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ORIGINAL ARTICLE

Detection and Prevention of Post-Operative Deep Vein Thrombosis [DVT] Using Nadroparin Among Patients Undergoing Major Abdominal Operations in India; a Randomised Controlled Trial

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Abstract Deep vein thrombosis [DVT] is one of the most dreaded complications in post-operative patients as it is associated with considerable morbidity and mortality. Majority of patients with postoperative DVT are asymptomatic. The pulmonary embolism, which is seen in 10% of the cases with proximal DVT, may be fatal. Therefore it becomes imperative to prevent DVT rather than to diagnose and treat. Only one randomized trial has been reported from India to assess the effectiveness of low molecular weight heparin in preventing post-operative DVT. To assess the risk of DVT in North Indian patients following major abdominal operations and to evaluate the effectiveness of Nadroparin, A Low Molecular Weight Heparin (LMWH) therapy in preventing post-operative DVT. Sixty five patients were randomised preoperatively into Group-I; Nadroparin prophylaxis and Group-II: No prophylaxis. The primary outcome was the occurrence of DVT, diagnosed by bilateral lower limb venogram performed, seven to ten days after operation. Secondary outcome measures included adverse effects of radio-opaque dye, intra-operative blood loss, operating time, postoperative platelet count, intraoperative blood transfusion requirements and the total duration of postoperative bed rest. No case of DVT occurred in either group. There was no statistical difference in the risk of secondary outcome measures in the two groups. DVT was not observed in any of the patients, even with several high risk factors indicating a possible protective mechanism in the North Indian population.

Keywords Deep vein thrombosis · Post-operative DVT · Low molecular weight heparin · Nadroparin · Venography

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Introduction

Deep Vein thrombosis is a common complication observed among Caucasian population in postoperative period. The prevalence of Deep Vein Thrombosis (DVT) in various series involving Western population ranges from 15% to 40% among patients undergoing major general surgical procedures [1]. The autopsy studies document that 50% of all patients dying in hospital have DVT [2]. Around 10–30% of these patients have pulmonary embolism secondary to proximal DVT [3]. It is believed that the DVT is less prevalent among the Indians and Asians [4]. There have been very few studies on DVT in postoperative period in Asian patients. The reported incidence of DVT varies from 1.3% in spinal surgery to 41.7% following colorectal surgery among the Asians [5–9].

The majority of the patients developing post-operative DVT are asymptomatic. It's complications like pulmonary embolism can be lethal; hence prevention of DVT assumes

paramount importance. As a sequel to DVT, venous valves become incompetent or destroyed, resulting in chronic venous hypertension and subsequent development of varicose veins, lipodermatosclerosis and venous ulcers causing considerable disability. Several randomised trials have shown that both unfractionated heparin (UHF) and low molecular weight heparins (LMWH's) are effective in the prevention of DVT [10, 11]. In an earlier randomized study on 100 patients, we compared Enoxaparin prophylaxis with control subjects not receiving any DVT prophylaxix. Only 2 patients in the control arm were found to have a partial thrombus in the popliteal vein on colour Duplex study [12]. The colour Duplex scan has been reported to have a low sensitivity in identifying post-operative DVT, hence in the present trial we employed contrast venography for the detection of DVT.

Patients and Methods

Sixty five patients were studied.

The protocol was approved by the Institute Ethics Committee. A list of random numbers was generated using block randomisation method with equal allocation ratio of 1:1. The enrolled patients were randomised into two groups preoperatively by the numbered sealed envelopes. No randomization violation occurred. It was a two arm parallel design open randomized trial.

> **Inclusion Criteria**: 1. Age more than 40 years 2. Patients undergoing major abdominal operations lasting more than 30 minutes 3. Informed written and signed consent.
> **Exclusion criteria**: Patients having 1. bleeding disorders, 2. active peptic ulcer, 3. Bleeding haemorrhoids, 4. history of upper gastrointestinal bleed, 5. stroke, 6. intracranial haemorrhage, 7. recent history of major trauma in preceding 2 weeks, 8. renal failure, 9. allergy to heparin, 10. platelet count less than $1\times10^6/mm^3$ and haemoglobin less than 10 gm/dl.

Intervention Group-I: Nadroparin prophylaxis group: 0.3 ml of Nadroparin equivalent to 3075 Anti-Xa IU, was administered subcutaneously, in the abdominal wall or thigh, 2 hours before surgery and continued once daily for 7–9 days. Group-II: control Group—No DVT prophylaxis was given as this is the standard of care in our department.

