Original Article

Deep Vein Thrombosis: An Experience of 25 Years from North India

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Abstract

Background and Aim: Unfractionated heparin (UFH) or low-molecular-weight heparin is the treatment for established lower limb deep vein thrombosis (DVT). This study was performed to report our experience of treating the same with UFH.

Patients and Methods: This was a retrospective analysis of patients with lower limb DVT managed between 1983 and 2014 at Jawaharlal Medical College, Aligarh, India.

Results: This analysis included 83 males and 210 females. Mean age of patients was 34.5 ± 11.5 years. Most common age group involved in was 20–30 years (33.79%). Most common symptom was limb swelling (90.8%). Most common risk factor was postpartum period. Among postpartum group, primigravida was most commonly involved group. Left limb involvement was found in 195 patients (65.8%). Proximal DVT was present in 215 (73.33%) patients. In proximal patient group, 74.41% presented with more than 90% block while in distal patient group, 66.67% presented with more than 90% block of the venous system. After 3 weeks of treatment, 29.52% and 15.49% were found to have block of proximal and distal deep veins, respectively, which further declined to 1.78% and 3.45% after 6 months of presentation with continued treatment. Six patients died during the course of treatment.

Conclusion: Lower limb DVT respond well to UFH, hence should be used for treatment of same with comparable results. DVT can lead to fatal pulmonary embolism and patients should be admitted till target International Normalized Ratio is achieved.

Key Words: Deep vein thrombosis, International Normalized Ratio, low-molecular-weight heparin, unfractionated heparin

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are important and common pathologies that affect apparently healthy individuals as well as medical or surgical patients and is a preventable cause of death.[1,2] 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.[3]

Therapeutic objectives are essentially the 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.[4,5]

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.[6] 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.[7,8] The choice between UFH and LMWH for the treatment of patients with PE or DVT is controversial. Both classes of drugs have comparable efficacy and safety,[9] and data suggest that both are safe and effective.[10] In an experimental study, Moaveni et al. demonstrated that postthrombosis vein wall re-endothelialization is favorably modulated by LMWH.[11]

We report our experience of treating cases of lower limb DVT in a developing country with UFH, warfarin, and aspirin with good results. We further hypothesize that UFH favorsably modulates postthrombosis vein wall re-endothelialization helping in recanalization of thrombosed veins.

Patients and Methods

Retrospective review of all patients with lower limb DVT who were managed in the Cardiothoracic Vascular Unit of Surgery Department from 1983 to 2014 was performed. The data were extracted from a prospectively maintained peripheral vascular disease database. Patients with

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involvement of only superficial thrombophlebitis without involvement of deep venous system were excluded from this review.

All patients in our study group underwent color Doppler at the time of admission to confirm the diagnosis of DVT. Proximal and distal involvement of venous system was noted along with percentage block of the vein involved. As a protocol, all patients underwent color Doppler at 3-week and 6-month posttreatment. Proximal deep vein was defined as common iliac vein, external iliac vein, common femoral vein, deep femoral vein, superficial femoral vein, and popliteal vein. Distal deep vein was defined as anterior tibial, peroneal, and posterior tibial veins.

All patients confirmed with DVT were admitted and started on UFH. UFH was started at loading dose of 10,000 IU followed by 5000 IU in fixed dose 4–6 times a day and activated partial thromboplastin time (APTT) was regularly monitored. Simultaneously, Vitamin K antagonist (warfarin) was started at a starting dose of 5 mg along with aspirin 150 mg. Dose of warfarin adjusted until an APTT of approximately 2 min and International Normalized Ratio (INR) of 2–3 was achieved. UFH was stopped after target INR was achieved and aspirin along with warfarin was continued for a minimum of 6 months. Patients were also analyzed for the complication of treatment and postthrombotic syndrome (PTS).

Patients with symptoms subsided and on oral Vitamin K antagonist and aspirin were discharged and evaluated on the outpatient department (OPD) basis.

Results

During the period between July 1983 and May 2011, 293 patients were managed with symptomatic DVT. Mean age of patients was 34.5 ± 11.5 (range 13–69 years). The male:female ratio was 83:210 (2:5). Most common age group in our study was 20–30 years (33.79%), due to high number of postpartum patients presenting with DVT. Two hundred sixty-six (90.78%) complained of limb swelling and 231 patients (78.83%) of limb pain. Mean symptom duration was 8.4 ± 12.1 days [Table 1].

In our series, most common patients (43%) were of postpartum lower limb thrombosis. Incidence of DVT in this particular patient group was more in primigravida and deliveries conducted at home. Another important group was with no elicited definite cause on history and examination. Previous lower limb trauma, malignancies, estrogen intake, and prolonged surgeries were other risk factors in our series [Table 2].

