±3.69 cms after treatment. However, the mean calf girth at all the intervals and after treatment was comparable in group A and group B (p>0.050).

- The mean percentage rate of reduction in calf girth before and after treatment was slightly high in group A compared to group B (12.35± 3.31 vs 12.16±3.13 percent). But statistically same was not significant (p=0.817).

Overall, the low molecular weight heparin is as effective as unfractionated heparins in the treatment of deep vein thrombosis as measured by rate of reduction in lower limb girth.

BIBLIOGRAPHY

1. Kesieme E, Kesieme C, Jebbin N, Irekpita E, Dongo A. Deep vein thrombosis: a clinical review. J Blood Med 2011;2:59-69.

2. White RH. The epidemiology of venous thromboembolism. Circulation 2003;107(Suppl 1):I4-8.

3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ . Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158: 585-93.

4. Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. CMAJ 2006;175(9):1087-92.

5. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-64.

6. Kahn SR, Ginsberg JS. Relationship between deep venous thrombosis and the postthrombotic syndrome. Arch Intern Med 2004;164:17-26.

7. Anderson FA Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107 (23 Suppl 1):I9-16.

8. Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals. Council on Thrombosis

(in consultation with the Council on Cardiovascular Radiology), American Heart Association. Circulation 1996;93(12):2212–45.

9. Welsby I, Ortel TL. Is it time for individualized thromboprophylaxis regimens in the ICU. Crit Care Med. 2015;43:500-1.

10. Ageno W. Recent advances in the management of venous thromboembolism. Korean J Hematol 2010;45:8-13.

11. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960;1:1309-12.

12. Naqvi SE, Haseen MA, Beg MH, Ali E, Khan T. Deep vein thrombosis: An experience of 25 years from north India. Indian J Vasc Endovasc Surg 2016;3:2-6.

13. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 8th ed., Chest 2008; (133 6 Suppl): 454S-545S.

14. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: Examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med 2000;160:181-8.

15. Hirsh J, Levine MN. Low molecular weight heparin. Blood 1992;79:1-17.

16. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334(11):677-81.

17. Boneu B, Caranobe C, Cadroy Y, Dol F, Gabaig AM, Dupouy D, et al. Pharmacokinetic studies of standard unfractionated heparin and low molecular weight heparins in the rabbit. Semin Thromb Hemost 1988; 14:8-27.

18. Bara L, Billaud E, Gramond G, Kher A, Samama M. Comparative pharmacokinetics of a low molecular weight heparin (PK 10 169) and unfractionated heparin after intravenous and subcutaneous administration. Thromb Res 1985;39:631-6.

19. Young E, Prins M, Levine MN, Hirsh J. Heparin binding to plasma proteins, an important mechanism for heparin resistance. Thromb Haemost 1992;67: 639-43.

20. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. J Thromb Haemost 2013;11(3):402-11.

21. Ouriel K, Green RM, Greenberg RK, G. Clair DG. The anatomy of deep venous thrombosis of the lower extremity. J Vasc Surg 2000; 31(5): 895-900.

22. Piccioli A, Prandoni P, Goldhaber SZ. Epidemiologic characteristics, management, and outcome of deep venous thrombosis in a tertiary-care

hospital: the Brigham and Women's Hospital DVT registry. Am Heart J 1996;132:1010-4.

23. Venous Anatomy: Anatomic Classifications of the Venous System. Available from: http://venacure-evlt.com/endovenous-laser-vein-treatment/procedure/venous-anatomy/ Access Date: 22.05.2017.

24. Patel K, Brenner BE. Deep Venous Thrombosis (DVT). Available from: http://misc.medscape.com/pi/iphone/medscapeapp/html/A1911303-bus iness.html Access Date: 22.05.2017.

25. Deep Vein Thrombosis. Available from: http://www.lifescript.com/health/centers/dvt/related_conditions/deep_vein_t hrombosis.aspx Access Date: 22.05.2017.

26. Araki CT, Back TL, Padberg FT, Thompson PN, Jamil Z, Lee BC, et al. The significance of calf muscle pump function in venous ulceration. J Vasc Surg 1994;(6):872-7; discussion 878-9.

27. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692–699.

28. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med. 2004;350(25):2558–2563.

29. Keenan CR, White RH. The effects of race/ethnicity and sex on the risk of venous thromboembolism. Curr Opin Pulm Med. 2007;13(5):377–383.

30. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994;83(5):1251–1257.

31. Van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in the Netherlands. J Pediatr. 2001;139(5):676–681.

32. Parasuraman S, Goldhaber SZ. Venous thromboembolism in children. Circulation. 2006;113:e12–e16.

33. Stein PD, Kayali F, Olson RE. Incidence of venous thromboembolism in infants and children: data from the National Hospital Discharge Survey. J Pediatr. 2004;145(4):563–565.

34. Bates SM, Ginsberg JS. Pregnancy and deep vein thrombosis. Semin Vasc Med. 2001;1(1):97–104.

35. Gader AA, Haggaz A, Adam I. Epidemiology of deep venous thrombosis during pregnancy and puerperium in Sudanese women. Vasc Health Risk Manag. 2009;5(1):85–87.

36. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ, the American College of Chest Physicians Antithrombotic and thrombolytic therapy: American College of Chest Physicians evidence-based clinical practice guidelines, 8th ed. Chest. 2008;133(6 Suppl):110S–112S.

37. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med. 1989;82(4):203–205.

38. Parakh R, Kakkar VV, Kakkar AK. Management of venous thromboembolism. J Assoc Physicians India 2007;55:45-70.

39. Narani KK. Deep vein thrombosis and pulmonary embolism - Prevention, management, and anaesthetic considerations. Indian J Anaesth 2010;54: 8-17.

40. Plate G, Ohlin P, Eklöf B. Pulmonary embolism in acute iliofemoral venous thrombosis. Br J Surg 1985;72:912-5.

41. Hirsh J, Hoak J. Management of deep vein thrombosis and pulmonary embolism. Circulation 1996;93:2212-45.

42. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, *et al*. The long term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.

43. Brandjes DP, Heijboer H, Büller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal vein thrombosis. N Engl J Med 1992;327:1485-9.

44. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350:2257-64.

45. Nicolaides AN, Kakkar VV, Field ES, Renney JT. The origin of deep vein thrombosis: a venographic study. Br J Radiol 1971;44(525):653-63.

46. Brooks EG, Trotman W, Wadsworth MP, aatjes DJ, Evans MF, Ittleman FP, et al. Valves of the deep venous system: an overlooked risk factor. Blood 2009;114(6):1276-9.

47. Mitchell RN. Hemodynamic disorders, thromboembolic disease and shock. In: Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran Pathologic Basis of Disease. 7th ed. India: Elsevier; 2009. p. 133.

