PREVALENCE OF DEEP VEIN THROMBOSIS IN ACUTE STROKE.

Dissertation submitted to

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirement

for the award of degree of

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GENERAL MEDICINE

INSTITUTE OF INTERNAL MEDICINE
AND GOVERNMENT GENERAL HOSPITAL
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CERTIFICATE

This is to certify that this dissertation entitled " PREVALENCE OF DVT IN ACUTE STROKE" submitted by Dr. R.GAYATHRI ,post graduate student, Institute of internal medicine , madras medical college for the period of 2005-2008 appearing for M.D. Branch I General Medicine Degree examination in march 2008, is a bonafide work done by her under my direct audience and supervision in partial fulfillment of regulations of the Tamil nadu Dr.M.G.R. Medical university , Chennai. I forward this to the Tamil Nadu DR.M.G.R. Medical University, Chennai ,Tamil Nadu , India .

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DECLARATION

I solemnly declare that the dissertation titled " PREVALANCE OF DVT IN ACUTE STROKE" is done by me at Madras Medical College and Government General Hospital under the guidance and supervision of Prof. K. Raghavan,M.D.

The dissertation is submitted to the Tamil Nadu DR.M.G.R. Medical university towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General medicine.

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CONTENTS

INTRODUCTION

Venous thrombo embolism [VTE] is a frequent cause of preventable illness and death in hospitalized patients. 25% of all cases of venous thrombo embolism are associated with hospitalization and 50 to 75% of cases of VTE in hospitalized patients occur on those in medical wards.

In general, detection of deep vein thrombosis [DVT] in hospitalized patients not on thromboprophylaxis by venography is 10.5% to 14.9% [1] and by ultrasound venous Doppler is 5% [2] .Thrombosis was asymptomatic in 70% of cases. Pulmonary embolism occurred in 0.3 to 1.5 % of cases and proximal DVT in 2 to 4.9%. PE accounts for 5 to 10 % of deaths in hospitalized patients.

In One meta analysis of four studies of 5256 patients with DVT as end point and 5 studies of 7355 patients with death as end point and 9 studies of 19,958 patients with pulmonary embolism as end point anticoagulation decreased relative risk of pulmonary embolism [0.43; 95% CI 0.26- 0.71] and fatal pulmonary embolism [0.38; 95% CI 0.21 - 0.69] and non significant relative risk of DVT [

0.47; 95% CI 0.77 – 1.00] with no effect on overall mortality and non significant increase in relative risk of bleed [1.32; 95% CI 0.73 to 2.37][3]

Three randomized control trials with Enoxaparin [MEDENOX] $p<0.001$, the prospective evaluation of Dalteparin efficacy for prevention of VTE in immobilized patients trial [PREVENT] $p=0.002$, Arixtra for thromboembolism prevention in medical indication study [ARTEMIS] $p = 0.03$] using fondaparinux were done to assess the use of anticoagulation routinely in all immobilized patients. The end point was the presence of asymptomatic distal thrombi diagnosed by means of screening venography. The presence of DVT was found in 60% of the stroke patients thus stressing the use of routine anticoagulation in patients with extremity paresis or paralysis [4]

Analysis of data from IST , international stroke trial allows a comparison of the effect of medium dose heparin [12,500 U of UFH twice daily] initiated within 48 hrs of ischemic stroke and continued for two weeks to no heparin on a number of end points. Although this dosing regimen reduced the risk of PE and recurrent ischemic stroke , the reduction was more than offset by an increased risk of emorrhagic transformation and extra cranial hemorrhage. Overall there was an increased risk of death and or recurrent stroke and major non fatal

extra cranial bleeds of 0.5% and 1.5% respectively during the treatment period.[5]

White et.al studied the risk of warfarin related complications in 22,000 unselected group with subgroup of 1312 patients with h/o stroke, the readmission rate due to bleeding was 1.7%.The excess risk of intracranial hemorrhage in this subgroup was not specifically studied, though it was 0.1% in the group as a whole. [6]

AREAS OF UNCERTAINITY:

There is strong evidence from well conducted clinical trials that anticoagulation prophylaxis reduces the risk of asymptomatic DVT and proximal DVT. Less information is available regarding effects on improved outcomes in terms of fatal and non fatal pulmonary embolism.

Because entry into trials is mainly by patients in high risk group less information is available in a general hospital population. Further, trials are mostly done on surgical patients the end information cannot be applied to patients in general medical wards with comorbid conditions and especially stroke patients where the risk of bleeding should be weighed against prophylaxis for thromboembolism.

There is no consensual opinion available about the best prophylactic method for DVT.

AIMS OF THE STUDY:

With this background study was conducted to find out

- Prevalence of Deep vein thrombosis in patients admitted with acute stroke.
- The need for routine anticoagulation for prophylaxis against DVT in acute stroke patients

REVIEW OF LITERATURE

Stroke ranks second after ischemic heart disease as a cause of lost disability adjusted – life years in high income countries and as a cause of death worldwide. [7] The incidence of stroke varies among countries and increases exponentially with age. In western societies, about 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion and the remaining 20% are caused by hemorrhages.[8]

Venous thromboembolism[VTE] is a common potentially life threatening complication that incorporates signs and symptoms of two inter-related but distinct clinical conditions, deep vein thrombosis [DVT] and pulmonary embolism [PE];this is often a silent yet potentially fatal disease. When symptoms do occur ,they are non-specific and the first manifestation may be fatal PE. Long term morbidity is a consequence of VTE since unrecognized and untreated thrombo- embolic episodes predispose patients to recurrent events.

INCIDENCE OF DEEP VEIN THROMBOSIS AFTER STROKE:

Studies with I -125 fibrinogen screening in patients with acute hemiplegic stroke have shown an incidence of DVT of approximately 50% within two weeks in absence of heparin prophylaxis.The majority of these affect the paralysed leg and are asymptomatic.[9]

Approximately two thirds of these are below knee DVTs ,[10] in contrast to unselected [non-stroke] patients presenting with symptomatic DVT, in whom majority are proximal.[11]

DVTs develop as early as 2nd day with peak incidence between days 2 and 7. The risk of DVT correlates with degree of paralysis [12] and is greater in older patients[13] as well as those with AF[14].

Predeliction for paralysed leg is probably explained by loss of calf muscle pump and repeated minor trauma.[15]

DVT is also present in significant proportion of patients during rehabilitation phase of stroke, the risk being more in those who are immobile. In one study of 150 patients admitted in stroke rehabilitation unit, at an average, 9 weeks after stroke, bilateral venography revealed DVT in 33% [16].

CLINICAL SIGNIFICANCE OF ASYMPTOMATIC PROXIMAL DVT AFTER STROKE:

The main clinical significance of asymptomatic proximal DVT is its potential to cause fatal pulmonary embolism. Indeed, the majority of symptomatic PEs are unheralded and arise from previously subclinical DVT.[17]

In a study of unselected patients performed before anticoagulants were in routine use, untreated, clinically apparent DVT was associated with a mortality from PE of up to 37%.[18] The risk of fatal PE associated with untreated subclinical DVT is lower , though it remains significant. A recent overview in post operative patients has suggested that predominantly subclinical DVT diagnosed by I 125 fibrinogen scanning is associated with 5% risk of fatal PE[19 20].

Although there are few data on natural history of untreated subclinical DVT in stroke patients, in one study patients with proximal subclinical DVT had a 35% risk of clinical PE.[21]

Fatal PE usually arise from proximal DVT[22].3% of stroke patients succumb to PE in 3 months [23], a mortality confined to those

who develop DVT. Because one third of of these are proximal and most are silent, the data suggest that the mortality associated with untreated proximal subclinical DVT afterstroke is 15% which is similar to that in postoperative patients.

A secondary concern is the potential to cause the post thrombotic syndrome,characterized by persistent pain and swelling , with or without ulceration.[24] The incidence of this disorder approaches 90% in patients with untreated symptomatic DVT. Although it is recognized that many patients who present with this syndrome have no history of clinical

VTE [the entire process having been clinically silent],[25] the incidence after untreated asymptomatic DVT is unknown. The long term incidence in patients with symptomatic, treated proximal DVT is approximately 30%, however there are conflicting data as to whether it occurs in patients with adequately treated asymptomatic proximal DVT.[26 27]

CLINICAL SIGNIFICANCE OF ASYMPTOMATIC BELOW KNEE DVT AFTER STROKE:

A major concern in patients with untreated below knee DVT is the 20% risk of proximal extension,[28] a subgroup that cannot be predicted accurately on clinical grounds. Clinical PE can however occur even in the absence of propagation and routine VQ scanning demonstrate silent PE in up to one third of patients who have isolated below knee DVT.[29 30]

Although PE arising from below knee DVT are more likely to be small and asymptomatic and therefore less likely to be life threatening than those associated with proximal DVT ,[31 32] the risk of fatal PE attributable to unteated, non propagating below knee DVT has not yet been defined. Symptomatic, isolated, below knee DVT may cause the post thrombotic syndrome,[32]but it is unclear whether this entity is a sequela in asymptomatic cases.

INCIDENCE OF PULMONARY EMBOLISM AFTER STROKE:

The incidence of PE reported in the absence of heparin prophylaxis has varied considerably, depending on the methodology of the studies. In the international Stroke Trial [IST] the incidence was 0.8% at 2 weeks.[33] Similarly, in a retrospective study of 607 patients who had acute stroke,PE was reported in 1 % during the period of hospitalization.[34]

However prospective studies that focused specifically on venous thromboembolic complications reported incidences of 10% to 13%.[35]

The risk of PE also extends to rehabilitation phase. In a retrospective study of 363 patients who did not receive heparin prophylaxis and entered rehabilitation unit 4 weeks after stroke 4% developed PE.[36]

Only one small study prospectively screened for PE and found evidence of PE in 39%. Autopsy studies show that half of the patients who die in hospital after first 48 hours post stroke have evidence of

PE, [37]which suggest that pulmonary emboli are often subclinical and/or unrecognized after acute stroke.

