Original Article

# Safety and efficacy of low-molecular-weight heparins in prophylaxis of deep vein thrombosis in postoperative/ICU patients: A comparative study

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## Abstract

**Background:** Venous thromboembolism (VTE), although a very common problem in everyday clinical practice, remains asymptomatic in most cases. Clinical diagnosis helps identify those who are going to have thromboembolic episode. A combination of clinical scoring systems like Wells' score and D-dimer assay provide a useful diagnostic tool. Trauma (surgical or accidental) and critically ill patients are found to have greatest risk. Enoxaparin and dalteparin are amongst the most common low-molecular-weight heparins (LMWHs) used for deep venous thrombosis (DVT) prophylaxis in such patients. **Aim:** The present study is designed to compare their role in preventing DVT in postoperative or critically ill patients and to determine their relative safety profiles. **Materials and Methods:** The study included 36 critically ill adult patients. All the patients were allocated into three groups of 12 patients each. Group I patients received no prophylaxis, group II received inj. enoxaparin s/c 0.6-0.8 mg/kg twice daily, and group III received inj. dalteparin s/c 125-250 units/kg once daily. Routine investigations and coagulation profile were recorded on admission to intensive care unit (ICU) and at every third day thereafter. Patients were daily assessed for pretest probability of DVT using Wells' scoring, and D-dimer test was done on the 7$^{th}$ day. Occurrence of any bleeding (visible or occult) was noted, and incidence of DVT was determined in each group using positive results of D-dimer test and the clinical assessment with Wells' score. **Results:** A significant difference in Wells' score ($P < 0.05$) was found between groups I and III on day 5 and day 7. A lower, but insignificant difference in the incidence of DVT was found between the study and control groups. No significant difference in major bleeding or other side effects was found. Better hemodynamic status and arterial blood gases in the study groups may indirectly refer to absence of asymptomatic DVT or silent pulmonary embolism in this group. **Conclusion:** The present study suggests that LMWHs, namely, enoxaparin and dalteparin, provide effective means of preventing DVT in high-risk, critically ill or postoperative patients, without causing any significant increase in the risk of bleeding or other side effects. Dalteparin appears to be unaffected by low creatinine clearance as explained by its clearance by a non-saturable mechanism. Still, a more extensive study with larger population is needed to make the outcomes worthwhile.

**Key words:** D-dimer, deep vein thrombosis, low-molecular-weight heparin, venous thromboembolism

## INTRODUCTION

Deep vein thrombosis (DVT) commonly affects the leg veins or the deep veins of the pelvis. In high-risk hospitalized patients, most deep vein thrombi occur in the small calf veins, are asymptomatic, and are rarely detected, even if symptomatic. Vague aching pain, tenderness along the distribution of the veins, edema, and erythema are nonspecific and vary in frequency and severity. Tenderness, swelling of the whole leg, >3 cm difference in circumference between calves, pitting edema, and collateral superficial veins are the most specific signs. A combination of ≥3 signswith the absence of another likelydiagnosis makes DVT more probable

Although many thrombi are initially asymptomatic, in many cases, the affected extremity may be painful, swollen, red, and warm, with engorged superficial veins. In up to 25%

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of all hospitalized patients, there may be some form of DVT, which often remains clinically inapparent (unless pulmonary embolism develops).[1] In fact, pulmonary embolism remains the most common preventable cause of death in hospital.[2]

To identify clinically important thrombi in patients, Wells' score[3] for DVT have been developed. It combines many clinical parameters to increase the sensitivity. Recently, the revised Geneva score[4] has been introduced for determination of probability of pulmonary embolism. Along with these scoring systems, D-dimer assay is validated as a diagnostic tool to safely exclude the presence of venous thromboembolism (VTE) due to its high negative predictive value (NPV).[5,6]

Prophylaxis is preferred to treatment in patients at high risk of developing DVT. The present study was designed to assess and compare the efficacy of enoxaprin and dalteparin in preventing DVT in medical or post-surgical patients admitted to intensive care unit (ICU) and to determine their relative safety margins.

## MATERIALS AND METHODS

The present study was conducted in the ICU of Department of Anesthesiology, Nehru Hospital, B. R. D. Medical College, Gorakhpur. Adult patients of either sex admitted to the ICU were included in this study.

Exclusion criteria included: Active bleeding, congenital/acquired bleeding disorders or therapeutic anticoagulation, hemorrhagic stroke, brain/spinal/ocular surgery in ≤6 months, pregnancy/lactation, hypersensitivity to study drugs, or thrombocytopenia < $100 \times 10^9$/L.

A total of 36 patients were included in the study. All patients were routinely investigated and their coagulation profile was done on admission to ICU and at every third day thereafter. Serial hemoglobin concentration was obtained by daily arterial blood gas (ABG) analysis. Patients were assessed and scored for pretest probability (PTP) of DVT using Wells' scoring on admission and daily for ten consecutive days thereafter. Patients were continuously monitored for pulse rate, respiratory rate, non-invasive blood pressure (NIBP), temperature, electrocardiography, SpO2, and urine output.

