Comparison of Oral Anticoagulants and Low Molecular Weight Heparins (LMWH) on Outcome of Patients with Deep Vein Thrombosis (DVT)

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Abstract: Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT), is a potentially fatal disease. The outcome of treatment with initial LMWH followed by either oral anticoagulants or prophylactic LMWH for 4 months in Indian patients is lacking. The case records of patients with infra inguinal DVT on prophylactic oral anticoagulants or LMWH therapy for 4 months was analyzed in this retrospective observational study. The outcome was degree of revascularization and post thrombotic syndrome score. The degree of recanalization in patients on prophylactic oral anticoagulant (37%) was similar to those who received prophylactic LMWH (39%) (p>0.05). There was no significant difference between OAC and LMWH prophylaxis on the Villalta scoring and Post Thrombotic Syndrome grading at the end of 4 months of treatment. Bleeding is documented in 3 patients on prophylactic oral anticoagulant whereas no patient had bleeding on LMWH. The outcome of treatment assessed by degree of revascularization and post thrombotic syndrome was comparable with oral anticoagulants and LMWH in patients with DVT.

Key words: Oral anticoagulants - LMWH - Outcome of DVT

INTRODUCTION

Venous thromboembolism (VTE), which consists of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a potentially fatal disease. Long-term sequelae, particularly post Thrombotic syndrome (PTS) are frequent and often disabling. Many risk factors like advanced age, fracture of the pelvis, hip, femur or tibia, prior venous thromboembolic disease, obesity etc. have been identified for the occurrence of venous thromboembolic disease [1].

Following a first episode of deep vein thrombosis (DVT) of the lower extremities, almost 20% of the patients suffer a recurrent thromboembolic event and 20–50% develop the postthrombotic syndrome (PTS) within 2 years [2,3]. The PTS is a chronic complication and patients suffer of various symptoms of which the most prevalent are pain, swelling, pruritus and cramp of the affected leg. In severe cases even ulceration of the leg may result [4]. The syndrome is primarily diagnosed by the presence of typical symptoms and clinical signs in a limb that was affected by DVT. International Society of Thrombosis and Hemostasis (ISTH) approved Villalta scale, which is found to be a reliable and valid instrument to define the presence and severity of PTS in patients with previously confirmed DVT [5]. The Villalta scale is a clinical measure for PTS (Table 1); it looks at the severity of Villalta scale, which is found to be a reliable and valid instrument to define the presence and severity of PTS in patients with previously confirmed DVT [5]. The Villalta scale is a clinical measure for PTS (Table 1); it looks at the severity...
of 5 patient symptoms and 6 clinical signs, which a clinician has to assess. Basically, a point is given for each of those symptoms and signs (0=no symptom/sign, 1=mild, 2=moderate, 3=severe). A patient is considered to have PTS if he or she has a total added score of 5 or more. This scale was specifically developed to measure the postthrombotic syndrome and has shown to be valid when measured against quality of life and anatomical and physiologic markers of the postthrombotic syndrome, has good-to-excellent inter-observer reliability and is responsive to clinical change [6,7].

A 25-year population-based study reported an annual incidence of symptomatic VTE as 117 per 100,000 persons in 1998. The incidence of deep vein thrombosis (DVT) in hospitalized patients has increased from 0.8% to 1.3% over a period of 20 years (reported in 2005). A high incidence of DVT has been found in patients undergoing surgical procedures. Without thromboprophylaxis the incidence of DVT is about 14% in gynaecological surgery, 22% in neurosurgery, 26% in abdominal surgery and 45%-60% in patients undergoing hip and knee surgeries. Though the exact incidence of VTE in the Indian population is not known because of nonuniform reporting of such incidents, its incidence is not expected to be different from that in the western population [8]. Studies by several Indian authors reported incidence of DVT of 28%, 8%, 19.6%, 23.3%, 7.8%, 9.9% respectively in India [9].