MORBIDITY AND MORTALITY DUE TO PE AFTER ACUTE STROKE:

PE account for 13 to 25% of early deaths after stroke.[38 – 40] Although they may occur as early as day 3 fatal emboli are unusual in the first week and are most frequent between second and fourth weeks , when they are the most common cause of death. Those more severely disabled are most likely to be affected, but PE may also occur in ambulatory patients.

The mortality attributed to untreated PE in unselected hospitalized patients is approximately 30%.[41] However PE in stroke patients may have a higher mortality than that in other clinical settings. In one series of stroke patients half of the clinical PE presented as sudden death.[42] The morbidity associated with non lethal PE should not be overlooked , this may manifest primarily as impaired cardiorespiratory reserve adversely affecting rehabilitation and potentially influencing functional outcome.[43]

DIFFICULTIES IN DIAGNOSIS OF SYMPTOMATIC PE AFTER ACUTE STROKE:

The signs and symptoms of PE are notoriously non specific and both misdiagnosis and under diagnosis are well documented , more commonly in the elderly. A number of factors make diagnosis even more difficult in post stroke patients, a group in whom ante mortem diagnosis is especially poor. Patients may not complain of symptoms because of dysphagia, cognitive impairment or mental obtundation.[44]

In addition pneumonia , the illness for which PE is most often mistaken [45] is also common after stroke. Indeed, pneumonia and PE can commonly occur together, but the possibility of coexistent PE in a patient with strong clinical evidence of pneumonia is rarely considered. Subtle clinical signs of PE like mild increase in respiratory rate are overlooked easily.

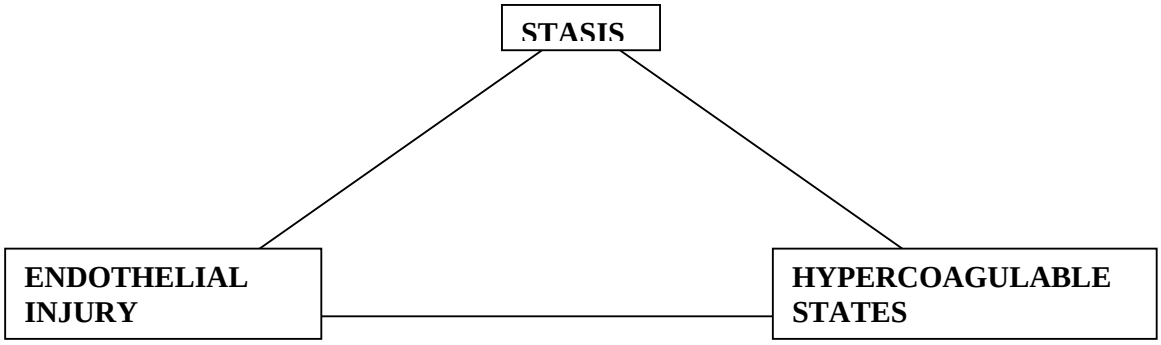
Stroke patients with subclinical PE will usually undergo VQ scanning as the imaging modality of first choice. The importance of integrating this information with an assessment of the clinical probability of PE, either derived subjectively or by using scoring systems, has been stressed.[46]

SUBCLINICAL VENOUSTHROMBOEMBOLISM:

Clinically manifested disease represents the tip of the thromboembolism iceberg. Screening studies in both stroke and post operative patients , together with the low incidence of symptomatic proximal DVT in patients with PE, demonstrate that the majority of DVTs are asymptomatic. Screening patients with symptomatic proximal DVT without clinical evidence of PE reveals evidence of subclinical PE in up to half. [47] Furthermore,VQ scanning in predominately asymptomatic post operative patients reveal PE in 12% to 18%.[48-50] Clearly only small proportion of pulmonary emboli produce symptoms.

PATHOGENESIS OF DVT:

VIRCHOWS TRIAD:



ENDOTHELIAL INJURY:

Mechanical venous injury clearly plays a role in thrombosis associated with direct venous trauma. The potential role of biochemical injury to venous endothelium has only lately become apparent.

The normal venous endothelium is antithrombotic,producing PGI2, glycosaminoglycan co-factors of antithrombin, thrombomodulin and tissue type plasminogen activator[t-PA].[50] However endothelium may become prothrombotic under some conditions producing tissue factor, vWF and fibronectin .It is conceivable that some thrombotic risk factors act through production of a procoagulant endothelium. Microscopic changes in the endothelial surface associated with

greater endothelial permeability and leucocyte adhesion have been demonstrated in response to distant injury.

Induction of procoagulant activity, suppression of anticoagulant mechanisms and exposure of neutrophil rceptor ligands may accompany such endothelial perturbation.[51]

Associated inflammatory cells may be capable of both initiating and amplifying thrombosis. The importance of cytokine – mediated expression of tissue factor procoagulant activity under clinical conditions is unknown, but both IL-1 and TNF may induce fibrin deposition through a combination of endothelial procoagulant expression and fibrinolytic depression.[52] In such situations, Virchows' concept of venous injury may be more important at the molecular level than macroscopic level.

STASIS:

Regardless of etiology, most venous thrombi originate in areas of low blood flow, either in soleal veins of the calf or behind valve pockets. Further more many risk factors of DVT are associated with immobilization and slow venous flow, and several mechanisms have been advanced to explain the role of stasis in thrombogenesis:

1. In comparison to pulsatile flow, static streamline flow is associated with profound hypoxia at the depths of venous valve cusps and may induce endothelial injury [53]. The effects of hypoxia in cultured endothelial cells have been noted to include stimulation of cytokine production and leucocyte adhesion molecule expression.

2. Furthermore, stasis allows accumulation of activated coagulation factors and consumption of inhibitors at sites prone for thrombosis.

Stasis in large veins is particularly important ,because the low surface to volume ratio may prevent interaction with endothelial inhibitory pathways, particularly the endothelium bound thrombomodulin- protein C system.[52]

Despite these observations ,there is little evidence that stasis can activate coagulation in isolation, stasis appears to be an inadequate stimulus for thrombosis.

HYPERCOAGULABLE STATES:

Activation of coagulation appears to be critical in the pathogenesis of DVT. The coagulation cascade functions through serial activation of zymogens in the intrinsic and tissue factor

pathways , with the ultimate generation of thrombin by pro-thrombinase complex. Anti thrombin and the thrombomodulin – protein C systems are the primary inhibitors of coagulation , whereas the fibrinolytic system serves to further limit fibrin deposition. Although hemostatic system is continuously active, thrombus formation is ordinarily confined to sites of local injury by a precise balance between activators and inhibitors of coagulation and fibrinolysis. A prethrombotic state may result either from imbalances in the regulatory and inhibitory systems or from activation exceeding antithrombotic capacity.

Ordinarily activated coagulation factors are rapidly cleared from the circulation. When localized in regions of stasis , however, the coagulation cascade allows activated factors to rapidly amplify the thrombotic stimulus, leading to platelet aggregation and fibrin formation.[54]

DVT thus appears to be a multi factorial phenomenon , with convergence of several pathologic factors often required to produce a thrombotic event.

EARLY COURSE:

The factors contributing to clinically important thrombosis have been most thoroughly evaluated in the valve pockets of lower extremity veins. In flow models, primary and secondary vortices are produce beyond the valve cusps, which tend to trap red cells in a low shear field near the apex of the cusp.[55] The early nidus for thrombus formation is likely to consist of RBC aggregates forming within these eddies; however these aggregates are probably transient until stabilized by fibrin in the setting of locally activated coagulation.

Once formed in the valve pocket, early thrombi may become adherent to endothelium near the apex of the valve cusp. These valve pocket thrombi appear to form on structurally normal endothelium and largely to spare the valve cusp. Laminated appositional growth may then occur outward from the apex of the cusp, with propagation beyond the valve pocket probably depending on the relative balance between activated coagulation and thrombolysis. Once luminal flow is disturbed prograde and retrograde propagation may occur.

Clinical symptoms, present in a minority of hospitalized patients, develop only when a sufficient fraction of venous flow is occluded. If present, such symptoms develop 24 – 36 hours after the

first pearance of thrombus detectable by radioactive iodine- fibrinogen [I 125] scanning.

Early thrombi may fail to propagate with evidence of aborted thrombi appearing as endothelialised fibrin fragments within the valve pockets. A significant number of early thrombi spontaneously resolve after serial I-125 fibrinogen scanning.[56]

RISK FACTORS FOR VTE:

1. Surgery
2. Trauma[major or lower extremities]
3. Immobility
4. Malignancy
5. Cancer therapy[hormonal, chemotherapy or radiotherapy]
6. Previous VTE
7. Lactation
8. Pregnancy and post partum period
9. Estrogen containing hormone replacement therapy or oral contraceptives
10. Selective estrogen receptor modulators
11. Acute medical illness
12. Heart or respiratory failure
13. Inflammatory bowel disease

14.Nephrotic syndrome

15.Myeloproliferative disorders

16. Paroxysmal nocturnal hemoglobinuria

17. Obesity

18. Smoking

19.Varicose veins

20. Central venous catheterization

21. Inherited or acquired thrombophlebitis

SYMPTOMS OF DVT:

Many patients are asymptomatic; however , the history may include the following,[57]

- Edema , principally unilateral , is the most specific symptom. Massive edema with cyanosis and ischemia [phlegmasia cerulea dolens] is rare.