Isolated left limb involvement was found in 195 patients (65.8%). Isolated right limb was involved in 60 (20.4%) patients. In the remaining 58 (19.8%) patients, both limbs were involved. In all groups, left limb was more involved as compared to right except in femoral catheterization patients where the right limb was more commonly involved and most of these patients were catheterized for temporary pacemaker implant. Average differences between normal and affected limb at the time of presentation were 10.25 and 8.00 cm at the level of thigh and leg, respectively. After treatment, the girth of both limbs was comparable [Table 3].

Proximal DVT was present in 215 (73.33%) patients, and distal DVT was present in 78 (26.26%). In all patient groups, involvement of proximal venous system was more common as compared to the distal venous system. In proximal patient group, 74.41% presented with more than 90% block while in distal patient group 66.67% presented with more than 90% block of the venous system. After 3 weeks of treatment, 29.52% and 15.49% were found to have block of proximal and distal deep veins which further declined to 1.78% and 3.45% after 6 months of presentation with continued treatment [Table 3].

**Table 1: Demographic profile of treated patients**

| Condition                      | Demographic detail |
|--------------------------------|--------------------|
| Total patients                 | 293                |
| Males                          | 83                 |
| Females                        | 210                |
| Average age (years)            | 34.5 ± 11.5        |
| Most common age group (years)  | 20–30              |
| Complaint of limb pain (%)     | 231 (78.83)        |
| Complaint of limb swelling (%) | 266 (90.78)        |

**Table 2: Risk factors present in our patients**

| Condition                                      | Percentage population affected |
|------------------------------------------------|-------------------------------|
| Postpartum status (%)                         | 126 (43)                      |
| History of estrogen intake with no other risk factor (%) | 12 (4)                      |
| Previous history of lower limb trauma (%)     | 42 (14.3)                     |
| Advanced malignancy (%)                       | 30 (10.3)                     |
| History of major surgery (%)                  | 26 (8.8)                      |
| No definite risk factor found (%)             | 57 (19.4)                     |

**Table 3: Examination and Doppler findings in our patients**

| Condition                                      | Percentage population affected |
|------------------------------------------------|-------------------------------|
| Isolated left limb involvement (%)             | 195 (65.8)                    |
| Isolated right limb involvement (%)            | 60 (20.4)                     |
| Bilateral lower limb involvement (%)           | 58 (19.8)                     |
| Proximal DVT (%)                               | 215 (73.3)                    |
| Distal DVT (%)                                 | 78 (26.6)                     |
| Average difference in girth of thigh in case of unilateral DVT (cm) | 10.25                      |
| Average difference in girth of calf in case of unilateral DVT (cm) | 8.00                       |
| Percentage of patients with >90% luminal blockage in proximal group | 74.41                      |
| DVT: Deep vein thrombosis                     | 66.67 in distal group         |
Approximately a quarter (n = 76, 25.93%) of patients in our study suffered from PTS [Table 4]. Most common presentations were generalized limb swelling and pain. Other symptoms were itching, varicose veins, venous eczema, skin ulceration, and lipodermatosclerosis.

There were no incidences of major bleeding in our study. Four patients had episodes of minor bleeding (two cases of hematuria, one vaginal bleeding, and one nose bleeding).

In our study, six patients died during hospitalization. All patients had proximal DVT involving iliac veins. Two patients in advanced malignancy, two patients postmajor surgery DVT, one in postpartum, and one in catheterization group died. Two patients had documented massive pulmonary embolus on computed tomography pulmonary angiography. Four patients suffered sudden death with suspected PE before diagnostic investigations [Table 4].

Discussion

DVT is a common disease that occurs in hospitalized surgical and medical patients and the community. Epidemiologic studies have shown that DVT is highly prevalent in Western populations. In the United States, 116,000 to more than 250,000 new case of clinically recognized DVT per year are recorded.[2] While some studies[12,13] suggest that Asians are less likely to develop DVT, other studies suggest that DVT incidence is increasing, affects younger generation, and nearly 60% are proximal.[14,15]

Although advancing age is a risk factor for DVT, in our study percentage of young patients was higher because of a significant number of postpartum females presenting as symptomatic DVT. In postpartum females, DVT was more common in primigravida, leading to more patients in younger age group in our study. In our study, more female patients were involved with DVT as compared to male. Our results conflict with those of Andreou et al. and Bauersachs et al. These authors have analyzed over 1300 DVT patients and found that the prevalence of DVT was higher in men than in women.[16,17] This may be because of more postpartum patients in our study.

Left limb was more frequently involved (65.87% vs. 27.30%) in our population. Patients with anatomical compression of the left common iliac vein by the left common iliac artery are prone to develop venous flow stasis in the left limb. This is also the reason for high prevalence of left limb DVT in pregnancy.

Presenting symptoms in our study were swelling followed by leg pain, skin changes, raised limb temperature, Moses, and Homan signs which are in accordance with the literature.[18]

Risk factors in our study were most commonly postpartum period, idiopathic, trauma, postoperative, femoral catheterization, immobilization, and malignancy. In our study, most common risk factor had been postpartum period particularly primigravida patients with deliveries conducted at home by dais (local untrained help). This may have been because of restriction of mobility in deliveries conducted at home and pain in the postpartum period. This is in contrast to the literature where multiparity has been a risk factor.