The demographic parameters such as age, gender, height, weight, body mass index and operative procedure were recorded.

Measurement of Variables: Main Outcome Variable The outcome of main interest was the occurrence of DVT in the lower limbs. All the patients were subjected to bilateral lower limb venogram (Ascending Phlebography) using diluted non-ionic iodinated contrast (76% Sodium Diatrozoate), 7 to 10 days after operation to document any development of DVT. The DVT was defined as the presence of a filling defect in more than one view or the presence of abrupt cut-off in the venous column in the venogram. The venograms were examined by a Professor in Radiology (DNS-an expert in vascular imaging) without the knowledge of clinical parameters or treatment group.

Secondary Outcome Variable

1. Blood loss during and after operation in the vacuum suction drains from operative site, measured in ml coded as a continuous variable.
2. Requirement of blood transfusion coded as a binary variable as yes/no.
3. Platelet count recorded as a continuous variable.

The results of the study were analyzed to calculate the risk of DVT and other secondary outcome variables among the patients receiving Nadroparin compared to those in the control group. Two sample "t" for the continuous variables and chi-square test for the binary data were employed for Null Hypothesis testing.

Results

Sixty five patients above the age of 40 were included in the study. Thirty four patients were randomised into Group-I (Nadroparin prophylaxis) and thirty one patients into Group-II (Control). Both the groups were comparable regarding age [Group I; Mean age=56.9 years (range 43–77, SD 10.89) and Group II; mean age=55.9 years (range 40–82, SD 10.59)], body mass index (BMI); Nadroparin group: mean BMI= 24.63 (range 18–34) compared to mean BMI=23.39 (range 19–32) in control group. There were 21 males and 13 females in Group I and 18 males with 13 females in Group II.

The patients could be stratified into 3 groups according to criteria of Geerts et al. 2004 [13] as follows:

> **Very high risk**: Age >60 years with malignancy, obesity or any other risk factor.
> **High risk**: Age 40–60 years with malignancy or obesity.
> **Moderate risk**: Age >40 years with no risk factors.

Both the Nadroparin (N) and Control group (C) had similar risk factor distribution. There were 14 patients in the high risk, 14 patients in the moderate risk and 6 cases in the very high risk category in the Nadroparin group. The control group had: high risk = 15; moderate risk = 13 and very high risk = 3 patients.

The patients in Nadroparin and control groups underwent similar types of operative procedures (Table 1). The exploratory

Table 1 Types of operations performed

Operation	Group-I (N)	Group-II (C)	Total
Cholecystectomy	5	3	8
CBD exploration	4	4	8
Rectal Operation	3	3	6
Exploratory laparotomy	14	14	28
Adrenalectomy	1	2	3
Oesophagectomy	1	0	1
Ilio-Inguinal lymph node dissection	3	4	7
Nephrectomy	3	1	4
Total	34	31	65

laparatomy was the commonest operation performed. The indications for exploration were as follows: Intestinal obstruction—15 cases, Peritonitis—4 cases, stoma fashioning for sepsis—4 cases, stoma closure—3 cases and tuberculosis of the intestine and lymph nodes—2 cases.

The mean blood loss and blood transfusion requirement were slightly higher in the Nadroparin group. However, the difference was not significant statistically (Table 2).

The mean duration of operation and postoperative immobilization was comparable in both the Nadroparin and Control arms (Table 3).

The mean platelet count was 177,100/mm^3 on the day of surgery and 157, 130/mm^3 on postoperative day 5, among the patients with Nadroparin group. The difference was not statistically significant. (p=0.069).

Bilateral Venography It was attempted in all the patients during postoperative day 7 to 10, to document the occurrence of DVT. Venography was completed in 61 patients. In 4 cases due to difficulty in cannulating dorsal foot veins, only unilateral Venography could be performed. None of the patients developed any allergic reactions to iodinated contrast or Nadroparin. There was no evidence of DVT on venogram in any patient.

Discussion

The DVT is common after surgery because of venous stasis (peri-operative immobilization), vessel wall abnormalities (endothelial damage due to trauma or release of inflammatory mediators) and a procoagulant state (release of tissue thromboplastin like factor and dehydration). The risk of DVT in Asian population is generally reported as low as 1.3% (Table 4).

The risk of DVT varies depending upon the type of operation. This is due to factors such as period of immobilization, presence of malignancy and degree of trauma to the vascular endothelium, which varies among different surgical procedures.