- Leg pain occurs in 50%, but this is non- specific. Pain can occur on dorsiflexion of foot [Homans ‘ sign].

- Tenderness occurs in 75% patients. The pain and tenderness associated with DVT does not usually correlate with the size, location or extent of thrombus.

- Clinical signs and symptoms of PE as the primary manifestation occur in 10% pf patients with confirmed DVT.

- Warmth and erythema of skin can be present over the area of thrombosis.

SIGNS OF DVT :

- Edema, principally unilateral

- Tenderness , if present, is usually confined to the calf muscles or over the course of deep veins in the thigh

- Pain and /or tenderness away from these areas is not consistent with venous thrombosis and usually indicates other diagnosis.

- **HOMANS' SIGN** : discomfort in the calf muscles on forced dorsiflexion of the foot with the knee flexed at

30*. However this sign is present in less than one third of patients with confirmed DVT.

- **BANCROFT'S SIGN**:tenderness on antero posterior, but not on lateral compression of the calf.

- **LOUVEL SIGN**: worsening of pain along the course of thrombotic vein on coughing or sneezing.

- **LOWENBERG SIGN** after inflation of sphygmomanometer cuff around each calf, pain is experienced in the affected calf at a lower pressure than in the unaffected one.

- Venous distension and prominence of the subcutaneous veins. Superficial thrombophlebitisis characterized by the finding of a palpable , indurated , cord-like, tender subcutaneous venous segment . Patients with superficial thrombohlebitis without coexisting varicose veins and no other obvious etiology are at high risk because associated DVT is found in 40% of these patients.

- Fever : patients may usually have low grade fever

- Phlegmasia cerulean dolens: Patients with venous thrombosis may have variable discolouration of the lower extremity.the most common abnormal hue is reddish purple from venous engorgement and obstruction. In rare cases , the leg iscyanotic from massive ileofemoral obstruction. Petechiae are usually present.

- Phlegmasia alba dolens: painful white inflammation was originally used to describe massive ileofemoral venous thrombosis and associated arterial spasm.the affected extremity is often pale with poor or even absent pulses. The physical findings may suggest arterial obstruction , but the presence of swelling, petechiae and distended superficial veins points to DVT.

- Clinical findings of PE: These are the primary manifestation in 10% of patients with DVT . In patients with angiographically proven PE , DVT is found in 45-70%. In the vast majority of these patients DVT is clinically silent.

METHODS OF SCREENING FOR DVT:

The choice of screening tool for DVT is problematic, because it would have to be non invasive, inexpensive and highly sensitive.

DUPLEX ULTRASONOGRAPHY:

It is the most widely used diagnostic test now for acute DVT. Duplex scanning is non invasive, widely available and portable with minimal complications. Evaluation of lower extremities includes an assessment of venous compressibility, intra luminal echoes, venous flow characteristics and luminal colour filling. Among these venous compressibility is the most widely used and objective criterion for the diagnosis of DVT.[58] [59] Incompressibility has excellent sensitivity and specificity for the detection of proximal DVT. Although compression ultrasonography appears superior to standardized doppler ultrasonography,incompressibility used in combination with the absence of phasic flow and visible thrombus can achieve a sensitivity of 95% and specificity of 83%

Limitations:

Adequate evaluation of tibial and peroneal veins may be impeded by large calf size , edema or operator inexperience. Difficult compressibility and musculoskeletal structures may similarly limit

evaluation of iliac, superficial femoral and upper extremity veins. However the use of colour flow Doppler significantly improves the accuracy of detecting isolated calf vein thrombosis.

The utility of the technique for detecting asymptomatic below knee DVT after stroke has not specifically been evaluated .

RADIOLABELLED FIBRINOGEN UPTAKE:

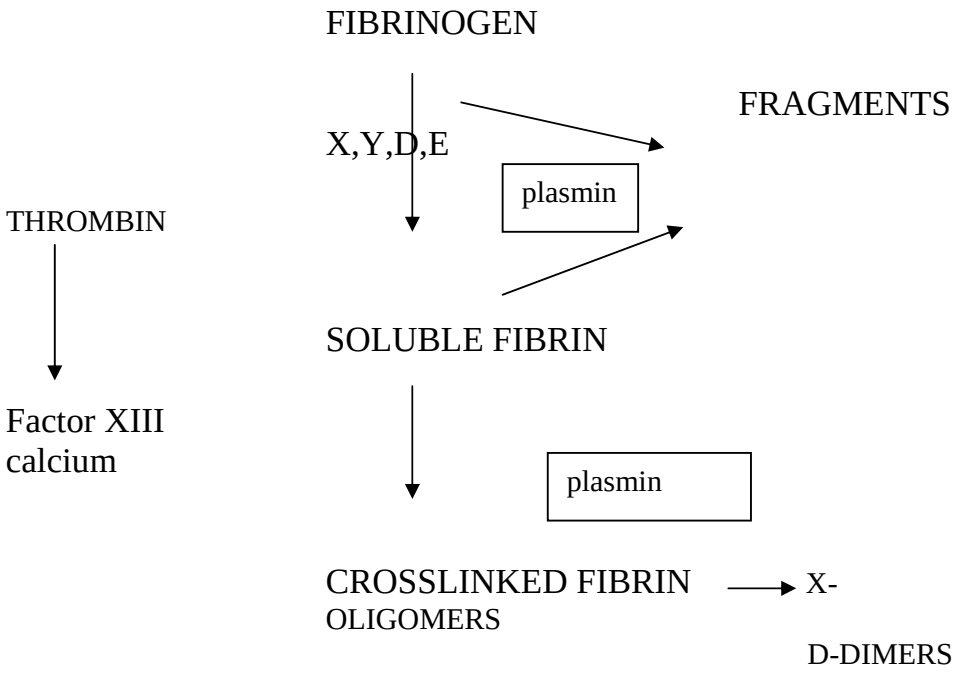
Fibrinogen uptake radionuclide scanning was extensively used in1960s. It is more sensitive for DVTs in calf than in the thighs. But it has risk of transmission of infection with injected fibrinogen and also gives false positive results and hence not used widely now.[57]

IMPEDANCE PLETHYSMOGRAPHY [IPG] :

IPG is a sensitive method for evaluating the rate of venous return from lower extremities. This method detects increased venous outflow resistance in the deep veins of proximal lower extremities. It is safe, non invasive, rapid, inexpensive, has no radiation hazard and can diagnose symptomatic proximal DVT. Limitations include: operator dependent and cannot diagnose asymptomatic proximal DVT and non obstructing thrombi.

D- dimer ASSAY:

D- dimers are products of the degradation of cross linked fibrin by plasmin. D – dimers level in blood reflect the presence of intravascular fibrin and are sensitive for diagnosis of venous thromboembolism. When measured by ELISA , the reference standard the sensitivity for the diagnosis of DVT is as high as 96.8%. However it is also elevated in DIC, malignancy, postoperative states, pre eclampsia, infection and trauma. Owing to low specificity and positive predictive value, a positive D-dimer assay requires confirmatory testing.[57]



D-dimers may have a useful role in identifying the subgroup of patients who need targeted screening but cannot be extrapolated to acute stroke as non lacunar ischemic stroke patients have increased D- dimer level and it falls to baseline after 30 days. Further studies are required to examine the utility of D – dimmer as a screening test for DVT in stroke.,[60,61]

VENOGRAPHY:

Ascending venography has been the gold standard confirmatory test for acute DVT. Not used frequently now as it is invasive , contrast agents can be painful or they may extravasate into tissues and results in skin necrosis. They are also irritating to the venous endothelium and may initiate thrombosis in 1.3 to 9% of patients. Cannulation of vein also requires expertise. Cannot be done urgently. [57]

RADIO ISOTOPE VENOGRAPHY:

Tc- 99 labelled RBCs or macro aggregated albumin can be used to detect DVT. It can be performed in conjunction with lung scanning. Scintigraphy using autologous labeled platelets can detect active DVT sites that are not readily evaluated by ultrasonography.[57]

Limitations:

1. It does not provide direct information on cause of DVT
2. Unreliable in calf due to presence of multiple vessels
3. Cannot distinguish intrinsic from extrinsic compression
4. Accuracy decreases in patients with previous DVT or congenital duplication of deep venous system above the knee.

CT VENOGRAPHY:

Indirect venography is performed in spiral CT by volumetric acquisition from upper abdomen to popliteal fossa. Combined CT venography and pulmonary angiography is a single examination that combines multidetector CT pulmonary angiography and CT venography of the abdomen, pelvis and lower extremities.[57]

Disadvantages: expensive, not portable and needs a contrast bolus comparable to angiogram.[57]

MAGNETIC RESONANCE IMAGING:

MRI is non invasive and allows simultaneous imaging in both lower limbs. In addition pelvic veins and IVC thromboses are accurately identified. MR venography compares favorably with

contrast venography for the diagnosis of symptomatic proximal DVT but has not been evaluated for asymptomatic DVT. MR direct thrombus imaging has shown excellent sensitivity and specificity for the diagnosis of symptomatic above and below knee DVT. This technique allows direct visualization of thrombi so that equally favorable results might be expected in asymptomatic patients.[57]

PRETEST PROBABILITY OF DVT:

The WELLS clinical prediction score provides a reliable estimate of the pretest probability of DVT

CLINICAL PARAMETER	SCORE
Active cancer[treatment ongoing or within previous 6 months]	1
Paralysis, paresis of lower extremity	1
Recently bedridden for more than 3 days or surgery within 4 weeks	1
Localized tenderness along deep venous system	1
Entire leg swelling	1
Calf swelling >3 cm compared to asymptomatic leg	1
Pitting edema	1
Collateral superficial veins	1
Alternative diagnosis as likely or greater than DVT	- 2

LOW RISK: 0 points

MODERATE RISK: 1-2 points

HIGH RISK : > 3 points

PROPHYLAXIS FOR DVT:

FEATURES OF IDEAL PROPHYLACTIC METHOD:

- Effective
- Safe
- Good compliance with patient , nurses and physicians
- Ease of administration
- No need for lab monitoring
- Cost effective

SPECIFIC PROPHYLACTIC METHODS:

Intermittent leg compression:

The use of intermittent pneumatic leg compression prevents Venous thrombosis by enhancing blood flow in deep veins of the legs ,there by avoiding venous stasis. It also raises blood fibrinolytic activity, which may contribute to its anti – thrombotic property. Intermittent pneumatic compressions is virtually free of significant side effects and offers a valuable alternative in patients who have a high risk of bleeding.

