Venous thromboembolic events that occur after surgery include deep vein thrombosis (DVT) and pulmonary embolism. These are a major cause of morbidity and mortality in patients undergoing major abdominal and orthopedic surgery. In western countries, DVT occurs in 45%–84% of patients after hip and knee surgery in the absence of prophylaxis. Studies from the West as well as from Asia indicate a lower predilection for DVT and pulmonary embolism among Asians.

Cancer is associated with a hypercoagulable state and patients with colorectal cancer undergoing pelvic surgery are especially at risk for thromboembolic episodes due to the lithotomy position in which surgeries have to be carried out over 2–4 hours.

Three studies related to DVT have been published from India. Of the two studies conducted in orthopedic patients, one reported a high and the other a very low incidence of DVT. Although the third study reported a high incidence of DVT, the incidence of associated pulmonary embolism was very low (1.9%).

As such there is no randomized study of DVT and thromboprophylaxis in colorectal cancer patients in India. And hence, this study was undertaken to determine the incidence of DVT following colorectal cancer (pelvic) surgery in patients receiving perioperative low-molecular heparin versus no thromboprophylaxis.

Methods
An open-label, prospective, randomized study was done on patients with colorectal cancer who were selected for curative resection at the Tata Memorial Hospital between March 2002 and January 2004. Patients who were to undergo colorectal surgeries under general anesthesia in the lithotomy position, were aged 30 years or more, and those in whom a preoperative Duplex ultrasound showed no DVT, were included. Patients excluded were those with severe or accelerated hypertension, renal or hepatic failure, documented systemic bleeding diathesis, or septic endocarditis; or those who had received prior anticoagulants, NSAIDs or antiplatelet therapy; or had hypersensitivity to heparin, LMWH or contrast media. Patients were excluded if they had cerebral hemorrhage 3 months before surgery, or eye, ear or CNS surgery less than a month before surgery, weighed <40 kg, were pregnant or lactating, had systemic sepsis or acute infectious disease, were enrolled simultaneously in other studies conducted by the Tata Memorial Hospital.

Written, informed consent was obtained before enrolling the patients for the study. The protocol was approved by the Ethics and Scientific Review Committee of the hospital. The preoperative assessment included a Duplex ultrasonography study to establish baseline status of the deep venous system, as well as to eliminate patients with preexisting chronic DVT. Examination of the bilateral external iliac, common femoral, superficial femoral,
popliteal, and anterior and posterior tibial veins was carried out. All color Doppler studies were evaluated by the same radiologists. The diagnosis of DVT was made when a thrombus was visualized, flow was absent, or there was a lack of compressibility, or lack of augmentation. In case of patients complaining of chest pain, tachypnea and having a strain pattern on ECG suggestive of pulmonary embolism, a computed tomography (CT) angiography was performed.

Patients in group 1 were randomized to receive LMWH prophylaxis with dalteparin sodium (Fragmin – Pharmacia India Private Limited, Gurgaon) 2500 IU subcutaneously about 2 hours before surgery, followed by 2500 IU daily subcutaneously in the morning, and those in group 2 did not receive any prophylaxis. Randomization was done by using sealed envelopes provided by Pharmacia and Upjohn. Prophylaxis was continued till postoperative day 6±1. Patients were monitored clinically for the symptoms and signs of DVT. If clinical signs of DVT (pain, swelling, redness) or any other signs suggestive of pulmonary embolism developed before the completion of treatment, Duplex ultrasonography was performed. If a negative result was obtained (no DVT), the prophylaxis was continued until day 6±1. Duplex ultrasonography was repeated on day 6±1 in all the patients. The patients in group 2 were monitored in an identical fashion for thromboembolic events. Patients with confirmed DVT and/or pulmonary embolism were to be treated with conventional therapy after stopping prophylaxis, at the discretion of the treating physician. Hematological investigations done following surgery in all the patients on day 0, 1, 3, and 6±1 were: hemoglobin, hematocrit, platelet counts, renal function tests and prothrombin time. Concomitant medications administered during the treatment period were recorded. Drugs containing acetylsalicylic acid, dextran, NSAIDs, dipyridamole, ticlopidine and clopidrogrel were not administered. The occurrence of bleeding, blood transfusion requirements, re-operation due to bleeding, and an assessment of allergic or anaphylactic reactions, were also recorded.

Sample sizes were calculated on the basis of expected reduction in the incidence of confirmed DVT (based on literature) from 6%–9% in the observation group to 2–5% in the prophylaxis group. To detect this difference with a type I error of 0.05 and power of 80%, the sample size was calculated to be 189 patients.