48. Kahn SR, Solymoss S, Lamping DL, Abenhaim L. Long-term outcomes after deep vein thrombosis: postphlebitic syndrome and quality of life. J Gen Intern Med 2000;15(6):425-9.

49. Anderson FA, Wheeler HB. Physicians practices in the management of venous thromboembolism: a communitywide survey. J Vasc Surg 1992;16(5):707-14.

50. Rosendaal FR. Risk factors for venous thrombosis: prevalence, risk, and interaction. Semin Hematol 1997;34(3):171-87.

51. Prandoni P. Acquired risk factors for venous thromboembolism in medical patients. Pathophysiol Haemost Thromb 2006;35(1–2):128-32.

52. van Aken BE, Reitsma PH, Rosendaal FR. Interleukin 8 and venous thrombosis: evidence for a role of inflammation in thrombosis. Br J Haematol 2002;116:173-7.

53. Clayton TC, Gaskin M, Meade TW. Recent respiratory infection and risk of venous thromboembolism: case–control study through a general practice database. Int J Epidemiol 2011;40(3):819-27.

54. Gertziafas GT. Risk factors for venous embolism in children. Int Angiol 2004;23(3):195-205.

55. Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. J Thromb Haemost. 2009;7(Suppl 1):301-4.

56. Deep vein thrombosis and pulmonary embolism. 4 th ed. Anaesthesia and co-existing disease. In: Stoelting RK, Dierdorf SF editors. Philadelphia: Churchill Livingstone; 2003. p. 169-76.

57. Weinmann EE, Salzman EW. Deep vein thrombosis. N Engl J Med 1994;331:1630-42.

58. Oudega R, Moons KGM, Hoes AW. Limited value of patient history and physical examination in diagnosing deep vein thrombosis in primary care. Family Practice 2005;22(1):86-91.

59. Tapson VF, Carroll BA, Davidson BL, Elliott CG, Fedullo PF, Hales CA, et al. The Diagnostic Approach to Acute Venous Thromboembolism. Clinical Practice Guideline. American Thoracic Society. Am J Respir Crit Care Med 1999;160(3):1043-66.

60. Kahn SR. The clinical diagnosis of deep vein thrombosis: integrating incidence, risk factors and symptoms and signs. Arch Intern Med 1998; 158(21):2315-23.

61. Ikard RW, Ueland K, Folse R. Lower limb venous dynamics in pregnant women. Surg Gynecol Obstet 1971;132(3):483-8.

62. Oudega R, Hoes AW, Moons KG. The Wells rule does not adequately rule out deep venous thrombosis in primary care patients. Ann Intern Med 2005;143(2):100-7.

63. Wells PS, Hirsh J, Anderson DR, Lensing AW, Foster G, Kearon C, et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995;345(8961):1326-30.

64. Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet. 1997;350(9094):1795–1798.

65. Pabinger I, Ay C. Biomarkers and venous thromboembolism. Arterioscler Thromb Vasc Biol. 2009;29:332–336

66. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 2003;349:1227-35.

67. Hirsh J, Lee AY. How we diagnose and treat deep vein thrombosis. Blood. 2002;99:3102-10.

68. Tovey C, Wyatt S. Diagnosis, investigation, and management of deep vein thrombosis Clinical review. BMJ 2003;326:1180-4.

69. Zierler BK. Ultrasonography and diagnosis of venous thromboembolism. Circulation 2004;109(12 Suppl 1):I9–I14.

70. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998;129(12):1044-9.

71. Rose SC, Zwiebel WJ, Nelson BD, Priest DL, Knighton RA, Brown JW, et al. Symptomatic lower extremity deep venous thrombosis: accuracy, limitations, and role of color duplex flow imaging in diagnosis. Radiology 1990;175(3):639-44.

72. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep vein thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann Intern Med1998;128(8):663-77.

73. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg 1972;104(2):134-44.

74. Ting AC, Cheng SW, Cheung GC, Wu LL, Hung KN, Fan YW. Perioperative deep vein thrombosis in Chinese patients undergoing craniotomy. Surg Neurol 2002;58(3–4):274-9.

75. Albrechtsson U, Olsson CG. Thrombotic side-effects of lower-limb phlebography. Lancet. 1976;1:723-4.

76. Erdman WA, Jayson HT, Redman HC, Miller GL, Parkey RW, Peshock RW. Deep venous thrombosis of extremities: role of MR imaging in the diagnosis. Radiology. 1990;174(2):425-31.

77. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Ann Intern Med. 2002;136(2):89-98.

78. Parakh R, Kapadia S, Agarwal S, Grover T, Bukhari S, Yadav A, et al. Assessment of total load in symptomatic patients with venous thromboembolism. Clin Appl Thromb Hemost 2006;12:369-72.

79. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991;100:598-603.

80. Whitaker IS, Izadi D, Oliver DW, Monteath G, Butler PE. Historical article: Hirudo medicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history. Br J Oral Maxillofac Surg 2004;42:133-7.

81. Bauer G. Nine years' experience with heparin in acute venous thrombosis. Angiology 1950;1:161-9.

82. Bauer G. Thrombosis; early diagnosis and abortive treatment with heparin. Lancet 1946;1:447-54.

83. Holden WD. Treatment of deep venous thrombosis with reference to subcutaneous injection of heparin and use of dicumarol. Arch Surg 1947;54: 183-7.

84. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M. A comparison of low-molecular-weight

heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996;334:677-81.

85. Boccalon H, Elias A, Chale JJ, Cadene A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Arch Intern Med 2000;160:1769-73.

86. Partsch H, Bl€attler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg 2000;32:861-9.

87. Blattler W, Gerlach HE. Implementation of outpatient treatment of deep-vein thrombosis in private practices in Germany. Eur J Vasc Endovasc Surg 2005;30:319-24.

88. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997;349:759-62.

89. DeWeese J. Treatment of venous disease – the innovators. J Vasc Surg 1994;20:675-83.

90. Greenfield LJ. Historical reminiscence: origin of the Greenfield filter. Am Surg 2010;76:1319-20.

91. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in

patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998;338:409-15.

92. Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972;287(7):324-7.

93. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep venous thrombosis. Arch Intern Med 1997;157(22):2562-8.

94. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):188S-203S.

95. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001;119(1 Suppl):176S-93S.

96. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53.

97. Ramzi DW, Leeper KV. DVT and pulmonary embolism: Part II. Treatment and prevention. Am Fam Physician. 2004;69:2841-8.

98. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al. Optimal duration of oral anticoagulation therapy: a randomized trial comparing four weeks with three months of Warfarin in patients with proximal deep vein thrombosis. Thromb Haemost. 1995;74(2):606-11.

99. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. N Engl J Med 1995;332(25):1661-5.