Limitations:

Poor compliance

The rate of pressure rise and maximum pressure applied to various part of the leg were less than anticipated most of the time in patients undergoing intermittent pneumatic compression.

Graduated compression stockings:

Graduated compression stockings increase the velocity of venous blood flow . it is by no means clear how graduated compression stockings achieve a thromboprophylactic effect.

Advantages: simple, safe and moderately effective

Contraindication : peripheral vascular disease.

Their use is recommended in patients with low risk for thromboembolism and as an adjunct in those with medium or high risk.

Low dose unfractionated Heparin:

Heparin [UFH] molecules contain a unique pentasaccharide sequence that binds to antithrombin. Once bound to UFH the natural

anticoagulant effect of antithrombin is potentiated , resulting in accelerated binding and inactivation of serine proteases such as factor xa and thrombin.[54]

The duration of initial therapy with heparin has been reduced to five days to minimize hospital stay . The combination of heparin with warfarin is routinely recommended for prophylaxis of thromboembolism. Treatment with heparin requires regular monitoring of aPTT levels and aPTT value of 1.5 times the mean of control value or upper limit of normal range is maintained.

Low molecular weight Heparins:

LMWHs are derived from enzymatic or chemical cleavage of UFH. They have limited antithrombin activity compared to anti factor xa activity.

Advantage : Superior bioavailability, limited non specific binding and non dose dependant half life facilitate once or twice daily administration.

No need for lab monitoring.

LMWHs are cleared by renal mechanisms therefore multiday usage in patients with renal insufficiency should be avoided.[54]

In randomized control trials comparing LMWHs with low dose unfractionated heparin, the LMWHs given once or twice daily have been shown to be as effective or more in preventing thrombosis

ORAL ANTICOAGULANTS:

COUMARIN DERIVATIVES:

Warfarin inhibits vitamin k epoxide reductase and vitamin k reductase, thus inhibiting gamma decarboxylation of select glutamic acid residues in the N- terminus of prothrombin, factor VII , IX and X , Protein C and S. This leads to synthesis of hypo functional coagulation proteins that are unable to bind to cellular surfaces to mediate coagulation reactions.The half life of warfarin in plasma is 36 Hrs. Heparin therapy should overlap Warfarin at least for a period of at least 4 days initially. Warfarin dosage is influenced by body stores of vitamin k, liver function, co existing medical disorders presence or absence of cytochrome p 450 2C9 mutations.Initial dosing of 2.5 to 7.5 mg/d is started to achieve INR of 2 to 3 and then chronic anticoagulation for 6 months continued and dose adjusted to maintain INR of 1.5 to 2.

NEWER DRUGS:

DIRECT THROMBIN INHIBITORS :

Indications:

1. The persistent prothrombotic tendency associated with HIT
2. the presence of thrombus in HIT with thrombosis
3. patients' original indication for heparin therapy

Some direct thrombin inhibitors available are Argatroban, Bivalirudin, Ximelagatran, Lepirudin. Ximelagatran is promising as a treatment of acute VTE, chronic management of atrial fibrillation and prevention of VTE in high risk settings such as following surgery and HIT.[54]

PENTASACCHARIDES:

They cause selective indirect inhibition of factor X a. Fondaparinux is a synthetic pentasaccharide and it is primarily used for thrombo prophylaxis in surgery. Idraparinux is a long lasting penta saccharide with once daily using.[54]

MATERIALS AND METHODOLOGY:

PLACE OF STUDY:

Institute of Internal medicine

Madras Medical College and Government General Hospital

Chennai 03.

STUDY DESIGN:

Cross sectional – hospital based prevalence study

STUDY PERIOD:

The study was conducted for a period of 7 months from December 2006 to June 2007.

ETHICAL APPROVAL: Obtained

FINANCIAL SUPPORT: NIL

CONFLICT OF INTEREST: NONE

LIMITATIONS:

1. small number of cases
2. d- dimer assay was not done for comparison due to financial restraints.

INCLUSION CRITERIA:

1. Patients with acute stroke of less than two weeks duration.
2. Recovery of power from admission till the end of study period less than 3/5
3. Patients with or without known history of diabetes mellitus, systemic hypertension.
4. Patients with risk for accelerated atherogenesis such as smoking or alcoholism.

EXCLUSION CRITERIA:

- Duration of stroke more than two weeks
- Recovery of power from time of admission to screening for DVT is more than 3/5
- Pregnancy
- Patients on treatment with drugs like aspirin, OCPs or anticoagulants
- Patients with underlying procoagulant states previously known
- Patients with underlying connective tissue diseases.

STUDY POPULATION:

Out of 145 patients enrolled for the study after applying the exclusion criteria 50 patients were selected for duplex ultrasonography of lower limb venous system.

METHODOLOGY:

All patients admitted with c/o acute stroke of less than two weeks in our hospital, were screened preliminarily with a proforma to assess the presence of predisposing conditions of CVA like diabetes, systemic hypertension, ischemic heart disease and valvular heart diseases. Also patients were specifically questioned on their medications which could affect coagulation as well as any history of addictions. Detailed physical examination was done. Basic investigations like CBC, Random blood sugar, Serum fasting lipid profile and ECG were taken for all patients included in the study. CT brain was also done. Evaluation of cardio vascular system with echo-cardiography was done.

The patients were examined and their improvement with regards to general physical condition, control of blood pressure and improvement in neurological status with special attention to recovery

of tone and power was assessed daily. Signs and symptoms for development of DVT were specifically looked for.

Patients with Diabetes, ischemic heart disease and other underlying diseases were treated for their respective diseases in addition to receiving anti edema measures, antibiotics and anti ulcer drugs as well as aspirin in recommended dose for patients with ischemic stroke.

Physiotherapy to the paralysed limb was started as early as day1 of admission and patients and their care givers were encouraged to continue it all through their hospital stay.

Patients with persistent hypotonia and power < 3/5 at the end of 14 days were screened for the presence of DVT of the paralysed limb with ultra sound venous colour flow Doppler on day of admission and day 14 and the results documented. Patients who had developed DVT despite intensive physiotherapy were treated with leg elevation, graded compressive stockings and LMWHs. They were followed up during the entire course of hospital stay with repeated USG venous Doppler.

STATISTICAL ANALYSIS

Statistical analysis was carried for 50 subjects. Age, presence of diabetes, systemic hypertension, ischemic heart disease, smoking, and alcoholism in DVT positive and negative group were analyzed. The statistical significance calculated using chi-square test.

Statistical significance taken when p value < 0.05.Statistical analysis were carried out using standard formulae. Microsoft excel 2003 and SPSS [statistical package for social sciences] version 13.0 soft wares were used for data entry and analysis.

OBSERVATIONS:

We included 50 patients with acute stroke in our study and all of them had venous Doppler done for lower limb venous system.

Table 1: prevalence of DVT in acute stroke patients

Total number of patients in whom venous doppler was done	DVT positive	Percentage
50	3	6%

TABLE : 2 Patient characteristics

Characteristics	Present (No)	%	Absent (No)	%
DM	9	18	41	82
SHT	15	30	35	70
IHD	2	4	48	96
SMOKING	22	44	28	56
ALCOHOLISM	14	28	36	72

TABLE : 3 CT findings:

CT	Number	%
Infarct	42	84
Hemorrhage	8	16
Total	50	100

TABLE: 4 Sex distribution of DVT

Sex	Number	DVT positive	DVT negative
Male	36	1	35
Female	14	2	12
Total	50	3	47

TABLE : 5 Risk factor analysis in DVT positive patients

5 a)DM Vs DVT

DM	DVT PRESENT	DVT ABSENT	TOTAL
PRESENT	0	9	9
ABSENT	3	38	41
TOTAL	3	47	50

P VALUE:0.40259 Odds' ratio – 1.0789 , CI [0.990,1.176]

5 b) SHT Vs DVT:

SHT	DVT PRESENT	DVT ABSENT	TOTAL
PRESENT	0	15	15
ABSENT	3	32	35
TOTAL	3	47	50

P VALUE: 0.24219 Odds' ratio – 1.0938, CI [0.998,1.211]

5 c) IHD Vs DVT

IHD	DVT PRESENT	DVT ABSENT	TOTAL
PRESENT	0	2	2
ABSENT	3	45	48
TOTAL	3	47	50

P VALUE: 0.71536, Odds' ratio – 1.0666, CI [0.9915, 1.1475]

5 d) SMOKING Vs DVT:

SMOKING	DVT PRESENT	DVT ABSENT	TOTAL
PRESENT	1	21	22
ABSENT	2	26	28
TOTAL	3	47	50

P VALUE: 0.7011, Odds' ratio – 1.0279, CI [0.896,1.179]

5 e) ALCOHOL Vs DVT:

ALCOHOL	DVT PRESENT	DVT ABSENT	TOTAL
PRESENT	1	13	14
ABSENT	2	34	36
TOTAL	3	47	50

P VALUE: 0.83195, Odds' ratio – 0.983, CI [0.833,1.160]

In our study the prevalence of DVT in acute stroke was analysed by ultrasound venous Doppler of lower limbs. The analysis of co morbid conditions like diabetes , systemic hypertension, ischemic heart disease, smoking and alcoholism were analysed to find out if there was any association between their presence and occurrence of DVT. In all these parameters compared within the group of DVT positive patients the p value was more than 0.05 which is statistically insignificant.

