The Use of Enoxaparin to Prevent Venous Thromboembolism in Patients Undergoing Radical Retropubic Prostatectomy: Feasibility and Utility

Kogenta Nakamura, Ali Kasraeian, Saif Yacoub, John Pendleton, Satoshi Anai, Charles J. Rosser

Division of Urology (KN, SY, JP, SA, CJR), University of Florida, Jacksonville, and Department of Urology (AK), University of Florida, Gainesville, Florida, USA

ABSTRACT

Objective: To assess the utility of enoxaparin in prevention of venous thromboembolism (VTE) in men poorly compliant with pneumatic compression stockings (PCS) in the immediate postoperative period after a radical retropubic prostatectomy (RP).

Materials and Methods: This retrospective study included 47 men who underwent RP at an inner-city tertiary care hospital. All patients were started on enoxaparin 40 mg subcutaneously 6-8 hours postoperatively and daily while hospitalized. Preoperative, operative, and postoperative data were collected and analyzed. Median follow-up was 18 months.

Results: Median patient age was 64 ± 7 years, median prostate-specific antigen level was 4.9 ng/mL and median prostate biopsy-determined Gleason score was 6. Forty-one men (87%) underwent a pelvic lymph node dissection. Median operative time was 181 minutes (range 164-450 minutes). Median estimated blood loss was 700 mL. Approximately 36% of the men wore PCS the recommended > 19 hours/day. On average PCS were worn 10.3 ± 7.5 hours/day. Postoperative complications were not increased in this cohort. Two patients developed pulmonary embolism requiring long-term anticoagulation. There were no mortalities.

Conclusions: In men non-compliant with PCS, initiation of enoxaparin in the immediate postoperative setting was well-tolerated and maintained a low (4%) rate of VTE. Thus, enoxaparin may be useful in adjunct with PCS in these patients.

Key words: enoxaparin; prostatectomy; prostate cancer; venous thrombosis; pneumatic compression stockings

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INTRODUCTION

In the US, radical prostatectomy (RP) is the most common treatment for localized prostate cancer (1) and results in durable, disease-free survival with few complications (2,3). The way we currently perform anatomic RP is due in part to the extensive research and operative experience of a select group of practiced urologists who have refined this procedure. For example, following adoption of the meticulous dissection technique reported by Walsh et al. (4), physicians reported a decrease in blood loss, lower rates of positive surgical margins, and a decrease in postoperative morbidity (e.g., incontinence and erectile dysfunction). The most common cause for death in the immediate postoperative setting is from a venous thromboembolism (VTE): deep venous
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Thromboembolism or pulmonary embolism. The incidence of VTE after RP is 1-3% (5,6).

Lower rates of VTE events after RP in men who wear pneumatic compression stockings (PCS) has been demonstrated clearly by previous research (7,8). The efficiency of PCS is directly related to the time they are worn. Westrich & Sculco reported that patients must wear PCS ≥ 19 hours/day after major surgery as an inpatient in order for them to be efficacious (9). But what of the men who are not compliant with wearing PCS? Could we alleviate their potential risk of developing a VTE without causing an increase in complications if we initiated enoxaparin in the immediate postoperative period? Herein, we present the results of 47 men who underwent RP for localized prostate cancer and were at high risk of developing VTE who were treated prophylactically with subcutaneous enoxaparin.

MATERIALS AND METHODS

Study Population

The study included the first 51 consecutive patients with localized prostate cancer who underwent anatomic RP performed at the University of Florida & Shands Jacksonville from October 2003 to December 2005. All data needed for this study was collected and recorded as part of a standard-of-care for these patients. In 2006, Institutional IRB approval was obtained to examine the medical records and gather the pertinent information.

Pretreatment evaluation included medical history, physical examination with digital rectal examination, measurement of initial prostate-specific antigen (PSA) level, and measurement and determination of Gleason score by prostate needle biopsy. Different laboratories were used to measure PSA of different patients. Further evaluations with bone scan or computed tomography were done according to the preference of the treating urologist.

Patients underwent an anatomic RP utilizing a 10 cm infraumbilical midline incision for optimal exposure. Furthermore, the kidney rest on the table was elevated and the table flexed. Median surgical time was 181 minutes (range 164 - 450 minutes).

Tumor Grading and Staging

The 2002 Tumor-Node-Metastasis (TNM) staging system was used for clinical staging (10).