Results

By the end of January 2004, a total of 132 patients were screened of whom 99 patients (65 men; mean age 53.3 years) were included in the study as they fulfilled the inclusion criteria. Fifty-one patients were randomized to group 1 and 48 patients to group 2. The two groups were comparable with respect to age and sex. The average weight was 57.8 kg and the average height was 173 cm.

The types of surgery done were abdominoperineal resection in 46 (46.5%) patients, anterior resection in 38 (38.4%), laparoscopic anterior resection in 6, total proctocolectomy in 3, laparoscopic abdominoperineal resection in 3; pelvic exenteration, revision anterior resection, and subtotal colectomy were done in one patient each. The average blood loss in group 1 was 506 cc as compared with 445 cc in the control arm (group 2). At the end of recruitment of 99 patients, no instances of DVT were documented in either group, and no cases of pulmonary embolism were seen. There were no postoperative deaths in either group. There was no increase in blood transfusion requirements postoperatively nor was re-operation required for complications related to bleeding. No allergic or anaphylactic reactions were noted in group 1 patients.

Since no DVT was detected in 99 patients, a review meeting was held to decide whether the trial should be continued with the same design and power. It was decided to terminate the trial since the anticipated incidence of DVT may have been overestimated.

Discussion

The risk of postoperative venous thromboembolism is reported to be twice as high in patients with cancer compared to those without cancer undergoing comparable surgery.8 This risk is also high in patients undergoing surgery for colorectal cancer as compared to patients having an abdominal surgery without malignancy (9%–15% vs. 6%–9%).9 Thromboembolic complications are responsible for about half the deaths following elective colorectal surgery.10 The highest rate (1.8%) of fatal pulmonary embolism was reported in patients following colorectal surgery, with a 3.3-fold increase over the rate for all surgical patients in a retrospective 10-year review from Switzerland.11 This increased risk has been attributed to a number of factors such as malignancy-related hypercoagulable state of cancer patients, postoperative infectious complications, the lithotomy position, prolonged surgery and the pelvic dissection undertaken.10

There are very few studies on the incidence of DVT in Asian patients with general surgical problems/cancer. Most of these studies have reported a lower incidence compared to that in the West. Lee et al12 in a study on Chinese patients undergoing colorectal surgery without DVT prophylaxis demonstrated asymptomatic calf vein thrombosis in 41.7% of patients using serial Duplex ultrasound studies. Only 1 out of 20 patients required anticoagulation due to propagation of thrombus.
No data exist on the incidence of DVT in Indian patients with colorectal cancer. There is only one study on the Indian population involving a general surgical procedure. Stein et al in their prospective randomized study of 104 patients undergoing orthopedic limb surgery found the incidence of DVT to be 43.2% in patients receiving prophylaxis versus 60% in those who did not. Jain et al in a prospective study found DVT in only 2 patients who had undergone hip surgery. None of their patients received DVT prophylaxis.

One possible limitation in our study was that screening for DVT was performed by Duplex ultrasonography—a technique that is now known to have a lower sensitivity (especially for detecting DVT below the knee) than some of the more recent investigative modalities. However, at the time of the design and performance of the trial, Duplex ultrasonography matched venography (the gold standard for the detection of DVT at that time) in terms of sensitivity and specificity as far as proximal DVT was concerned. Besides, it avoided the known complications associated with venography such as thrombophlebitis, and the risk of anaphylactic reaction to the dye.

One factor that could have contributed to the absence of DVT in our study was that the patients included in our study were candidates for curative surgery, i.e., they were more likely to have early cancers and were ambulatory, thus obviating an important high-risk factor for DVT. However, the impact of genetic factors on the low prevalence of DVT in Asians cannot be ruled out. Stein et al attributed this to a lower prevalence of the thrombophilic trait known as factor V Leiden mutation and possible lower mean levels of fibrinogen, factor VIIc, and factor VIIIc. Another thrombophilic genetic variant, thrombin gene G20210A, is associated with increased plasma prothrombin and may also be less prevalent in Asians.

To conclude, this randomized study aimed to assess the role of LMWH in patients with colorectal cancer in India undergoing curative surgery, but was prematurely terminated because of an unexpectedly low incidence of DVT in these patients. Further studies are needed to confirm this low risk of DVT among surgical patients in India.

References


Correspondence to: Dr Shukla, Associate Professor, Department of Gastrointestinal Surgical Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India

E-mail: pjs@doctors.org.uk

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