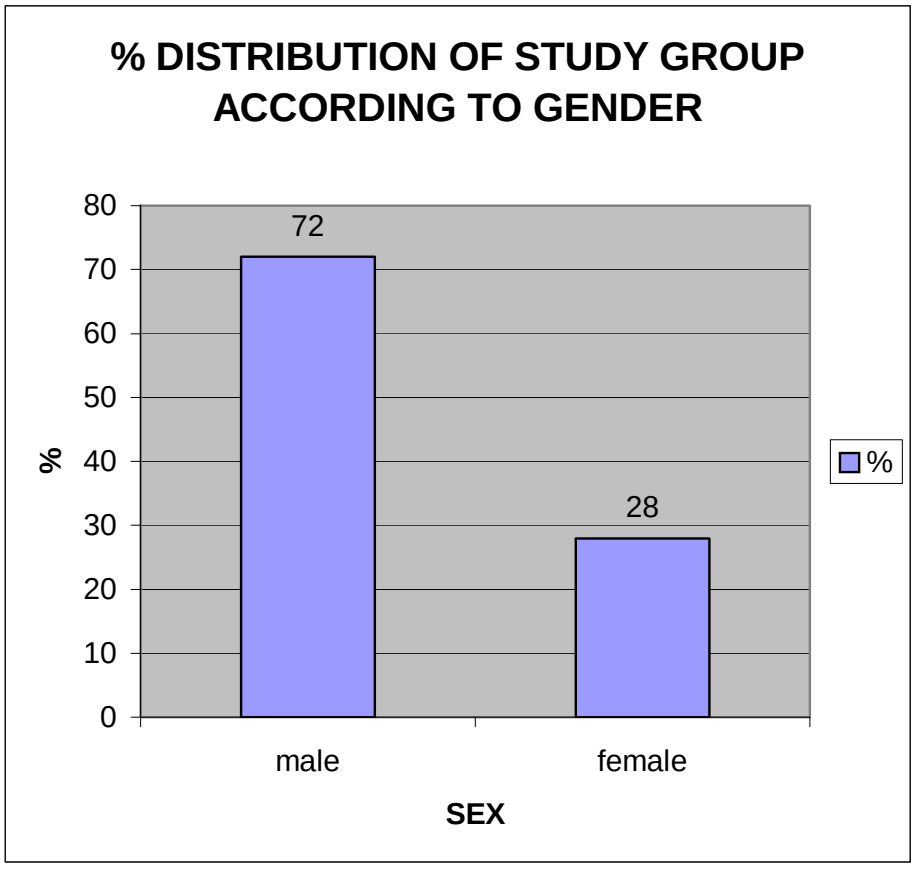
The important observations noted in the study were:

1. The prevalence of DVT was found in 6% of Stroke Patients.

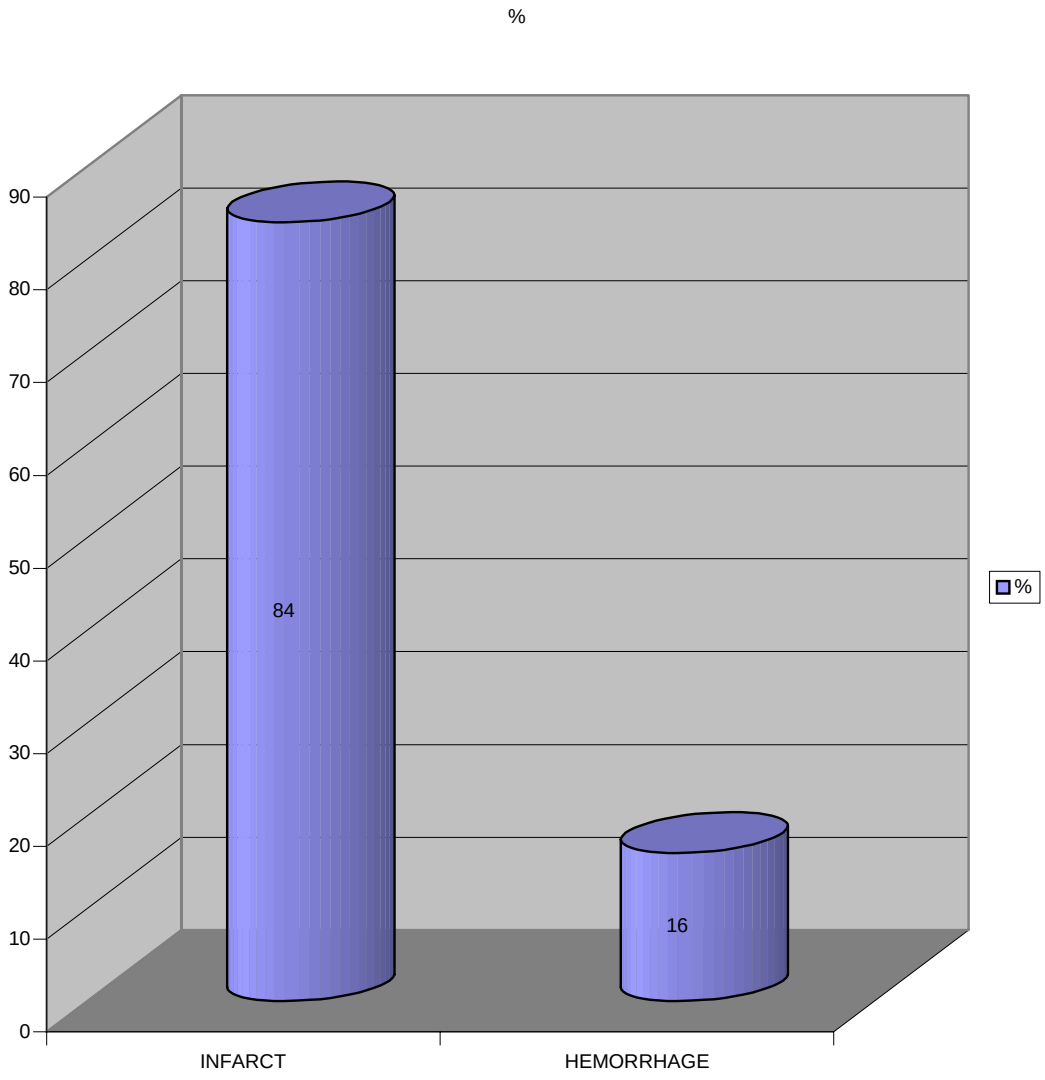
2. The prevalence of DVT was found more commonly in women than in men

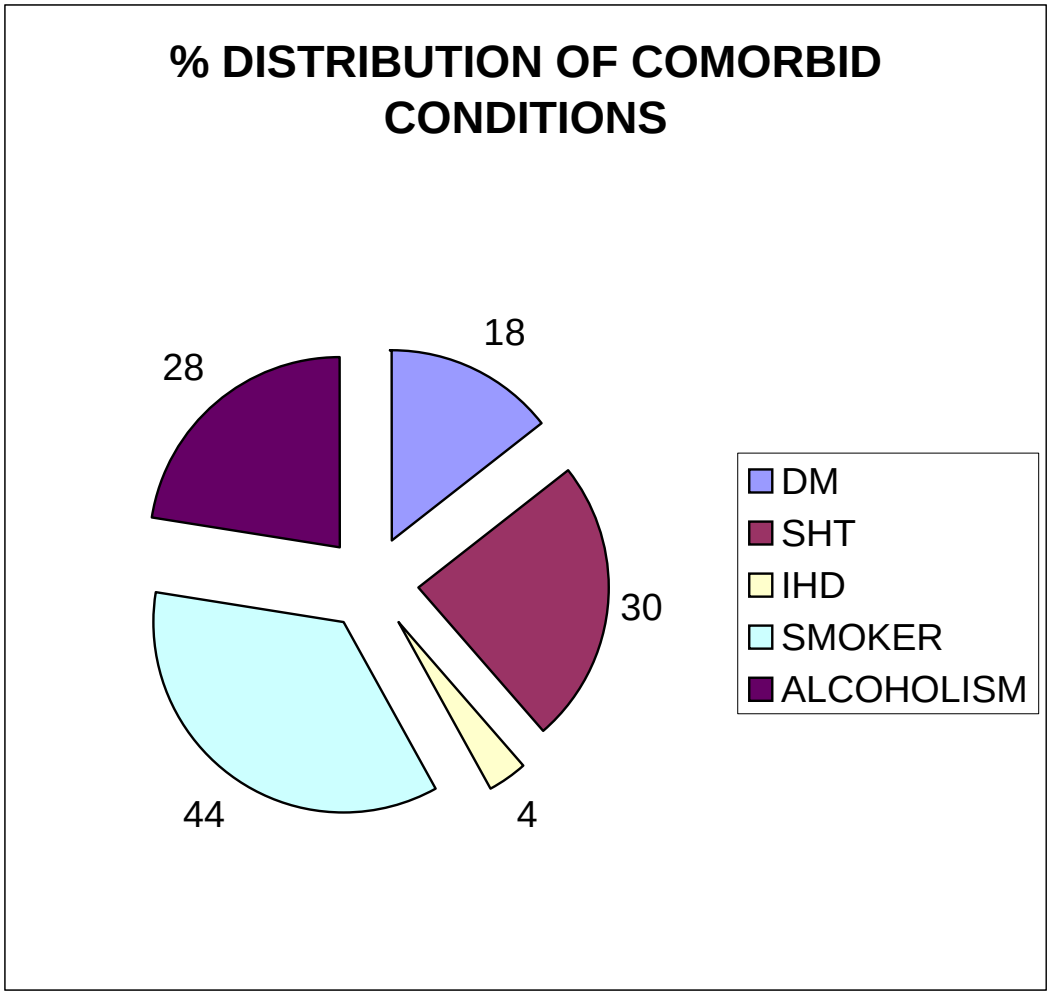
3. The occurrence of DVT in acute stroke is independent of the presence of co morbid conditions like diabetes, systemic hypertension, ischemic heart disease and high risk behaviors like smoking and alcoholism.