All the patients were randomly allocated into three groups of 12 patients each and received prophylaxis with one of the following dosing regimens:

- Group I: Patients receiving no prophylaxis (control group)
- Group II: Patients receiving enoxaparin s/c 0.6–0.8 mg/kg twice daily
- Group III: Patients receiving dalteparin s/c 125–250 units/kg once daily

Patients received prophylaxis for adequate duration, but the study period was the first 10 days of admission. The first dose was given 12–24 h after surgery in postoperative patients. In non-surgical patients, prophylaxis was started on the day of admission. In all the patients, therapy was continued as per dosing regime being followed for DVT prophylaxis based on the Eighth American College of Chest Physicians (ACCP) Consensus Conference recommendations.[7]

The patients were daily assessed for the occurrence of any bleeding from the surgical site or any visible or occult bleeding. Thromboprophylaxis was stopped in case of bleeding, and International Normalized Ratio (INR) and platelet counts were repeated.

The most important efficacy parameter was incidence of VTE in the first 10 days. The incidence of DVT was determined in each group using positive results of D-dimer test and the clinical assessment with Wells' score.[8] Assay was done on the 7$^{th}$ day. The patients developing DVT were treated with anticoagulating doses of low-molecular-weight heparin (LMWH).

Other safety parameters included incidence of side effects like ecchymoses, skin rashes/pruritus, and thrombocytopenia (<$100 \times 10^9$/L) or more than 3 times elevation in alanine aminotransferase (ALT) levels.

### Statistical analysis

Statistical evaluation was done using independent variable Student's *t*-test and Chi-square test. Two software programs were used, namely, Decision analyst, Inc 1998 version 1.1 and Javastat. Difference between variables was considered as nonsignificant with *P* value >0.05, significant at *P* value <0.05, highly significant at *P* value <0.01, and very highly significant at *P* value <0.001.

## RESULTS

All the three groups were comparable in their demographic profile [Table 1]. Each group was composed of 58.33% and 41.67% each of medical and surgical patients, respectively. Hemodynamic parameters like pulse rate, blood pressure, respiratory rate, and $PaO_2$ were taken into account as indicators of asymptomatic DVT or silent pulmonary embolism [Table 2]. Multiple readings were recorded over 24-h period and their mean was calculated. Group I had higher mean pulse rates as compared to groups II and III.

Group I had lower mean diastolic blood pressure. But statistical comparison of study and control groups using independent *t*-test showed no significant difference in mean pulse rates, systolic, diastolic pressures, respiratory rates, and mean partial pressures of oxygen at different time intervals ($P > 0.05$). Similarly, there was no significant difference in Wells' scores on day 1 and day 3. But significant difference was found between groups I and III on day 5 ($P < 0.05$), and a highly and very highly significant difference on day 7 between groups I and III (<0.01) and between groups I and II ($P < 0.001$), respectively. Study groups (groups II and III) showed lower incidence of DVT (one patient each) than group I (three patients), but statistical comparison using Chi-square test showed no significant difference in the incidence of DVT ($P > 0.05$) [Table 3].

There was no mortality during the study period. Only a single patient developed ecchymoses (group III). No case of thrombocytopenia, skin rash, pruritus, or rise in serum ALT level was seen. Group I had only a single incidence of bleeding as indicated by sudden fall in daily hemoglobin levels of >2 g/dl and required blood transfusion. Group II had two patients showing fall in serial hemoglobin and one patient with surgical site bleeding. Group III similarly had two patients showing fall in serial hemoglobin concentration and one patient with hematuria. But statistical comparison of study and control groups showed no significant difference in hemoglobin concentration, incidence of major bleeding, and INR at different time intervals.

**Table 1: Demographic data**

| Groups | Male:Female (*n*) | Age (years) | Height (m) | Weight (kg) | BMI (kg/m²) |
|---|---|---|---|---|---|
| I | 6:6 | 58.2±11.9 | 1.5±0.1 | 53.7±7.2 | 23.1±4.6 |
| II | 7:5 | 57.7±11.1 | 1.6±0.6 | 55.5±5.8 | 23.8±4.3 |
| III | 7:5 | 58.6±10.9 | 1.5±0.1 | 53.7±5.2 | 23.7±3.2 |

## DISCUSSION

DVT is a common, but highly preventable complication in hospitalized patients. If not provided prophylaxis, nearly 40% of ICU patients; 30% of general surgical patients; and 15% of general medical patients develop DVT.[1] The most common risk factors are recent surgery or hospitalization.

This study is aimed at determining the relative efficacies of the two commonly used LMWHs, i.e. enoxaparin and dalteparin, in ICU patients (medical/surgical) for DVT prophylaxis and assessing and comparing their safety margins.