100. Curry N, Keeling D. Venous thromboembolism: the role of the clinician. J R Coll Phys Edinb 2009;39:243-6.

101. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th ed. Chest 2008;133(Suppl 6):454S-545.

102. Patterson BO, Hinchliffe R, Loftus IM, Thompson MM, Holt PJ. Indications for catheter-directed thrombolysis in the management of acute proximal deep venous thrombosis. Arterioscler Thromb Vasc Biol. 2010;30(4):669-74.

103. Popuri RK, Vedantham S. The role of thrombolysis in the clinical management of deep vein thrombosis. Arterioscler Thromb Vasc Biol 2011;31(3):479-84.

104. Streiff MB. Vena caval filters: a comprehensive review. Blood. 2000;95(12):3669-77.

105. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 1998;338(7):409-15.

106. Joels CS, Sing RF, Heniford BT. Complications of inferior vena cava filters. Am Surg 2003;69(8):654-9.

107. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. Br J Surg 1999;86(8):992-1004.

108. Amaragiri SV, Lees TA. Elastic compression stockings for the prevention of deep vein thrombosis. Cochrane Database Syst Rev 2000;3:CD001484.

109. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev 2008;4:CD005258.

110. Hilleren-Listerud AE. Graduated compression stocking and intermittent pneumatic compression device length selection. Clin Nurse Spec 2009;23(1):21-4.

111. Chin PL, Amin MS, Yang KY, Yeo SJ, Lo NN. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial. J Orthop Surg (Hong Kong) 2009;17(1):1–5.

112. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. N Engl J Med 1988;318(18):1162-73.

113. Leonardi MJ, McGory ML, Ko CY. The rate of bleeding complications after pharmacologic deep venous thrombosis prophylaxis: a systematic review of 33 randomized controlled trials. Arch Surg 2006;141(8):790-7.

114. Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anaesthetic management. Anesth Analg 1997;85:874-85.

115. Warkentin TE, Levine MN, Hirsch J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332(20):1330-5.

116. Weitz JI, Hirsh J, Samama MM. New Antithrombotic Drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th ed. Chest 2008;133:234S-56.

117. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. RE-COVER Study Group Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.

118. Dahl OE, Huisman MV. Dabigatran etexilate: advances in anticoagulation therapy. Expert Rev Cardiovasc Ther 2010;8(6):771-4.

119. Effective single-drug approach is welcomed for deep-vein thrombosis treatment. Cardiovasc J Afr 2010;21(5):301.

120. Chen T, Lam S. Rivaroxaban: an oral direct factor Xa inhibitor for the prevention of thromboembolism. Cardiol Rev 2009;17(4):192-7.

121. Tsai J, Georgiades CS, Hong K, Kim HS. Presumed pulmonary embolism following power-pulse spray thrombectomy of upper extremity venous thrombosis. Cardiovascular and interventional radiology. 2006;29(4):678-80.

122. Ramacciotti E, Araújo GR, Lastoria S, Maffei FH, Karaoglan de Moura L, Michaelis W, Dietrich-Neto F; CLETRAT Investigators. et al. An open-label, comparative study of the efficacy and safety of once-daily dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis. Thromb Res 2004;114(3):149-53.

123. Hull RD, Raskob GE, Hirsh J. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal vein thrombosis. NEJM. 1986:315:1109-14.

124. Wan B, Fu HY, Yin JT, Ren GQ. Low-molecular-weight heparin and intermittent pneumatic compression for thromboprophylaxis in critical patients. Exp Ther Med. 2015 Dec;10(6):2331-6.

125. Heydari AA, Jafari R, Bojdy A, Farokhnia M, Ghaboulishahroodi J, Soltani AK, et al. The Role of Daily Measurement of Lower Limb Circumference in Early Diagnosis of Deep Vein Thrombosis in the Presence of Other Risk Factors in Patients Admitted to Infectious Diseases Ward of Imam Reza

Hospital, Mashhad, during 2012-2013. Patient Saf Qual Improv2015;3(4): Autumn 2015 286-90.

126. Holm HA, Ly B, Handeland GF, Abildgaard U, Arnesen KE, Gottschalk P, et al. Subcutaneous heparin treatment of deep venous thrombosis: a comparison of unfractionated and low molecular weight heparin. Haemostasis 1986;16:Suppl 2:30-7.

127. Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis. Thromb Haemost 1990;64:506-10.

128. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992;326:975-82.

129. Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993;153:1541-6.

130. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al Enoxaparin Clinical Trial Group.. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001 Feb 6;134(3):191-202.

131. Stromberg J, Sadr-Azodi O, Videhult P, Hammarqvist F, Sandblom G. Incidence and risk factors for symptomatic venous thromboembolism following cholecystectomy. Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie. 2015 May;400(4):463-9.

ANNEXURE I- CONSENT FORM

Dear Mr./Mrs./Dr. _____, you are kindly requested to enroll yourself in a research study tilted, **"A ONE YEAR RANDOMIZED CONTROL TRIAL TO COMPARE LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN IN THE RATE OF REDUCTION OF LOWER LIMB GIRTH IN A CASE OF DEEP VEIN THROMBOSIS"** being conducted by Dr. **** ****** , a post graduate student in M.S. General Surgery and the study will be carried out under the direct supervision and guidance of Dr. **** *******, Professor and HOD, Department of General Surgery, Jawaharlal Nehru Medical College, Belagavi.

You have been requested to participate in this as you fit into the laid out criteria for a study 'subject'/ participant.

Your participation in study is voluntary. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. Your decision whether or not to participate in the study will not affect your treatment in any form during your hospital stay. If you decide to participate you are free to withdraw at any time.

Title of the study "A ONE YEAR RANDOMIZED CONTROL TRIAL TO COMPARE LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN IN THE RATE OF REDUCTION OF LOWER LIMB GIRTH IN A CASE OF DEEP VEIN THROMBOSIS."

Purpose of the study

To compare Unfractionated heparins and LMWH in the rate of reduction in lower limb girth in a case of deep vein thrombosis.

Procedures involved

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly.

You will be randomly allocated using computer generated numbers into group A (administering LMWH) and group B (administering unfractionated heparin).

On admission, DVT will be diagnosed and confirmed with a Color Doppler study of lower limbs and/or PT INR, aPTT method. Other causes that are responsible for lower limb swelling will be excluded. The lower limb girth will be measured after confirming the diagnosis in the affected limb, as well as the normal limb, in the standing position with weight equally distributed on both lower limbs. It will be measured at the point of largest circumference of the calf. It will be done using a new metal tape measure. Measurement will be done by me, in a way that the tape is not too tight, not too loose, tape lying flat on the skin, and is horizontal. After the diagnosis is confirmed, in one group, therapeutic dose of LMWH (Inj. ENOXAPARIN 1 mg/kg B.W. subcutaneously) will be administered, and in another group, Inj. Heparin I.V infusion will be administered. Rate of heparin infusion will be adjusted according to the need of time with regular monitoring of aPTT values.