CHARTS:

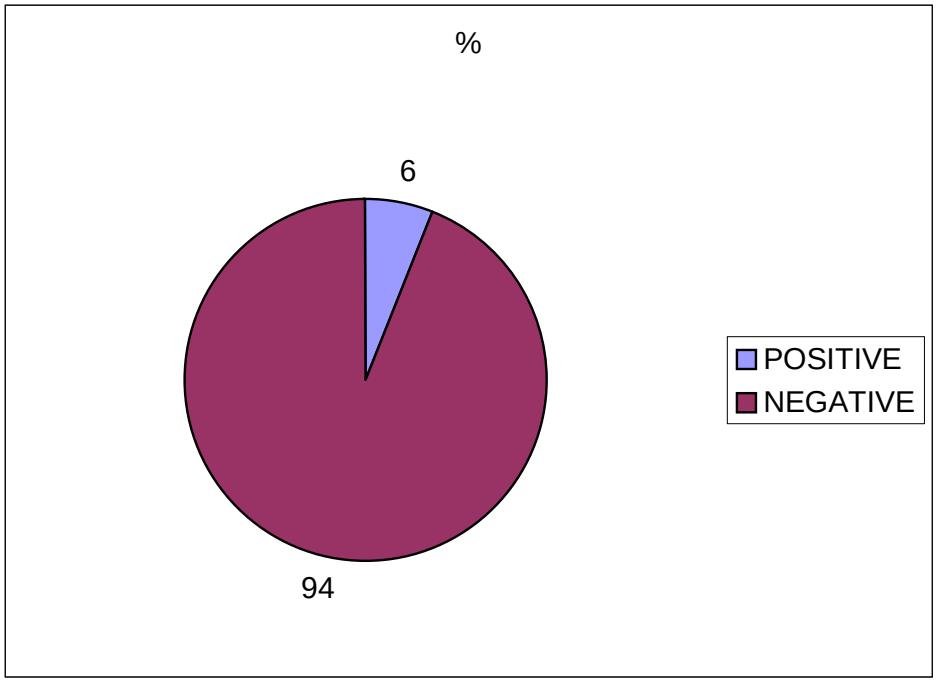

% DISTRIBUTION OF STUDY GROUP ACCORDING TO GENDER
80
70
60
50
40
30
20
10
0
%
72
28
male
female
SEX
%

CT FINDINGS IN STUDY GROUP:

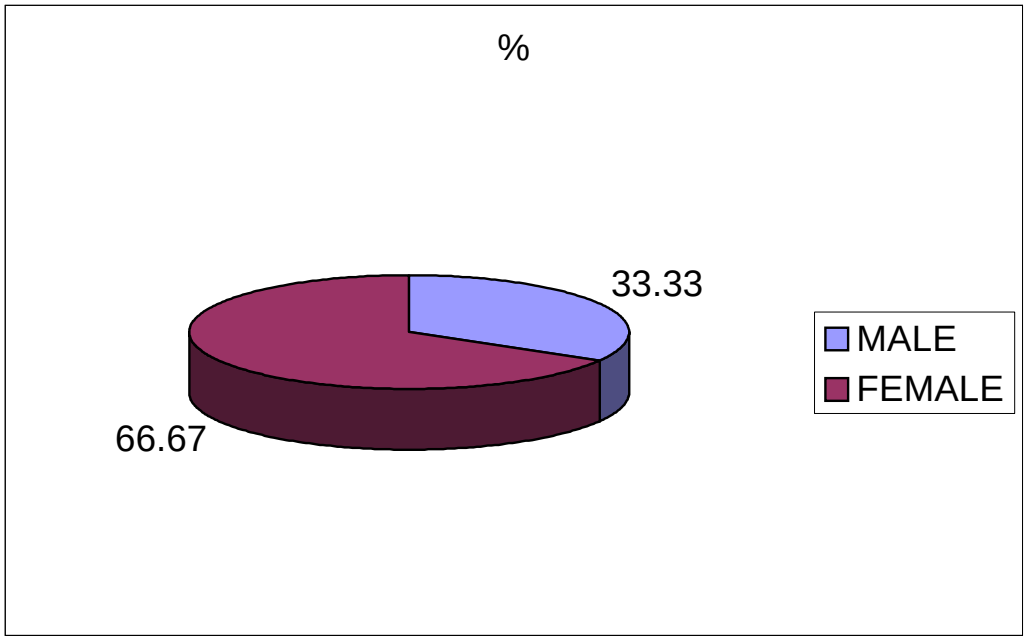


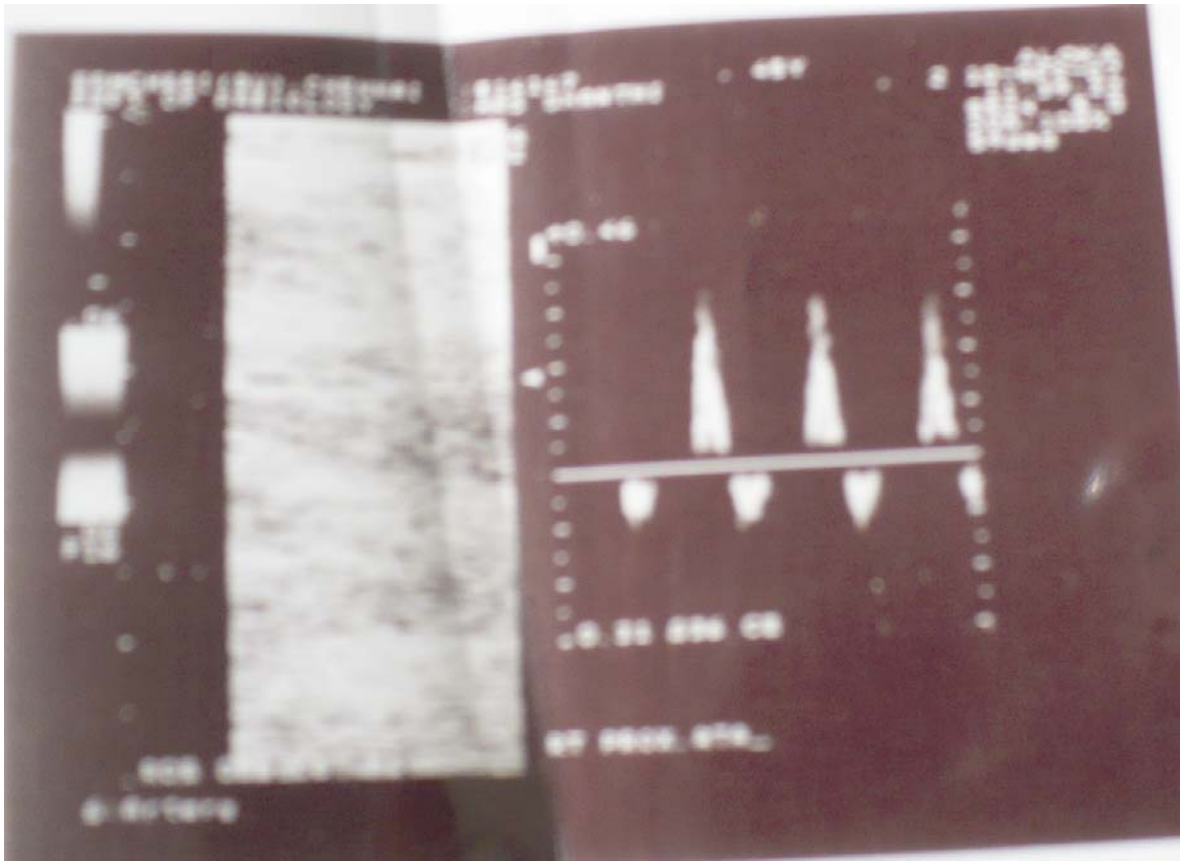

% DISTRIBUTION OF COMORBID CONDITIONS
18
28
30
44
4
DM
SHT
IHD
SMOKER
ALCOHOLISM

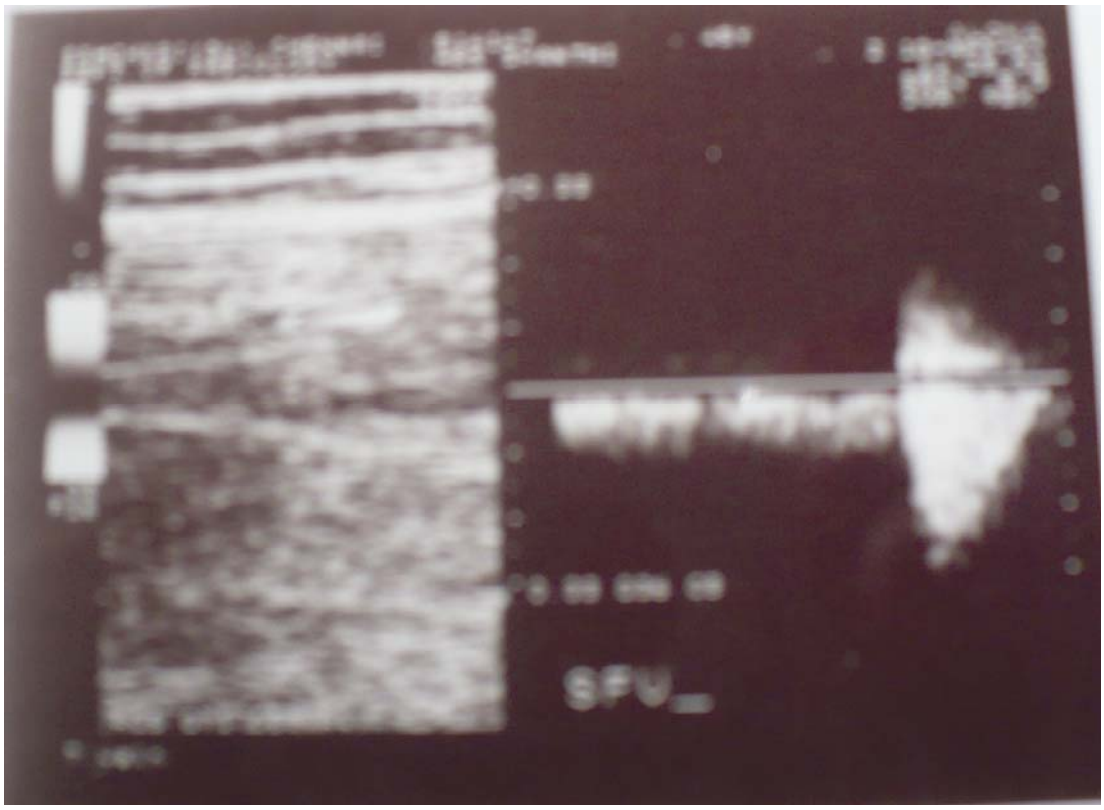
% PREVALENCE OF DVT IN STUDY GROUP:



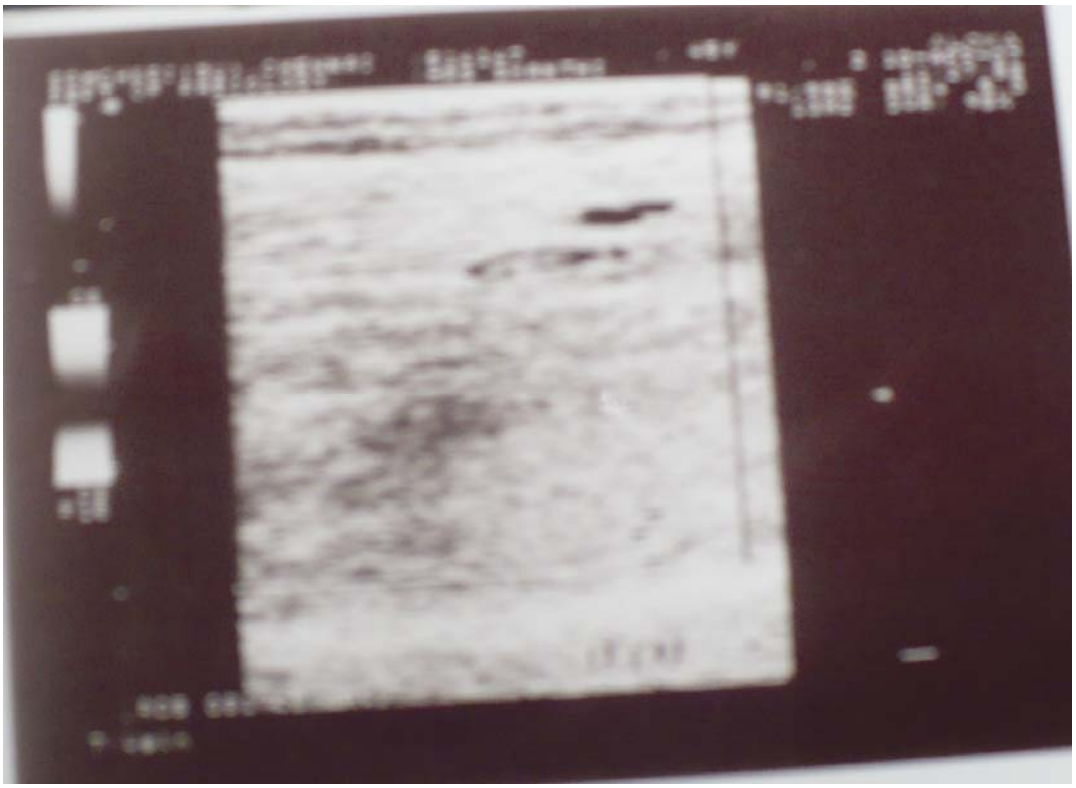
% DISTRIBUTION OF DVT ACCORDING TO GENDER






SFU


POP. VEIN



DISCUSSION:

The prevalence of DVT in patients with acute stroke admitted into government general hospital is found to be 6% as against a prevalence of 60% reported in western literature. The exact cause for this discrepancy is not known but there does seem to be difference in occurrence of DVT in different ethnic groups as revealed by studies. The incidence of post op DVT in Europe is twice that of North America, similarly autopsy series showed prevalence of thrombo embolism is 40.6% in Boston and 13.9% in Kyushu, Japan. This may probably be explained due to regional variation in underlying medical conditions or true variation in genetic and environmental factors.

There are also studies published reporting increases in incidence of DVT with age. In elderly probably there is an increase in number of thrombotic risk factors or there exist an acquired thrombotic state, with anatomic changes in soleal veins with more pronounced stasis in valve pockets.

The prevalence of DVT both asymptomatic and symptomatic in acute stroke patients in our hospital was only 6% and the exact occurrence of pulmonary embolism in these patients is not known.

Though there are widely conducted trials in the west on routine prophylaxis of DVT with anticoagulants as early as day 2 of stroke, such studies are not available in Indian population and the data from west cannot be extrapolated to our population as the prevalence of DVT is found to be very low and majority are asymptomatic.

The mortality and morbidity rate of patients with acute stroke in our study population was not significantly affected by withholding routine anticoagulation therapy.

Risk associated with anticoagulation in acute stroke should also be taken into consideration. In the IST , treatment with low dose unfractionated heparin [5000 U s.c. twice daily] significantly reduced death and recurrent stroke at 14 days from 12 to 10.8%, a benefit attributable to decreased risk of recurrent ischemic stroke as PE was not significantly reduced. There was also increased risk of hemorrhagic transformation and extra cranial bleeds.

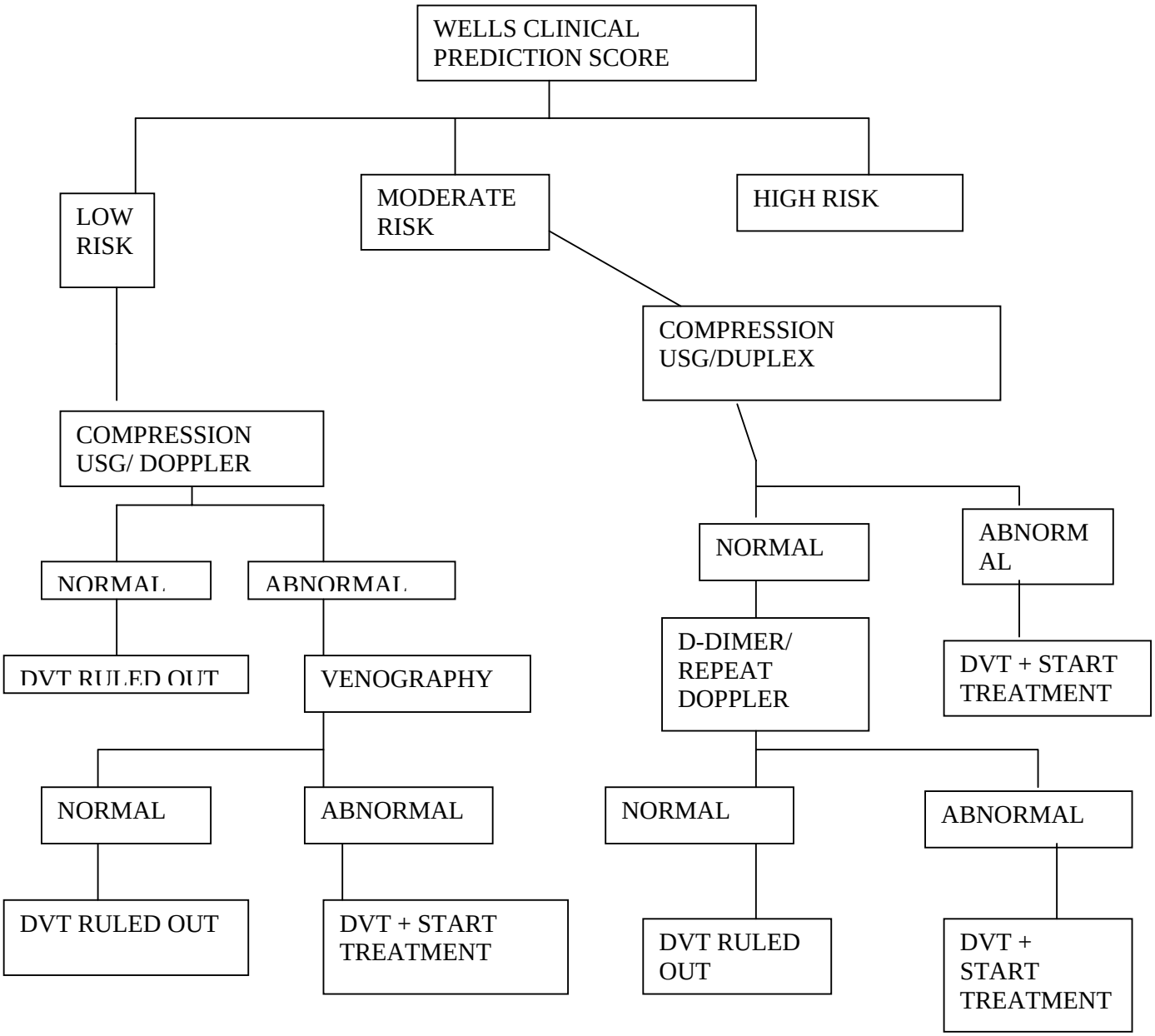
The balance of risks might therefore favor initiation of anticoagulation treatment in established venous thrombo embolism