RP specimens were processed as reported previously (11). Although pelvic lymph node dissection can be omitted in patients with a low likelihood of lymph node involvement (< 2% according to Kattan nomograms) (12), the majority of patients (87%) underwent pelvic lymph node dissection for a concomitant protocol assessing the presence of infectious agents in primary prostatic tumors and regional lymph nodes. Lymph nodes removed during bilateral pelvic lymph node dissection were examined either immediately by frozen section and subsequently by permanent sections, or by permanent section only. RP specimens were graded histologically according to the Gleason grading system (13) and categorized pathologically as organ-confined with negative margins (pT2-), positive margins without evidence of extraprostatic extension (pT2+), extraprostatic extension with negative or positive margins of resection (pT3a- and pT3a+, respectively), or seminal vesicle invasion (pT3b) (14,15).

Outcome Assessment

PCS were placed bilaterally on all patients immediately before surgery and continued until their discharge. Approximately 6-8 hours postoperatively, patients were started on enoxaparin 40 mg administered subcutaneously, which was continued daily during hospitalization. Only four (8%) patients required intraoperative blood transfusion. Because of their propensity to bleed in the operating room, these four patients were not given enoxaparin postoperatively and thus are not included in the final analysis. Hospital records of the 47 patients were reviewed for several key outcomes, estimated blood loss, intraoperative complications, length of hospital stay, and postoperative complications.

Follow-up

Patients returned for evaluation 6 to 8 weeks after surgery and at 4 to 6 month intervals thereafter. Follow-up evaluations included PSA monitoring and digital rectal examinations. Biochemical failure was defined as detectable serum PSA (≥ 0.1 ng/mL). No
patient developed a clinical recurrence without a biochemical recurrence. Follow-up information was obtained from each patient's hospital record or by contacting outside physicians or other hospitals. Median follow-up of the cohort was 18 months.

RESULTS

Characteristics of the study population are presented in Table-1. The patients ranged in age from 45 to 74 years; the median age was 64 ± 7 years. Twenty-eight participants (60%) identified themselves as Caucasian, 17 (36%) identified themselves as African Americans, and 2 (4%) identified themselves as being of another race or ethnicity.

Of the 47 men in the study, 13 (28%) underwent a bilateral nerve-sparing RP, 22 (47%) underwent a unilateral nerve-sparing RP, and 12 (26%) underwent a non-nerve-sparing procedure. Forty-one men (87%) underwent a pelvic lymph node dissection. The median estimated blood loss was 700 mL (range = 300-1500 mL).

As assessed from nursing staff records, compliance with PCS was approximately 36% (i.e., 36% of men wore the pneumatic compression stockings ≥ 19 hours per day during their hospitalization). The mean length of time PCS were worn was 10.3 ± 7.5 hours/day.

No intraoperative complications were noted. Seventeen postoperative complications were noted. (Table-2). One patient developed a significant drop in his hemoglobin on postoperative day 1 (from 9.6 grams to 7.2 grams). Enoxaparin was discontinued and hemoglobin stabilized by postoperative day 2 with conservative measures. No patients developed clinical signs or symptoms of a lymphocele. The most severe complication was pulmonary embolism, which occurred in 2 (4%) men. Evaluation of PE included arterial blood gas, EKG, chest radiograph, chest computed tomography with contrast, and lower extremity Doppler. The lower extremity Doppler also assessed the pelvic vasculature. No evidence of thrombosis or lymphoceles was evident in the pelvis. One of these two men had a history of cerebrovascular accident and congestive heart failure. More importantly, the two men with pulmonary embolism had reported persistent, excessive sedentary life style upon discharge from the hospital. There were no deep venous thromboses, cardiac events, cerebrovascular accidents, or deaths in the study cohort.

Table 1 – Clinicopathologic characteristics of study cohort.

<table>
<thead>
<tr>
<th>N of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Median (years)</td>
<td>64 ± 7</td>
</tr>
<tr>
<td>Range (years)</td>
<td>45 - 74</td>
</tr>
<tr>
<td>Race / Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>28</td>
</tr>
<tr>
<td>African American</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Clinical tumor classification</td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>34</td>
</tr>
<tr>
<td>T2</td>
<td>11</td>
</tr>
<tr>
<td>T3</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative PSA level</td>
<td></td>
</tr>
<tr>
<td>≤ 4.0 ng/mL</td>
<td>12</td>
</tr>
<tr>
<td>4.1-10 ng/mL</td>
<td>25</td>
</tr>
<tr>
<td>&gt; 10 ng/mL</td>
<td>10</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>5</td>
</tr>
<tr>
<td>Microscopic disease*</td>
<td>1</td>
</tr>
</tbody>
</table>

*Gleason score not given.