After the administration of LMWH/UFH, oral ACITROM was given to both the groups once daily for a period of 3 months to keep PT INR in the range of 2-3.

Pain management was standardized in both the groups. Both group patients received Inj. Tramadol I.V in 100 ml NS infusion in case of severe pain and Tab. Ultracet for mild to moderate pain.

Outcome i.e. swelling size was assessed with a measure tape by measuring the calf at the point of largest circumference i.e 10 cm below the tibial tuberosity.

Time of measurement

On admission, then 6th, 12th, 24th hourly, 48 hours, 72 hours and 96 hours after starting the treatment, and then the readings recorded.

Risks and benefits

The potential risks involved are if the patient ambulates in a severe case of DVT, the clot may get dislodged and he may likely develop symptoms of pulmonary embolism. But the patient will be explained clearly regarding the condition.

No major side effects of both the drugs involved. If any minor side effect is observed, then adequate treatment will be given to reverse the side effect. If the patient is sensitive to heparin or has a history of HIT, then it will be checked prior.

Benefits of taking part in this research

Both the treatment modalities are individualized according to patient factors. So, the chosen treatment modality will ensure the maximum efficacy, minimal side effects, and minimize dosing of the drug. Patient will get the benefit of maximum compliance.

No bias will be done to the patients who are not willing to participate in the study from the treatment point of view.

Voluntary participation / withdrawal from the study

Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

Alternatives

Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

Privacy and confidentiality

All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

In emergency to protect your rights AND welfare.

If required by law.

Authorization to publish result:

The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

Financial incentives for participation

No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

Compensation

In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

Questions/contact details

You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

Dr. ** *******
MS (Post Graduate Student)
Department of General Surgery
Jawaharlal Nehru Medical College,
Nehru Nagar, KLE Hospital Road,
Belagavi - 590 010
Mobile – ****** ******

Dr. *** *******
MBBS, MS GENERAL SURGERY,
Professor and HOD,
Department of General Surgery
Jawaharlal Nehru Medical College,
Nehru Nagar, KLE Hospital Road,
Belagavi - 590 010
Mobile – ***** ******

In case you need any further information regarding your rights as study participant you may contact:

Dr. *** *********
Professor of Pathology &Chairman,
JNMC Institutional Ethics Committee
On Human Subjects Research,
Jawaharlal Nehru Medical College
Nehru Nagar, KLE Hospital Road
Mobile – ***** ******

CONSENT STATEMENT

I the undersigned Mr./Mrs./Dr._____ do hereby give consent for my participation in this research study after being explained in-depth about the important elements of this study in my own vernacular language.

I give this consent voluntarily in my sound mind and good faith, knowing very well the risks involved and been given enough time to clear my doubts and other queries to participate as a 'subject' in this study. I do hereby also give consent for publication of this article in any media / journal and have no objections whatsoever.

Signature or left thumb print of participant or legally authorized representative

Participant's name: _____

Signature: _____

Witness/guardian name: _____

Signature_____

Investigator's name: Dr. **** ******

Signature_____

Guide's name: Dr. **** ******

Signature_____

Date: ___/___/_____Place: _____

ANNEXURE II – PROFORMA

The proposed proforma/questionnaire to be used for data collection for the study tilted, **"A ONE YEAR RANDOMIZED CONTROL TRIAL TO COMPARE LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN IN THE RATE OF REDUCTION OF LOWER LIMB GIRTH IN A CASE OF DEEP VEIN THROMBOSIS"** is as follows:

Patient details:

In / Out Patient Department Number:

Date of admission:

Date of discharge:

Name:

Sex:

Age:

Address:

Chief Complaints

Swelling in the leg:

Yes / No Duration

Pain in the lower limb: Yes / No

Type of pain

Chest pain or dyspnoea on minor exertion

Able to walk

History of heparin induced thrombocytopenia (hit) or heparin sensitivity

Paralysis, paresis or recent plaster immobilization of lower extremity:

Pitting edema of the symptomatic leg:

Recently bedridden for 3 days or more or any major surgery in last 12 weeks (under ga or ra):

History of side effect or intolerance to tramadol: Yes / No

Calf girth at the time of admission:

History of smoking:

General examination

Built and Nourishment:

Weight:

Pulse:

Blood pressure:

Respiratory rate:

Temperature:

	Normal	Abnormal findings
Cardiovascular system:		
Respiratory:		
Central nervous system:		

Investigations

Complete blood count:

Random blood sugar:

Blood Urea:

Serum Creatinine:

Urine

Routine:

Microscopy:

PT INR:

Control:

Test:

INR:

APTT:

Control:

Test:

Ratio:

Colour Doppler lower limb:

Assessment of lower limb swelling: (at the level of largest circumferencei.e.10 Cms below the tibial tuberosity)

Calf girth at the time of admission:

Calf girth before starting treatment (Gb)

Calf girth after 6 hours:

Calf girth after 12 hours:

Calf girth after 24 hours:

Calf girth after 48 hours:

Calf girth after 72 hours:

Calf girth after 96 hours:

Calf girth after treatment (Ga)

Rate of reduction of calf girth from the time of admission to the time of discharge:

$$\frac{Gb - Ga}{Gb} \times 100$$

Measurement of calf girth: tape measure

ANNEXURE III – KEY TO MASTER CHART

A	-	Afebrile
aPTT	-	Activated partial thromboplastin time
cm	-	Centimeter
cumm	-	Cubic millimeter
f	-	Febrile
F	-	Female
gm	-	Gram
INR	-	International normalized ratio
Kg	-	Kilogram
L	-	Left
M	-	Male
MB	-	Moderately built moderately nourished
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
n	-	No
N	-	Normal
PB	-	Poorly built poorly nourished
PT	-	Prothrombin time
R	-	Right
TLC	-	Total leukocyte count
WB	-	Well built well nourished
Y	-	Yes