The risk factors for venous thrombosis are as follows: age above 40 years, malignancy, previous history of venous thrombosis or pulmonary embolism, major abdominal pelvic, hip or knee operations lasting more than 30 minutes.

The risk of DVT among surgical patients has been stratified into low, moderate, high and very high risk by Geerts et al. [13] This was devised in the seventh ACCP conference of thrombosis and its prevention held in 2001.

Several pharmacological and non-pharmacological methods were evaluated for the prevention of DVT. Pharmacological methods were found to be more efficient in DVT prevention. Heparin was found to be effective in low doses. Since unfractionated heparin administration carries a significant risk of bleeding in the surgical patients, low molecular weight heparins (LMWH) have been isolated to reduce the haemorrhagic complication. With the advent of low molecular weight heparins, they have become the most common chemoprophylactic agents for DVT prophylaxis. Many studies have demonstrated lesser complications and greater

Table 2 Mean blood loss and transfusion requirement

Group	Mean amount of blood loss (ml) [S,D]	No. of Patients transfused (%)	No. of patients not transfused
Group I (N)	147.79 [103.05]	13 [38.2%]	21
Group II (C)	124.52 [93.8]	8 [25.8%]	23
p value	0.558 (t test)	0.250 (chi-square test)	

Table 3 Operating time and duration of immobilisation

Group	Mean operating time in minutes [S.D]	Duration of Immobilisation in days [S.D]
Group I (N)	142.5 [51.35]	2.76 [0.96]
Group II (C)	137.74 [54.69]	2.84 [0.90]
p-Value	0.695 (t test)	0.621 (t test)

efficiency of LMWHs in preventing DVT compared to unfractionated heparin [14–17].

We assessed the risk of DVT in patients above 40 years with several risk factors undergoing major operations lasting more than 30 minutes. Thirty out of the 65 patients had malignant disease. The general anesthesia is associated with greater incidence of DVT [18]. In our study group all the patients received general anesthesia. Immobilization for more than 48 hours is a risk factor for developing DVT [19]. The mean duration of immobilization was 2.8 days and 60% of the patients had more than 2 days of immobilization. All the patients included in our study were in the moderate, high or very high risk category for the development of DVT. Even with all these risk factors, there was no evidence of DVT in any patient.

All the patients enrolled in the study underwent venogram in between 7th to 10th day, depending on the ambulatory status of the patient. The venogram could not be completed on both sides in four patients (7%) due to the difficulty in cannulating the dorsal veins. None of our patients developed adverse reaction to radio-opaque contrast. The 7% incidence of incomplete venograms is similar to the reports by Bergquist et a1 and Camerota et al. [2, 20].

The amount of blood loss was not significantly different between those who received or did not receive LMWH. The transfusion requirements for the patients receiving LMWH was higher when compared to the control group, though the difference was statistically not significant (p=0.250). This is similar to the results in the study done by Le Gagneux et al. and Valle et al. [21, 22].

The platelet counts were estimated in patients receiving LMWH on postoperative day one and five. There was no significant decrease in the platelet counts on day five, on LMWH administration. This shows that the complication of allergic thrombocytopenia, which was highly prevalent with unfractionated heparin administration, does not occur with LMWH. These results are comparable to the studies conducted by Gazzaniga et al. [23].

None of the 65 patients in our study revealed DVT on venogram.

In an earlier randomized trial on 100 patients (12) we had assessed the risk of postoperative DVT. In that study 50 patients received DVT prophylaxis with Enoxaparin 40 mg subcutaneously, first dose given 2 hours before surgery and repeated daily for 5 to 7 days until the patients became ambulatory. The control patients did not receive any DVT prophylaxis. The DVT was assessed with a Colour Duplex scan. In that study, popliteal vein DVT was detected in two patients in the control arm, while none of the subjects in the Enoxaparin arm developed any DVT. If we add the subjects of our Enoxaparin study to the present Nadroparin study, we get 84 subjects receiving low molecular weight heparin and 81 subjects in the control arm. Of these, DVT was detected only in 2 subjects in the control arm and none in the LMWH group. Thus 2 of 81 or 2.46% control subjects and none of the LMWH patients developed DVT.