Table 2 – Perioperative complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative</td>
<td></td>
</tr>
<tr>
<td>Delayed bleed</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>2</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
</tr>
<tr>
<td>Bladder neck contracture</td>
<td>10</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
</tr>
</tbody>
</table>

Patients may have more than one complication.
Pathologic outcomes are summarized in Table-3. Seventy-seven percent of the patients had organ-confined disease (pT2). Thirty-four percent of the patients had poorly differentiated tumors (Gleason score 8-10). One patient had positive lymph nodes (non-microscopic disease). Surgical margins were positive in 19%. To date, 4 patients (1 with pN+ disease and 3 with pT3a+ disease with extensive margins) have developed biochemical recurrence.

**COMMENTS**

Enoxaparin is a low molecular weight heparin that has antithrombotic properties. Enoxaparin is indicated for the prophylaxis of deep venous thrombosis, which may lead to pulmonary embolism: in patients undergoing hip replacement, in patients undergoing knee replacement, in medical patients who are at risk of VTE due to severely restricted mobility, and in patients undergoing abdominal surgery who are at risk of VTE (16). Increased age, cancer, pelvic surgery, and extended sedentary periods are associated with a perioperative hypercoaguable state and patients with these characteristics are classified as a medium risk by the Thromboembolic Risk Factor Consensus Panel (16). Thromboembolic events are considered the most important nonsurgical complication following a major urologic procedure (17). One to 3% of contemporary patients undergoing prostatectomy experience a symptomatic VTE (5,6). The most common form of VTE prophylaxis in patients undergoing prostatectomy is PCS (7,8). PCS may only be effective if worn ≥ 19 hours/day (9). For unknown reasons, compliance with wearing PCS was extremely low in our cohort (mean time PCS were worn was 10.3 ± 7.5 hours/day), which is dramatically less than the time needed for greatest effect. Although our patients were non-compliant with PCS, we did not notice an appreciable increase in VTE. This led us to believe subcutaneous enoxaparin may be protective in the postoperative period for patients noncompliant with standard VTE prophylaxis.

The timing of the initiation of VTE prophylaxis may be important as well. Some would argue that in order to prevent VTE, prophylaxis should be started prior to the patient even entering the operating room.

<table>
<thead>
<tr>
<th>Table 3 – Pathologic characteristics of 47 patients undergoing radical prostatectomy and treated with enoxaparin in the immediate postoperative setting.</th>
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</thead>
<tbody>
<tr>
<td>N of Patients</td>
</tr>
<tr>
<td>Prostatectomy Gleason score</td>
</tr>
<tr>
<td>≤7</td>
</tr>
<tr>
<td>8-10</td>
</tr>
<tr>
<td>Pathologic tumor classification</td>
</tr>
<tr>
<td>Organ confined</td>
</tr>
<tr>
<td>Extracapsular</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>Nodal metastasis</td>
</tr>
<tr>
<td>Positive surgical margins</td>
</tr>
</tbody>
</table>

However, half of the clinically recognized pulmonary embolisms occur after hospital discharge and more than seven days after surgery (18). In addition, a study by Kearon and others evaluating the timing of VTE prophylaxis show little difference in efficacy if started preoperatively versus postoperatively (19). We chose to start the PCS therapy prior to surgical incision and continue their use throughout hospitalization.

Overall, morbidity and mortality in our study are similar to outcomes reported in other larger, recent studies (5,20). The most common postoperative complication in the present series was bladder neck contracture (19%). These patients were treated successfully with transurethral incision of bladder neck contracture without an adverse effect on continence. The most common major complication was VTE (4%). Although our cohort was noncompliant with standard VTE prophylaxis, we demonstrated VTE rates that would have been expected in PCS compliant patients by postoperative treatment with enoxaparin. The two patients who developed pulmonary embolisms were treated successfully with six months of anticoagulation therapy without any subsequent sequela.