The primary objectives for the treatment of deep venous thrombosis (DVT) are to prevent pulmonary embolism (PE), reduce morbidity and prevent or minimize the risk of developing the postthrombotic syndrome (PTS). The immediate symptoms of DVT often resolve with anticoagulation alone and the rationale for intervention is often reduction of the 75% long-term risk of PTS. The lack of a significantly reduced incidence of PTS after systemic thrombolysis (40-60%) likely reflects the inadequacy of the relatively low threshold volume of thrombus removal that was considered successful.

In 1960 Barritt and Jordan established that anticoagulation reduced the risk of death and of recurrent embolism in patients with pulmonary embolism, a conclusion subsequently supported by retrospective studies from Oxford and the United States [10-12].

Initial anticoagulation usually requires the overlap of a parenteral anticoagulant (unfractionated heparin, low-molecular-weight heparin [LMWH] or fondaparinux) with warfarin for a minimum of 5 days and until the international normalized ratio (INR) of the prothrombin time is above 2.0 for at least 24 hours [13].

The outcome of treatment with initial LMWH followed by either oral anticoagulants or prophylactic LMWH for 4 months in Indian patients is lacking and the majority of the studies have been conducted and published from the western countries where DVT is more commonly seen. Oral anticoagulants are still widely used for treatment as well as for prophylaxis in Indian patients due to its low cost and convenience of oral route, thus we proposed to compare the above treatments on outcome of DVT patients by degree of recanalization assessed by Doppler study and clinical villalta scoring.

**MATERIALS AND METHODS**

The case records of DVT patients from department of vascular surgery; Nizam’s Institute of Medical Sciences was collected. 100 case records of patients on oral acenocoumarol and 100 case records of patients on LMWH twice daily initially followed by once daily prophylactic LMWH therapy for 4 months was analyzed in this retrospective observational study. The severity of PTS as assessed by Villalta score, degree of recanalization detected by color Doppler and Post thrombotic syndrome grading at the end of 4 months of treatment was recorded in a case record form.

**Statistical Analysis:** The data is represented as mean±SD. Unpaired T test was used to compare mean involving independent samples. Chi square test is used as test of association for categorical data.

**RESULTS**

The age of patients who has received LMWH was higher than those who received OAC and the other baseline demographic data of both the groups was similar. (Table 1).

The degree of recanalization in patients on prophylactic oral anticoagulant (37%) was similar to those who received prophylactic LMWH (39%). (p>0.05).

The patients on prophylactic oral anticoagulants were divided into those with INR within normal range in more than and less than 50% of the test conducted. The complete recanalization was significant in patients who maintained INR within normal range in atleast more than 50% of test conducted 32 (47.05%) compared to those who maintained INR within normal range in less than 50% of test conducted 5 (15.62%). P<0.01.
Table 1: baseline demographic data of the patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LMWH</th>
<th>OAC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44.27±12.8</td>
<td>39.68±10.67</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>M:F</td>
<td>73:27</td>
<td>64:36</td>
<td>NS</td>
</tr>
<tr>
<td>Left:Right</td>
<td>20:80</td>
<td>17:83</td>
<td>NS</td>
</tr>
<tr>
<td>Primary: Secondary cause of DVT</td>
<td>55:45</td>
<td>64:36</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2: Degree of recanalization in patients receiving LMWH for different duration

<table>
<thead>
<tr>
<th>Duration</th>
<th>Prophylactic Number of patients Complete recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 days</td>
<td>34</td>
</tr>
<tr>
<td>91-119 days</td>
<td>25</td>
</tr>
<tr>
<td>90 days</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of DVT</th>
<th>Prophylactic Number of patients Complete recanalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>55</td>
</tr>
<tr>
<td>Secondary</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 3: mean villalta scoring and PTS grading in patients on prophylactic oral or LMWH

<table>
<thead>
<tr>
<th>Villalta score</th>
<th>LMWH</th>
<th>OAC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Villalta score</td>
<td>5.65±4.79</td>
<td>6.24±5.09</td>
<td>0.40</td>
</tr>
<tr>
<td>PTS grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45 (45%)</td>
<td>38 (38%)</td>
<td>0.52</td>
</tr>
<tr>
<td>2</td>
<td>44 (44%)</td>
<td>47 (47%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (11%)</td>
<td>15 (15%)</td>
<td></td>
</tr>
</tbody>
</table>

On analyzing the data of patients on prophylactic LMWH significant percentage of patients who received LMWH for at least 120 days had complete recanalization compared to those who received LMWH for 90 days.