ANNEXURE III - MASTER CHART

Serial number	In patient number	Group	Date of admission	Date of discharge	Sex	Age (Years)	Chief complaints			Chest pain or dyspnoea or ninot exertion	Ability to walk	Heparin induced thrombocytopenia or heparin sensitivity	Paralysis, paresis or recent plaster immobilization of lower extremity	Pitting edema of the symptomatic leg	Bedridden for 3 days or more for major surgery	History of side effect or intolerance to tramadol	Calf girth at the time of admission (cm)	Is the patient a smoker duration of smoking (years)	General physical examination							
							Duration of Swelling in leg (Days)	Pain in lower limb	Which limb?										Built and Nourishment	Weight (Kgs)	Pulse (/minute)	Blood pressure		Respiratory rate (/Minute)	Temperature	System examina
																						Systolic (mmHg)	Dialostic (mmHg)			Cardiovascular system	Respiratory
1	728014	A	#######	4/16/2016	M	54	3	Y	R	n	Y	n	n	Y	n	n	38.4	n	WB	68	74	130	80	18	A	N	N
2	729066	A	#######	4/20/2016	M	72	5	Y	R	n	Y	n	n	Y	n	n	36.2	n	MB	64	78	126	72	19	A	N	N
3	739483	A	#######	6/4/2016	M	50	2	Y	L	n	Y	n	n	n	n	n	34.8	n	MB	52	84	128	84	18	A	N	N
4	740620	A	#######	6/20/2016	M	54	10	Y	L	n	Y	n	n	Y	Y	n	35.0	Y	MB	68	62	138	90	16	A	N	N
5	749097	A	#######	7/24/2016	M	55	8	Y	R	n	Y	n	Y	Y	n	n	39.2	n	WB	72	70	110	68	20	A	N	N
6	749641	A	#######	7/30/2016	M	34	21	Y	L	n	Y	n	n	Y	n	n	33.6	n	PB	44	74	120	84	14	A	N	N
7	751017	A	#######	8/4/2016	F	32	14	Y	R	n	Y	n	n	n	n	n	30.4	n	WB	62	82	138	88	13	f	N	N
8	752546	A	8/2/2016	8/10/2016	M	34	4	Y	R	n	Y	n	n	n	n	n	32.8	n	WB	78	94	132	74	16	A	N	N
9	755739	A	#######	8/24/2016	F	28	2	Y	R	n	Y	n	Y	Y	n	n	37.6	n	MB	64	64	124	78	18	A	N	N
10	753842	A	#######	8/18/2016	M	46	3	Y	R	n	n	n	Y	n	n	n	38.9	n	MB	77	92	136	70	15	A	N	N
11	759471	A	9/7/2016	9/14/2016	M	54	8	Y	L	n	Y	n	n	Y	Y	n	39.2	n	MB	81	76	138	88	18	A	N	N
12	759858	A	#######	9/18/2016	M	68	10	Y	R	n	Y	n	n	Y	Y	n	31.8	n	MB	64	80	114	66	17	A	N	N
13	756077	A	#######	8/29/2016	F	22	4	Y	L	n	Y	n	n	n	n	n	29.4	n	PB	38	88	126	72	16	A	N	N
14	760084	A	#######	9/20/2016	M	37	7	Y	L	n	Y	n	n	n	n	n	31.2	n	PB	41	94	104	66	21	A	N	N
15	761642	A	#######	9/27/2016	M	37	2	Y	R	n	Y	n	n	n	n	n	35.4	n	MB	66	104	124	86	20	f	N	N
16	761172	A	#######	9/25/2016	M	70	6	n	L	n	Y	n	Y	Y	n	n	37.3	n	MB	69	72	126	78	16	A	N	N
17	763936	A	#######	########	F	25	1	Y	R	n	Y	n	n	Y	Y	n	30.6	n	MB	80	80	142	84	18	A	N	N
18	767260	A	#######	########	M	24	3	Y	R	n	Y	n	n	n	n	n	33.9	n	WB	78	94	120	104	17	A	N	N
19	770294	A	#######	########	F	50	13	Y	R	n	Y	n	Y	Y	n	n	36.8	n	MB	71	92	142	88	16	f	N	N
20	769491	A	#######	########	M	50	24	n	L	n	Y	n	n	Y	n	n	39.9	n	MB	74	68	132	84	14	A	N	N
21	769719	A	#######	########	M	68	3	Y	L	Y	n	n	Y	n	n	n	35.2	Y	WB	68	84	130	97	19	A	N	N
22	771757	A	#######	########	M	18	2	Y	R	n	Y	n	n	Y	n	n	33.4	n	MB	59	78	114	72	18	A	N	N
23	772202	A	#######	########	F	60	24	Y	R	n	Y	n	n	Y	n	n	34.9	n	MB	61	84	124	82	16	A	N	N
24	772199	A	#######	########	M	29	10	Y	R	n	Y	n	n	n	Y	n	32.2	n	MB	56	92	130	50	14	A	N	N
25	772243	A	#######	12/9/2016	M	38	8	Y	R	n	Y	n	n	Y	n	n	38.1	n	WB	78	76	120	70	14	A	N	N
26	776938	A	#######	########	M	55	24	Y	R	n	Y	n	n	Y	n	n	36.3	Y	MB	59	64	110	60	16	A	N	N
27	773280	A	#######	########	M	44	13	Y	L	n	Y	n	n	Y	n	n	35.5	n	MB	51	76	120	80	18	A	N	N
28	778285	A	#######	########	M	45	4	Y	L	n	Y	n	n	Y	n	n	37.3	n	MB	62	92	142	86	13	A	N	N
29	774933	A	#######	########	M	50	2	Y	R	n	Y	n	Y	Y	Y	n	40.0	Y	WB	81	84	130	92	14	A	N	N
30	778596	A	#######	########	F	30	4	Y	L	n	Y	n	n	n	Y	n	34.4	n	MB	52	104	136	88	17	A	N	N
31	727687	B	#######	4/7/2016	F	72	7	Y	L	n	Y	n	Y	Y	n	n	28.3	n	PB	40	78	110	68	19	A	N	N
32	727293	B	#######	4/10/2016	M	28	2	Y	R	n	Y	n	n	Y	n	n	30.6	n	MB	53	84	104	70	20	A	N	N
33	727543	B	#######	4/7/2016	M	39	20	Y	L	n	Y	n	n	Y	n	n	38.3	n	WB	77	92	116	80	14	A	N	N
34	727619	B	4/1/2016	4/8/2016	M	52	5	Y	R	n	Y	n	Y	Y	Y	n	34.6	n	WB	68	64	114	76	13	A	N	N
35	760149	B	#######	9/20/2016	M	62	10	Y	L	n	Y	n	n	Y	n	n	29.3	Y	PB	42	78	126	84	18	A	N	N
36	760014	B	#######	9/19/2016	M	48	3	Y	R	n	Y	n	n	n	n	n	32.3	n	MB	55	82	136	80	17	A	N	N
37	762842	B	#######	10/4/2016	M	52	8	Y	R	n	Y	n	Y	Y	Y	n	36.0	n	WB	69	56	144	90	16	A	N	N
38	746248	B	7/3/2016	7/11/2016	M	35	2	Y	R	n	Y	n	n	n	n	n	34.6	n	MB	58	68	124	70	14	A	N	N
39	739641	B	7/1/2016	7/10/2016	M	55	6	Y	R	n	Y	n	Y	Y	n	n	25.4	n	PB	42	108	110	72	13	A	N	N
40	761204	B	#######	9/30/2016	M	65	4	Y	L	n	Y	n	Y	Y	n	n	35.1	n	MB	58	56	114	76	15	A	N	N
41	718694	B	#######	8/24/2016	M	35	13	Y	L	n	Y	n	n	Y	n	n	40.9	n	WB	84	76	130	84	19	A	N	N
42	727337	B	3/9/2016	3/19/2016	M	61	3	Y	L	n	Y	n	n	Y	n	n	38.3	n	MB	52	92	124	80	18	A	N	N
43	718923	B	#######	2/27/2016	M	29	3	Y	R	n	Y	n	n	Y	n	n	34.3	n	MB	54	84	110	70	13	A	N	N
44	728096	B	#######	4/18/2016	M	44	2	Y	L	n	Y	n	n	Y	n	n	34.8	n	MB	50	68	124	80	14	A	N	N
45	730914	B	5/3/2016	5/11/2016	F	62	8	Y	L	n	Y	n	n	Y	Y	n	26.3	n	PB	38	80	130	84	13	A	N	N
46	743122	B	#######	6/23/2016	M	36	2	Y	L	n	Y	n	n	n	n	n	36.9	n	WB	62	90	140	90	15	A	N	N
47	727148	B	#######	4/4/2016	F	20	4	Y	L	n	Y	n	n	Y	n	n	32.4	n	MB	51	62	134	82	18	A	N	N
48	735184	B	5/8/2016	5/16/2016	M	40	4	Y	R	n	Y	n	n	Y	n	n	41.3	n	WB	85	66	106	68	16	A	N	N
49	765108	B	#######	########	F	31	1	Y	R	n	Y	n	n	n	Y	n	36.8	n	MB	50	76	110	70	14	A	N	N