The second most common group in our study has been idiopathic. Most of these patients were middle-aged male presenting in months of summer. It is likely that dehydration may have been a contributory factor in this patient group who were already having thrombophilic tendencies. No patients in idiopathic group developed an overt malignancy in follow-up period as suggested in some reports.

However, patients with malignancy presenting as DVT had both advanced malignancy with extensive involvement of the limb, sometimes presenting with both limb involvement. Furthermore, most of the malignancies presenting with DVT were overt and advanced as has been earlier reported. Malignant disease is highlighted as an important risk factor for DVT.[19] The probability of death for cancer patients with DVT is higher than that of patients with cancer alone.[12]

In the postoperative group, most patients were either operated for advanced abdominopelvic malignancy or neurosurgical patients. In most of such cases perioperative prophylaxis was not used.

One particular patient group in our study was that of patients with femoral catheterization particularly those with temporary pacemaker implants which have to be kept

| Table 4: Outcome of anticoagulation in our patients |
| Condition | Percentage population affected |
|-----------|--------------------------------|
| Percentage of patients with >50% luminal blockage after 3 weeks of treatment | 15.49 in distal group |
| Percentage of patients with >50% luminal blockage after 6 months of treatment | 3.49 in distal group |
| Postthrombotic syndrome (%) | 25 |
| Major intracranial bleed or other life-threatening bleeding | 0 |
| Ecchymoses postheparin therapy | 12 |
| Minor bleeding (hematuria, epistaxis, and vaginal bleeding) | 4 |
| Mortality (during hospital admission) | 6 (all in proximal group) |
| Documented pulmonary thromboembolism | 2 |
| Sudden death (probable pulmonary thromboembolism) | 4 |
| DVT: Deep vein thrombosis | |
for longer period of time. Several authors have reported a high incidence of femoral vein thrombosis rates of 6.6–25%.19,20

In our study, proximal deep vein involvement was more commonly seen (73.37%), which is same as confirmed in other studies.

Heparin discovered by McLean21 was used in unfractionated form and fixed dose regimen in our study. The efficacy and safety of continuous intravenous (IV) infusion of heparin has been compared with intermittent IV injection in several studies22-27 and with high-dose subcutaneous (sc) injection in many studies.28-30 From these studies, it is difficult to determine the optimal route of heparin administration because most were underpowered, total doses varied, and disparate criteria were used to assess outcome. A pooled analysis of 11 clinical trials involving 15,000 patients treated with either IV UFH (administered as an initial bolus of 5000 U followed by 30,000–35,000 U/24 h with APTT monitoring) or sc LMWH31 found the mean incidence of recurrent VTE 5.4% (fatal in 0.7%) and major bleeding 1.9% (fatal in 0.2%). That UFH is equivalent to LMWH has been reported in many studies. In the MATISSE PE study,32 2213 patients with acute PE were randomly allocated to treatment with sc fondaparinux or IV UFH. Recurrence of VTE at 3 months (3.8% vs. 5.0%) and major bleeding while on treatment (1.3% vs. 1.1%) were again similar between the two groups. That fixed dose UFH is effective for the treatment of DVT can be indirectly interpreted from our study by comparing the patients with percentage of involvement of veins (74.41% patients with >90% thrombosis in proximal and 66.67% patients with >90% thrombosis in distal at presentation, 29.52% proximal and 15.49% distal at 3 week, 2.56% proximal and 3.45% distal at 6 months). Continued effect of heparin over vein wall endothelialization may have contributed to recanalization of thrombosed vein even after stopping UFH after 3 weeks of treatment as demonstrated by Moaveni et al. in their experimental study using LMWH.

Incidence of PTS has been approximately 25% in our study. Most of patients presented as generalized limb swelling. PTS develops in one-third to one-half of patients with DVT33,34 even when appropriate anticoagulant therapy is used. Based on its high incidence and prevalence, PTS is the most frequent complication of DVT. PTS is a burdensome and potentially debilitating condition for which patients frequently seek medical advice. Manifestations of PTS vary from mild clinical symptoms or signs to more severe manifestations such as chronic leg pain that limits activity and ability to work, intractable edema, and leg ulcers.35 PTS has adverse effects on quality of life and productivity,36 and is costly as measured by health resource utilization and direct and indirect costs.37

**Conclusion**

DVT remains one of the most important causes of morbidity and mortality. Although easily printable by LMWH, patients with DVT respond well to cheap and safe UFH as has been found in our study. Hence, it is recommended that patient with established DVT be treated initially with UFH along with Vitamin K antagonist and aspirin with continuation oral therapy with Vitamin K antagonist and ecosprin after target INR is achieved. Severe proximal DVT can lead to fatal PE, therefore authors advise admission for these patients with OPD follow-ups only when therapeutic INR is achieved.

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**Conflicts of interest**

There are no conflicts of interest.

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