The reason for the very low incidence of DVT among the Indian patients could be racial, genetic or rheological. Further studies are needed to unravel the possible decreased prevalence of factor V Leiden mutation and G20210A mutation in the Indians which could explain the relative immunity of the Indian population for deep vein thrombosis. [24]

Conclusions

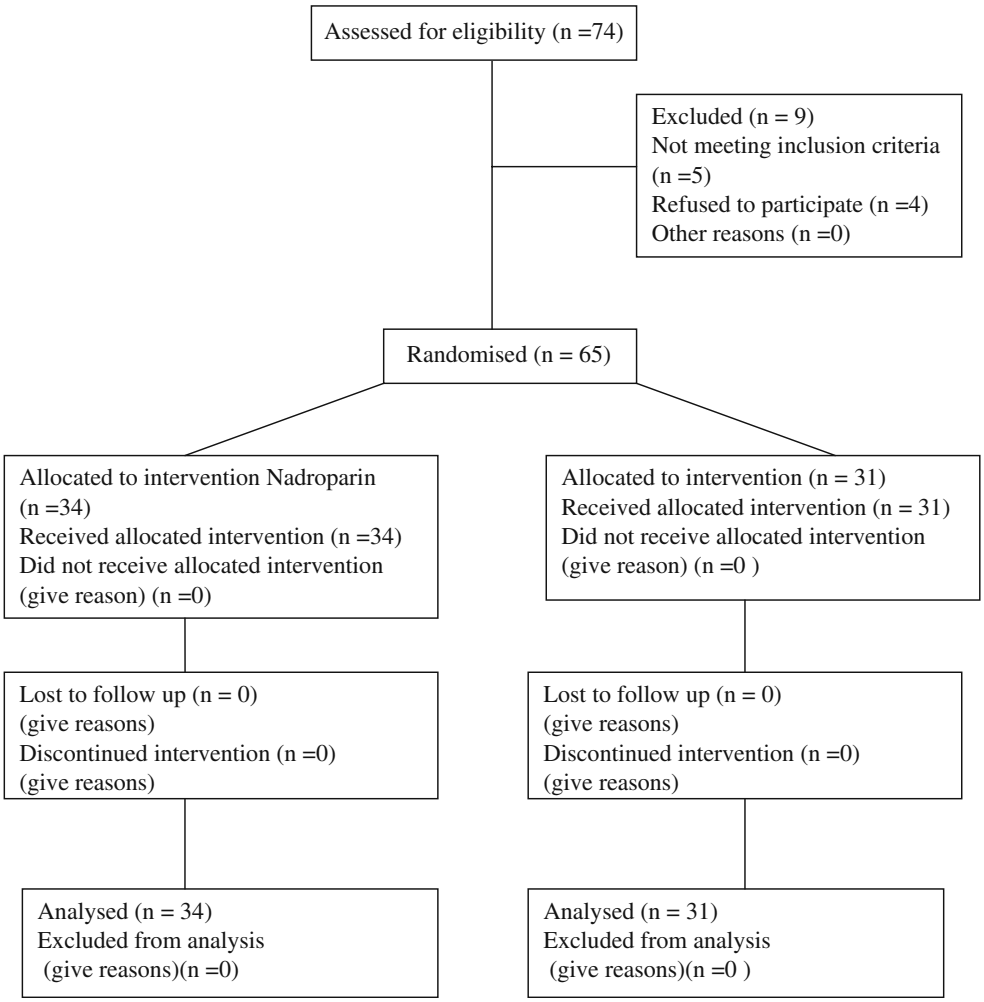
The prevalence of deep vein thrombosis is low in the post operative period, among North Indian patients. Thus routine prophylaxis against DVT with anticoagulants is not warranted in patients with moderate risk undergoing major abdominal surgery. The low molecular weight

Table 4 Studies on DVT Prevalence among Asians

Study	Number of Patients	Operations	Risk of DVT	Investigation
Nandi et al. (1980) [5]	150	Hip arthroplasty	2.6%	Fibrinogen study + Venography
Lee et al. (2000) [6]	313	Spinal surgery	1.3%	Duplex ultrasound scan
Pookarn et al. (2004) [8]	86	Knee arthroplasty	24%	Fibrinogen study
Nathan et al. (2003) [9]	128	Knee arthroplasty	4.8%	Duplex scan

heparins do not increase the blood loss or decrease the platelet count. Further Studies are needed to unravel the protective mechanisms such as genetic variation (Factor V

CONSORT Flow Diagram



Leiden and G20210A mutation) or possible changes in natural anticoagulant levels (Protein-C, protein-S and antithrombin-III levels) in Indian patients.

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