ANNEXURE III - MASTER CHART

Serial number	In patient number	mic ation	Investigations						Urine		Investigations							Assessment of Calf girth (Largest circumference i.e. 10 cms below the tibial tuberosity (cm)								Rate of reduction of calf girth (%)
											Coagulation profile															
		Central nervous system	Haemoglobin (gm%)	Random blood sugar (mg/dL)	Blood Urea (mg/dL)	Serum Creatinine (mg/dL)	Platelet count (lacks per cumm)	TLC (lacks per cumm)	Routine	Microscopy	PT Control	PT Test	INR	aPTT Control	aPTT Test	Ratio	Colour Doppler lower limb	Calf girth before treatment	6 hours	12 hours	24 hours	48 hours	72 hours	96 hours	Calf girth after treatment	
1	728014	N	12.4	138	40	0.9	3.2	6.2	N	N	11.2	36.4	3.21	28.8	35.1	1.22	1	38.4	37.8	37.2	36.4	35.3	34.5	33.8	31.6	17.71
2	729066	N	14.2	140	44	0.8	3.7	7.8	N	N	11.2	28.6	2.55	28.8	39.1	1.36	1	36.2	35.6	35.0	34.2	33.7	33.1	32.5	32.1	11.33
3	739483	N	15.1	156	48	1.1	2.9	6.1	N	N	11.2	15.8	1.41	28.8	82.0	2.85	1	34.8	34.2	33.4	32.8	32.1	31.4	31.0	30.6	12.07
4	740620	N	14.0	121	52	1.0	4.1	6.8	N	N	11.2	16.3	1.46	28.8	69.0	2.40	1	35.0	34.6	33.9	33.1	32.7	32.0	31.4	31.2	10.86
5	749097	N	13.3	142	38	0.4	1.9	9.4	N	N	11.2	20.5	1.82	28.8	72.3	2.51	1	39.2	38.4	37.8	37.0	36.2	35.1	34.3	32.5	17.09
6	749641	N	12.1	180	36	0.8	2.4	7.9	N	N	11.2	22.5	2.03	28.8	54.1	1.88	1	33.6	33.1	32.6	31.9	31.1	30.2	29.7	29.4	12.50
7	751017	N	14.2	240	60	1.5	3.2	14.3	N	N	11.2	15.5	1.38	28.8	37.4	1.30	1	30.5	30.2	29.6	29.1	28.9	28.6	28.5	28.4	6.89
8	752546	N	15.6	184	58	1.3	3.6	5.4	N	N	11.2	79.7	7.12	28.8	30.4	1.06	1	32.9	32.3	32.0	31.5	30.1	29.5	29.1	28.6	13.07
9	755739	N	12.8	141	34	0.3	3.8	10.3	N	N	11.2	12.2	1.09	28.8	31.4	1.09	1	37.6	37.0	36.4	36.0	35.6	35.0	34.6	33.5	10.90
10	753842	N	14.9	138	30	0.6	4.2	9.8	N	N	11.2	16.5	1.47	28.8	36.2	1.26	1	38.9	38.3	37.2	36.6	36.1	35.7	35.2	33.9	12.85
11	759471	N	14.2	126	42	0.8	2.9	7.6	N	N	11.2	11.5	1.03	28.8	30.8	1.07	1	39.2	38.3	37.8	37.2	36.7	36.2	35.8	32.9	16.07
12	759858	N	13.9	110	54	1.2	2.7	5.4	N	N	11.2	71.8	6.29	28.8	66.3	2.30	1	31.7	31.2	30.8	30.1	29.2	28.6	28.4	28.4	10.41
13	756077	N	10.3	128	60	0.9	2.8	7.8	N	N	11.2	26.6	2.38	28.8	33.0	1.15	1	29.4	29.0	28.4	27.6	27.4	27.0	26.3	26.1	11.22
14	760084	N	9.8	114	54	0.8	2.6	7.9	N	N	11.2	12.4	1.10	28.8	32.2	1.12	1	31.2	30.7	30.3	29.6	29.0	28.4	28.0	27.8	10.90
15	761642	N	15.2	136	41	0.8	1.2	15.2	N	N	11.2	17.0	1.07	28.8	31.8	1.10	1	35.4	35.0	34.2	33.7	33.3	32.9	32.6	32.4	8.47
16	761172	N	16.0	143	38	0.8	2.4	10.1	N	N	11.2	12.2	1.09	28.8	20.9	0.73	1	37.3	36.8	36.4	35.8	34.9	34.1	33.6	32.5	12.87
17	763936	N	13.1	148	26	0.4	2.9	10.8	N	N	11.2	33.9	3.00	28.8	107.5	3.73	1	30.7	30.5	30.0	29.4	29.0	28.8	28.5	28.4	7.49
18	767260	N	14.4	136	28	0.7	3.0	8.4	N	N	11.2	14.5	1.29	28.8	60.5	2.10	1	33.8	33.4	32.8	31.2	30.8	30.0	29.5	28.9	14.50
19	770294	N	11.4	106	41	0.6	4.1	12.4	N	N	11.2	40.0	3.53	28.8	68.3	2.37	1	36.8	36.2	35.4	34.9	34.1	33.3	32.7	32.4	11.96
20	769491	N	13.7	142	50	1.0	4.0	5.6	N	N	11.2	14.7	1.31	28.8	36.1	1.25	1	39.9	39.3	38.6	37.9	37.3	36.9	36.7	35.5	11.03
21	769719	N	14.1	138	68	1.4	2.2	6.0	N	N	11.2	19.1	1.71	28.8	35.4	1.23	1	35.2	35.1	34.5	33.5	32.0	31.1	30.4	29.8	15.41
22	771757	N	13.8	130	38	1.1	2.4	5.6	N	N	11.2	20.1	1.80	28.8	31.8	1.10	1	33.4	32.5	32.0	31.6	31.0	30.6	30.3	30.2	9.58