after stroke, where the risks of untreated VTE is high and mortality is proven to be reduced with anticoagulation therapy. The routine prophylaxis for patients with asymptomatic below knee DVT is still controversial and more studies are recommended before the benefits could be conclusively established.

Physiotherapy and mechanical anticoagulation with graded compressive stockings can be considered as the initial line of prophylaxis as there is no increased risk of bleeding. The sensitivity of duplex sonography in detecting DVT is 97% and it is a simple, non invasive reliable tool which can be done as early as day two and serial follow up can be done as and when required. The treatment of DVT can be initiated as soon as it is detected as the risk of PE is only by three to four weeks after stroke. This strategy helps in minimizing unwanted anticoagulation in stroke patients and risk of hemorrhagic transformation.

Further more, majority of early thrombi formed resolve spontaneously when followed up with I 125fibrinogen screening. Thus the role of routine anticoagulation in stroke is still inconclusive and controversial.

DIAGNOSTIC PATHWAY FOR DVT :



CONCLUSIONS:

1.The prevalence of DVT in acute stroke patients in our hospital group was 6% which is significantly less than that observed in western population.

2.Duplex USG is a useful tool which can be used as a screening tool for early diagnosis of DVT.

3.DVT occurs more commonly in paralysed limd than non paralysed limb.

4.VTE is a preventable cause of morbidity and mortality in stroke patients and there is a need for more anticipatory approach in diagnosis.

5.The presence of comorbid conditions like diabetes, SHT,IHD, smoking and alcoholism does not affect the occurrence of DVT in acute stroke thus it is an independent contributor to morbidity and mortality in stroke patients.

6.The use of routine anticoagulation in all stroke patients in our population requires further large scale trials before their benefits could be conclusively proven.

PROFORMA:

Name: I.p. no:

Age: Sex

D.O.A: D.O.D:

Onset and duration of illness:

Past h/o: DM/SHT/IHD

Drugs: ASA/Anticoagulants/OCPs

Personal h/o: smoker/ alcoholism

G.E:

P/I/Cy/Cl/PE/LN

PR: B.P.

CVS:

RS:

P/A:

CNS:

Higher functions:

Cranial nerves:

Motor system examination:

		R	L
Tone	UL		
	LL		
Power	UL		
	LL		
DTR:	UL		
	LL		
Plantar			

Sensory system examination:

Investigations:

CBC: RFT:

RBS: S.fasting lipid profile :

ECG: CT brain:

ECHO:

USG venous Doppler both lower limbs :

MASTER CHART

Sl.no	Name	Age	Sex	ECHO	CT	DOPPLER	DM	SHT	IHD	DRUGS	smoker
1	jayaraman	55	m	N	INF	N	N	Y	N	N	Y
2	palani	68	m	N	INF	N	Y	N	N	N	Y
3	masthan	45	m	LVH	HE	N	N	N	N	N	Y
4	nageshwarao	33	m	N	INF	N	N	N	N	N	Y
5	shantharao	54	m	N	INF	N	N	N	N	N	Y
6	nandan	50	m	N	INF	N	N	N	N	N	Y
7	suresh1	27	m	N	INF	N	N	N	N	N	N
8	ammavasi	54	m	N	INF	N	N	Y	N	N	Y
9	balakrishnan	55	m	N	INF	N	N	N	N	N	N
10	ravi	38	m	THR LA	INF	N	n	N	N	Y	Y
11	libinjohn	46	m	N	INF	N	Y	N	N	Y	Y
12	suresh2	25	m	N	INF	N	N	N	N	N	N
13	srinivasan	80	m	N	INF	N	Y	N	N	N	N
14	gopal	55	m	N	INF	N	N	Y	N	N	Y
15	elumalai	60	m	N	INF	N	N	N	N	N	Y
16	kanniappan	70	m	N	INF	N	N	N	N	N	N
17	rajendran	35	m	N	INF	N	N	N	N	N	N
18	venkatesan	54	m	LVH	INF	N	N	Y	N	Y	Y
19	govindaraj	53	m	N	HE	N	N	Y	N	Y	Y
20	sekar	45	m	N	INF	N	N	N	N	N	Y
21	lillyvasantha	58	f	N	INF	N	Y	N	N	N	N
22	rajendran	50	m	N	INF	N	N	N	N	N	N
23	lakshmiammal	70	f	N	INF	N	Y	N	N	N	N
24	duraikannammal	55	f	LVH	INF	N	Y	Y	N	Y	N
25	ganesan1	45	m	N	INF	N	Y	Y	N	N	Y

Sl.no	Name	Age	Sex	ECHO	CT	DOPPLER	DM	SHT	IHD	DRUGS	smoker
26	duraisamy	55	m	N	INF	N	N	N	N	N	N
27	shanthi	45	f	N	INF	LLDVT	N	N	N	N	N
28	gopal	62	m	N	INF	N	N	Y	N	N	Y
29	ganesan2	55	m	LVH	INF	N	N	Y	N	N	Y
30	chandran	58	m	N	HE	N	Y	Y	N	N	N
31	jayalakshmi	61	f	N	HE	N	N	Y	N	N	N
32	egathammal	85	f	N	INF	N	N	N	N	N	N
33	jayalakshmi	61	f	N	HE	N	N	Y	N	N	N
34	devi	23	f	N	INF	N	N	N	N	N	N
35	pacchaiammal	70	f	LVH	INF	N	N	N	Y	Y	N
36	jegatha	45	f	N	INF	N	Y	N	N	N	N
37	kasi	40	m	N	INF	N	N	N	N	N	N
38	subramani	60	m	N	INF	N	N	N	N	N	N
39	venkatraman	64	m	N	HE	N	N	N	Y	N	N
40	vijayalakshmi	64	f	N	INF	LLDVT	N	N	N	N	N
41	santhalingam	54	m	LVH	INF	N	N	Y	N	N	Y
42	devaraj	55	m	N	INF	N	N	N	N	N	N
43	pattamal	60	m	NOT	HE	N	N	Y	N	N	N
44	selvam	31	m	N	INF	N	N	N	N	N	Y
45	kathamuthu	55	m	N	HE	N	N	N	N	N	Y
46	parvathy	45	f	N	INF	N	N	N	N	N	N
47	kubarna	33	m	N	INF	RLDVT	N	N	N	N	Y
48	valliammal	70	f	LVH	INF	N	N	Y	N	N	N
49	muniammal	61	f	N	INF	N	N	N	N	N	N
50	veerabadhran	55	m	N	INF	N	N	N	N	N	Y

ABBREVIATIONS:

DVT - Deep vein thrombosis

PE - Pulmonary embolism

USG - Ultrasound

VTE - Venous thrombo embolism

DM -Diabetes mellitus

SHT - Systemic hypertension

IHD - Ischemic heart disease

ASA - Aspirin

LMWH- Low molecular weight heparins

CVA - Cerebro vascular accident

HIT - Heparin induced thrombocytopenia

IST - International stroke trial

UFH - Unfractionated heparin

aPTT - Activated partial thromboplastin

Tc 99 – technetium

I-125 – Iodine 125

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Ref. No.: 12299 / P&D / Ethics / Dean / GGH / Chennai, dated July 19th, 2007

Title of the Work: Prevalence of deep vein thrombosis in acute stroke

Principal Investigator: Dr. Gayathri

Department: Institute of Internal Medicine, MMC, Chennai

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on **July 19th 2007**, at the conference hall of the Dean, Tower Block I, GGH, Chennai.

The members of the committee, the secretary, and the chairman are pleased to
- approve the proposed work mentioned above, submitted by the principal investigator /
- ~~consider the proposed work but advised for revision and resubmission.~~

The principal investigator and their team are directed to adhere the guidelines given below:

01. You should get detailed informed consent from the patients / participants and maintain confidentiality.
02. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
03. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
04. You should not deviate form the area of the work for which I applied for ethical clearance.
05. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
06. You should abide to the rules and regulations of the institutions(s).
07. You should complete the work within the specific period, and if any extension of time is required, you should apply for permission again and do the work.
08. You should submit the summary of the work to the ethical committee on completion of the work.
09. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

Secretary,	Chairman,	Dean,
IEC, GGH, Chennai.	IEC, GGH, Chennai.	GGH & MMC, Chennai.