(* P<0.05 for degree of recanalization in patients receiving prophylactic LMWH anticoagulant therapy for 120 compared to 90 days, # p=0.09 for degree of recanalization between patients with primary and secondary causes of DVT receiving LMWH)

There was no significant difference between OAC and LMWH prophylaxis on the villalta scoring and Post Thrombotic Syndrome grading at the end of 4 months of treatment.

**DISCUSSION**

The mean age of patients on LMWH is 44 (range 20-78) and patients on OAC is 40 years (range 16-67). The mean age was 60 years and range was 29-94 years in a study conducted on routine chemoprophylaxis for DVT in Indian patients. although we observe a lower mean age group in our study as the data was collected from vascular surgery department which receives patients from different medical and surgical units unlike only surgery patients included in the above study, similar to the mentioned study the range of age remained wide in our stud [14]. similarly in a study conducted by Agarwala et al., at department of Orthopedics, PD Hinduja National Hospital and Medical Research Centre, Mumbai, average age of patients was 58 years with the range of 28-88 years [15].

Apart from male domination in both the groups, secondary cause of DVT was more common in LMWH group compared to OAC group. In both the groups most common secondary cause of DVT was prolonged morbidity associated with trauma and injury and malignancy was diagnosed in overall 11% of cases.

Venous thromboembolic disease in the form of deep venous thrombosis and pulmonary embolism is a major risk after general and orthopaedic surgeries apart from primary idiopathic cause. Patients undergoing vascular surgery have an additional high risk for VTE. Potential risk factors in vascular surgery include advanced age, limb ischemia, long duration of surgery and venous injury [16]. Low-molecular-weight heparin and orally administered anticoagulant, has been used historically to reduce the risk of deep venous thrombosis. In India, currently vitamin K antagonist (VKA) drugs like warfarin remains the number one agent of choice for oral anticoagulation based on physician comfort due to years of usage and the prohibitive cost of LMWH. There are certain issues with warfarin peculiar to India. Indians with their different dietary habits compared to their Western brethren are more prone for warfarin-food interactions. Another issue in India is monitoring of warfarin therapy. Majority of places including suburbs of large cities lack proper laboratories with standardized measurement of prothrombin time (PT)/INR [17].

In a meta-analysis of randomised clinical trials comparing Efficacy and safety of low molecular weight heparin and warfarin for thrombo-embolism prophylaxis in orthopaedic surgery, LMWH is significantly superior to warfarin in the prevention of DVT but results in significantly more minor bleeding when compared to warfarin [18].

Colwell et al., in a study Comparing enoxaparin and warfarin for the prevention of venous thromboembolic disease concluded that the benefit of LMWH is lost after the medication was discontinued, with no difference in the prevalences of venous thromboembolic disease between the two groups at three months after discharge from the hospital [19].
The efficacy and safety of oral anticoagulants compared to LMWH in Indian patients helps the treating physician in deciding the treatment strategy depending on resources available in terms of cost and monitoring. The present study clearly shows that the oral anticoagulants were comparable to LMWH in treatment of DVT with comparable rates of revascularization and similar mean villalta scoring with post thrombotic syndrome in both the groups at the end of 4 months. However the patients who received LMWH for 120 days had significant higher fraction of patients undergoing complete revascularization compared to 90 days of treatment. In patients who were on oral anticoagulants the response was better in patients who had maintained their INR within normal range in more than 50% of test conducted than those who have not maintained therapeutic INR. Thus oral anticoagulants can still be prescribed if the monitoring facilities with INR are available and the patients maintain therapeutic INR during the treatment. The outcome of treatment assessed by degree of revascularization and post thrombotic syndrome was comparable with oral anticoagulants and LMWH in patients with DVT. However prospective trials involving a larger number of patients in future are required to confirm findings of this research.

REFERENCES