23	772202	N	12.0	138	42	1.2	2.7	4.9	N	N	11.2	14.0	1.25	28.8	90.3	3.24	1	34.9	33.8	32.9	32.4	31.8	31.3	31.0	30.8	11.75
24	772199	N	12.8	124	56	1.4	3.4	9.8	N	N	11.2	19.6	1.75	28.8	97.3	3.38	1	32.2	31.6	31.2	30.8	30.2	30.1	29.9	29.8	7.45
25	772243	N	14.2	114	48	1.3	4.1	8.4	N	N	11.2	38.5	3.44	28.8	40.9	1.42	1	38.1	37.0	36.2	35.6	35.1	34.8	34.4	32.9	13.65
26	776938	N	12.8	128	34	0.9	2.9	10.1	N	N	11.2	12.0	1.07	28.8	30.9	1.07	1	36.3	35.3	34.6	34.0	33.3	32.0	32.1	31.4	13.50
27	773280	N	15.4	139	26	0.5	1.9	7.5	N	N	11.2	23.7	1.10	28.8	41.2	1.43	1	35.5	34.3	33.8	33.1	32.6	32.0	31.3	30.9	12.96
28	778285	N	14.7	154	24	0.4	2.4	10.4	N	N	11.2	12.0	2.08	28.8	45.2	1.57	1	37.6	35.8	34.9	34.2	33.5	32.9	32.5	31.9	15.23
29	774933	N	13.9	142	33	0.6	3.7	6.6	N	N	11.2	12.4	1.10	28.8	39.2	1.36	1	40.1	38.3	37.1	36.4	35.6	34.8	34.0	31.2	22.19
30	778596	N	11.2	154	39	0.7	4.1	8.4	N	N	11.2	24.3	2.17	28.8	46.2	1.60	1	34.4	33.4	32.9	32.6	32.1	31.9	31.6	31.4	8.72
31	727687	N	9.4	138	34	0.6	3.4	9.9	N	N	11.2	28.8	2.57	28.8	46.1	1.39	1	28.3	27.4	26.9	26.6	26.1	25.7	25.3	25.1	11.31
32	727293	N	13.4	106	38	0.8	4.2	10.1	N	N	11.2	14.3	1.27	28.8	38.6	1.34	1	30.6	29.3	28.6	28.1	27.7	27.1	26.4	26.1	14.70
33	727543	N	16.1	116	64	1.3	2.9	7.6	N	N	11.2	18.4	1.64	28.8	94.2	3.27	1	38.3	36.9	36.6	36.0	35.1	34.6	33.8	33.2	13.31
34	727619	N	14.5	128	54	1.1	2.8	5.6	N	N	11.2	12.9	1.15	28.8	29.6	1.03	1	34.6	33.7	33.2	32.9	32.8	32.6	32.3	32.4	6.36
35	760149	N	10.1	135	60	1.4	4.1	6.1	N	N	11.2	60.4	5.39	28.8	86.4	3.01	1	29.3	28.4	28.0	27.4	27.0	26.7	26.3	26.1	10.92
36	760014	N	15.2	134	84	1.4	3.4	8.9	N	N	11.2	38.6	3.44	28.8	64.3	2.23	1	32.3	31.2	30.6	30.0	29.3	29.0	28.6	28.3	12.38
37	762842	N	14.8	127	38	0.8	4.0	7.1	N	N	11.2	13.2	1.18	28.8	34.1	1.18	1	36.0	34.3	33.6	32.9	32.2	31.8	31.0	30.4	15.56
38	746248	N	13.9	140	76	1.0	2.9	7.5	N	N	11.2	16.4	1.46	28.8	29.2	1.01	1	34.6	33.6	33.0	32.4	32.0	31.3	30.8	30.3	12.43
39	739641	N	10.0	132	40	1.1	3.4	14.2	N	N	11.2	19.2	1.71	28.8	30.8	1.07	1	25.4	24.7	24.3	24.1	23.9	23.5	23.4	23.2	8.66
40	761204	N	12.4	149	49	0.8	3.4	8.4	N	N	11.2	12.0	1.07	28.8	36.4	1.26	1	35.1	34.0	33.3	32.8	32.4	32.0	31.6	31.4	10.54
41	718694	N	13.5	109	28	0.4	2.9	9.8	N	N	11.2	17.2	1.53	28.8	29.9	1.04	1	40.9	38.9	38.1	37.3	36.4	35.3	34.3	33.6	17.85
42	727337	N	15.4	120	42	0.6	4.4	4.9	N	N	11.2	21.3	1.90	28.8	40.2	1.39	1	38.3	35.9	35.0	34.3	33.1	32.4	31.9	31.4	18.02
43	718923	N	13.8	128	44	0.8	2.8	8.4	N	N	11.2	14.9	1.33	28.8	36.4	1.26	1	34.3	33.8	33.1	32.6	32.0	31.4	30.6	30.2	11.96
44	728096	N	12.4	140	54	0.9	2.6	8.9	N	N	11.2	27.4	2.45	28.8	29.4	1.02	1	34.8	34.3	33.8	33.1	32.6	32.1	31.8	31.4	9.78
45	730914	N	9.4	116	28	0.4	3.1	7.9	N	N	11.2	36.4	3.25	28.8	64.9	2.25	1	26.3	25.8	25.5	25.1	24.8	24.5	24.1	23.9	9.13
46	743122	N	15.4	124	66	1.4	3.8	4.3	N	N	11.2	64.4	5.75	28.8	38.9	1.35	1	36.9	36.3	35.9	35.4	34.9	34.4	33.7	33.4	9.48
47	727148	N	11.8	164	41	1.0	1.8	6.4	N	N	11.2	13.4	1.19	28.8	30.7	1.07	1	32.4	31.8	31.0	30.6	30.0	29.2	28.7	28.3	12.65
48	735184	N	14.2	146	56	1.7	4.1	10.2	N	N	11.2	13.1	1.17	28.8	41.2	1.43	1	41.3	40.6	40.0	39.4	38.7	38.1	37.2	36.4	11.86
49	765108	N	11.1	128	61	1.5	2.8	7.9	N	N	11.2	18.9	1.69	28.8	64.1	2.23	1	36.8	36.1	35.4	34.8	34.3	33.6	33.0	32.8	10.87