Bounameaux *et al.* (2002)[9] studied the diagnostic approaches to suspected DVT and pulmonary embolism and found the strategy of using clinical probability and D-dimer as first-line screen to be a safe and cost-effective approach, with a significant reduction for the need of ultrasound scans. Ten Cate-Hoek *et al.* (2005)[10] have shown that the approach of combining PTP with a modern D-dimer assay can safely exclude disease in up to half of the patients with suspected VTE, without the need for additional diagnostic investigations. In concurrence with these studies, we used Wells' criteria and D-dimer assay for detecting DVT.

In the present study, the probability of developing DVT during the study period, as assessed by Wells' clinical scoring system, was higher in the control group as compared to the study groups. This refers to a reduction in the probability of DVT in the study groups by LMWHs used for DVT prophylaxis.

Similarly, results of D-dimer assay showed a higher incidence (25% *vs.* 8.33%) of DVT in group I as compared to study groups, but statistically it was not significant. This

**Table 2: Comparison of various hemodynamic parameters**

| | Pulse rate (per minute) | | Systolic blood pressure (mmHg) | | Diastolic blood pressure (mmHg) | | Respiratory rate | | $PaO_2$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Day 5 | Day 7 | Day 5 | Day 7 | Day 5 | Day 7 | Day 5 | Day 7 | Day 5 | Day 7 |
| Group I | 112.3±18.8 | 115.8±17.7 | 108.4±16.1 | 108.6±17.8 | 77.5±10.3 | 77.8±8.4 | 20.8±4.9 | 21.0±4.7 | 199.3±103.6 | 208.2±104.0 |
| Group II | 102.5±17.7 | 103.3±18.2 | 109.1±17.0 | 110.0±16.8 | 80.1±14.7 | 79.6±14.5 | 20.3±4.7 | 21.0±4.6 | 191.9±111.8 | 199.8±110.0 |
| Group III | 101.8±20.7 | 102.2±22.2 | 115.0±14.0 | 112.5±16.0 | 81.3±13.5 | 79.8±13.5 | 21.0±4.7 | 20.6±4.5 | 194.4±101.8 | 206.3±111.3 |

**Table 3: Comparison of DVT and major bleeding**

| | Wells' scores | | D-dimer on day 7>0.05 μg/dl or symptomatic DVT (*n*) | Incidence of major bleeding (*n*) |
|---|---|---|---|---|
| | Day 5 | Day 7 | | |
| Group I | 3.2±0.7 | 3.1±0.8 | 3 | 1 |
| Group II | 2.6±0.8 | 2.1±0.9* | 1 | 3 |
| Group III | 2.3±0.9* | 2.1±0.8* | 1 | 3 |

*Statistically significant on comparison with group I

denotes the efficacy of LMWHs in reducing the incidence of DVT in the study population, but significant results have not been found probably due to smaller group size. Similar results were obtained by Theodore *et al.* (1994)[11] who used different laboratory parameters to determine the most effective and safest dose of enoxaparin for high-risk surgical patients. They concluded that administration of 30 mg of enoxaparin 12 hourly or 40 mg once daily substantially reduced the incidence of DVT. In a similar study, Ribic *et al.* (2008)[12] systematically reviewed the effect of LMWH thromboprophylaxis in medical–surgical critically ill patients in the ICU**.** They reviewed data like LMWH use, clinical outcomes, laboratory outcomes, and methodological quality. Thrombocytopenia occurred in 9.3% of patients receiving LMWH, as compared to none in the present study. The frequency of VTE in patients receiving LMWH ranged from 5.1 to 15.5% (8.33% in the present study). Bleeding complications ranged from 7.2 to 23.1% (25% in the present study) and mortality ranged from 1.4 to 7.4% (nil in the present study).

On comparison of study and control groups, no significant difference in major bleeding was found at different time intervals ($P \geq 0.05$). This indicates that using LMWHs for DVT prophylaxis did not lead to an increase in the incidence of bleeding. This is consistent with the findings of Theodore *et al.* (1994)[11] who found that incidence of hemorrhagic episodes in the study groups was higher than in the control group, but the overall incidence of major hemorrhage was only 4–5%.

Further, on comparison of the study groups (II and III), no difference was found in the incidence of DVT or bleeding. But randomized trials in larger group are required for final inference. Likewise, in 2003, Chiou-Tan *et al.*,[13] in a prospective study comparing dalteparin and enoxaparin for DVT prophylaxis in patients with spinal cord injury, found similar compliance, health status, DVT, and bleeding. However, Cook *et al.* (2005)[14] studied the use of LMWH for thromboprophylaxis in patients with renal impairment and found that prophylactic doses of enoxaparin had to be reduced from 30 mg twice daily to 40 mg once daily for high-risk patients, while no such dose adjustment was required for dalteparin.

To summarize, we found that use of LMWHs, e.g. enoxaparin and dalteparin, is beneficial in reducing the incidence of DVT in postoperative/ICU patients, without causing significant side effects. However, studies recruiting larger number of patients are required for any recommendations.

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