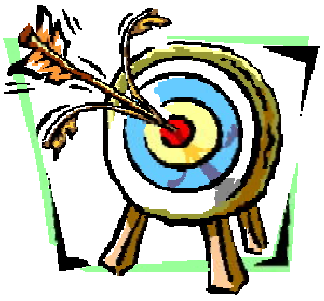
ANNEXURE III - MASTER CHART

Serial number	In patient number	Group	Date of admission	Date of discharge	Sex	Age (Years)	Chief complaints			Chest pain or dyspnoea or ninot exertion	Ability to walk	Heparin induced thrombocytopenia or heparin sensitivity	Paralysis, paresis or recent plaster immobilization of lower extremity	Pitting edema of the symptomatic leg	Bedridden for 3 days or more for major surgery	History of side effect or intolerance to tramadol	Calf girth at the time of admission (cm)	Is the patient a smoker duration of smoking (years)	General physical examination								
							Duration of Swelling in leg (Days)	Pain in lower limb	Which limb?										Built and Nourishment	Weight (Kgs)	Pulse (/minute)	Blood pressure		Respiratory rate (/Minute)	Temperature	System examina	
																						Systolic (mmHg)	Dialostic (mmHg)			Cardiovascular system	Respiratory
50	767260	B	#######	########	M	48	7	Y	L	n	Y	n	n	n	Y	n	36.0	n	MB	54	72	110	80	12	A	N	N
51	771426	B	#######	########	F	54	10	Y	R	n	Y	n	n	Y	n	n	28.3	n	MB	49	80	120	74	18	A	N	N
52	700480	B	#######	2/4/2016	M	50	9	Y	R	n	Y	n	n	Y	n	n	40.6	Y	WB	80	66	106	74	19	A	N	N
53	700682	B	#######	2/9/2016	M	28	1	Y	R	n	Y	n	n	n	n	n	38.4	n	WB	74	72	122	78	16	A	N	N
54	733393	B	#######	5/25/2016	F	55	6	Y	L	n	Y	n	n	n	n	n	28.1	n	PB	40	84	130	78	18	A	N	N
55	738031	B	#######	5/30/2016	M	50	15	Y	L	n	n	n	n	Y	Y	n	32.4	n	MB	50	88	144	78	15	A	N	N
56	725823	B	#######	4/3/2016	M	48	4	Y	R	n	Y	n	n	Y	n	n	34.1	n	MB	58	92	120	80	16	A	N	N
57	716838	B	#######	2/24/2016	M	34	3	Y	R	n	Y	n	n	Y	n	n	38.9	n	WB	72	68	140	86	18	A	N	N
58	736289	B	#######	6/20/2016	F	30	1	Y	R	n	Y	n	n	Y	Y	n	36.0	n	MB	60	84	130	82	20	A	N	N
59	743667	B	#######	6/24/2016	M	30	2	Y	R	n	Y	n	n	n	n	n	41.7	n	WB	88	72	140	84	18	A	N	N
60	751973	B	8/1/2016	8/10/2016	M	61	4	Y	L	n	Y	n	n	n	Y	n	35.5	n	MB	64	78	110	68	14	A	N	N

ANNEXURE III - MASTER CHART

Serial number	In patient number	mic ation	Investigations								Investigations							Assessment of Calf girth (Largest circumference i.e. 10 cms below the tibial tuberosity (cm)								Rate of reduction of calf girth (%)
									Urine		Coagulation profile															
		Central nervous system	Haemoglobin (gm%)	Random blood sugar (mg/dL)	Blood Urea (mg/dL)	Serum Creatinine (mg/dL)	Platelet count (lacks per cumm)	TLC (lacks per cumm)	Routine	Microscopy	PT Control	PT Test	INR	aPTT Control	aPTT Test	Ratio	Colour Doppler lower limb	Calf girth before treatment	6 hours	12 hours	24 hours	48 hours	72 hours	96 hours	Calf girth after treatment	
50	767260	N	16.0	121	49	0.9	2.2	5.4	N	N	11.2	16.4	1.46	28.8	60.4	2.10	1	36.0	35.2	34.4	33.9	33.2	32.6	31.9	31.5	12.50
51	771426	N	10.8	116	22	0.4	3.3	6.3	N	N	11.2	28.2	2.51	28.8	36.4	1.26	1	28.3	27.8	27.0	26.3	25.8	25.3	24.9	24.8	12.37
52	700480	N	14.4	145	54	0.8	3.6	8.2	N	N	11.2	24.8	2.21	28.8	29.8	1.03	1	40.6	39.8	39.1	38.3	37.6	36.5	35.1	33.9	15.02
53	700682	N	12.8	141	49	0.7	4.2	8.9	N	N	11.2	13.4	1.20	28.8	42.4	1.47	1	38.4	37.8	37.1	36.3	35.8	35.2	34.7	34.2	10.94
54	733393	N	10.1	136	36	0.5	3.8	5.9	N	N	11.2	12.0	1.07	28.8	40.4	1.40	1	28.1	27.6	27.2	26.8	26.6	26.1	25.8	25.4	9.61
55	738031	N	13.6	156	42	1.0	2.8	10.8	N	N	11.2	11.1	0.99	28.8	31.3	1.09	1	32.4	31.9	31.3	30.6	30.0	29.3	28.6	28.1	13.27
56	725823	N	15.2	124	38	0.9	1.8	5.8	N	N	11.2	19.1	1.71	28.8	39.9	1.39	1	34.1	33.6	32.9	32.1	31.6	30.9	30.1	29.5	13.49
57	716838	N	14.9	161	84	0.9	1.6	7.4	N	N	11.2	15.4	1.38	28.8	47.2	2.63	1	38.9	38.1	37.5	36.9	36.1	35.3	34.4	33.6	13.62
58	736289	N	12.4	142	42	0.8	2.4	9.8	N	N	11.2	12.4	1.11	28.8	28.2	0.98	1	36.0	36.4	35.1	34.8	34.7	34.5	34.4	34.4	4.44
59	743667	N	16.1	128	39	0.4	4.2	4.8	N	N	11.2	12.8	1.14	28.8	40.1	1.39	1	41.7	41.1	40.3	39.5	38.8	38.1	37.4	36.2	13.19
60	751973	N	10.3	108	26	0.3	3.9	6.2	N	N	11.2	10.6	0.95	28.8	34.8	1.21	1	35.5	34.4	33.5	32.5	31.1	32.0	29.4	28.9	18.60

Introduction



Objectives

Review of Literature

Methodology

Results

Discussion

Conclusion

Summary

Bibliography

Annexure-I

Annexure-II

Annexure-III