With the use of anticoagulation in the immediate postoperative period, there is the potential for increased lymphatic drainage after a pelvic lymph node dissection. Catalona and others reported an increased rate of lymphoceles and/or lymphatic drainage (38%) in patients who received heparin prophylaxis before a RP and lymph node dissection.
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(21). This finding was not evident in the present study. In fact, there were no symptomatic lymphoceles or prolonged lymphatic drainage in our cohort. We believe this is due to our meticulous surgical technique while performing the pelvic lymph node dissection, which ensured complete ligation of the proximal and distal lymphatic channels.

We recognize that our study has several limitations. First, this is a small retrospective study conducted by a single surgeon in an inner-city, tertiary care facility. These results may not be extrapolated easily to other surgeons or centers. In addition, this study did not assess a control group of men treated with PCS alone. Furthermore, the sample size was not large and the follow-up was short. Because of these limitations, we urge other large facilities to assess VTE rates following RP or other surgeries. If their VTE rates are above those reported here and in the literature, they should consider the initiation of a clinical trial in which enoxaparin is utilized in the immediate postoperative period.

Deep venous thrombosis and pulmonary embolism are serious complications after RP that are largely preventable. Limited prospective data are available describing the optimal form of prophylaxis in these patients. PCS are the most common form of prophylaxis currently used in this group; however, PCS are reported to be effective only if worn for extended periods throughout the day (i.e., ≥ 19 hours/day). In men non-compliant with PCS, the initiation of enoxaparin in the immediate postoperative setting was well tolerated and maintained a low (4%) rate of VTE. Thus, in the postoperative setting in men non-compliant with conventional prophylactic techniques for thromboembolic events, enoxaparin may be helpful.

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Doctors Kogenta Nakamura and Ali Kasraeian contributed equally to the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES


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Correspondence address:
Dr. Charles J. Rosser
Department of Urology
University of Florida, College of Medicine
Suite N2-3, PO Box 100247, USA
Fax: +1 352 392-4504
E-mail: charles.rosser@urology.ufl.edu

EDITORIAL COMMENT

Venous thromboembolism (VTE) is one of the most serious postoperative complications of radical prostatectomy (RP). Although the rate of VTE events has been decreased in men who use pneumatic compression stockings (PCS) after RP, we still face the patients fail to VTE after RP. The authors showed here that the use of enoxaparin to prevent VTE in patients undergoing RP was well tolerated without any major complications. This is an important study for men non-compliant with conventional prophylactic techniques for thromboembolic events in the postoperative setting. Continued validation to elucidate if the use of enoxaparin in the postoperative period is meaningful for the patients will be critical in the future.

Dr. Hirotsugu Uemura
Department of Urology
School of Medicine, Kinki University
Osaka, Japan
E-mail: huemura@med.kindai.ac.jp
Venous thromboembolism (VTE) is a common complication in patients undergoing surgery and pulmonary embolism (PE) is the most preventable death in patients hospitalized for surgical procedures (1). In particular, VTE is considered the most important nonsurgical complication following major urologic procedures (2). Among patients undergoing major urologic surgery, 1 to 5% experienced symptomatic VTE. However, postoperative deep vein thrombosis (DVT) is often asymptomatic and fatal PE (estimated to occur in 1:500 patients) (3) may be the first clinical manifestation. Therefore, it is inappropriate to rely on early diagnosis of asymptomatic DVT to prevent serious PE. Actually, it is well known that routine ultrasonographic screening for asymptomatic DVT of lower limbs have a low sensitivity and is quite impractical (4).

Most of the information about VTE prevention in this field is derived from patients undergoing open prostatectomy. Other urologic procedures, including major renal surgery and transplantation, radical cystectomy, and urethral reconstruction, are also associated with an increased risk for thrombosis. Instead, transurethral prostatectomy is associated with a low risk of VTE. Studies published in the last decade have shown that changes in surgical care, more rapid mobilization, and possibly greater use of prophylaxis may have reduced the rate of VTE after major urologic procedures, particularly radical prostatectomy, over time. On the other hand, it should be noted that patients undergoing urologic surgery often carry multiple risk factors for VTE, such as malignancy, advanced age, pelvic surgery with lymph node dissection. A recent prospective study, aimed to evaluate incidence and risk factors for clinically overt VTE occurrence in urologic cancer patients (5), reported an incidence < 1%, but the half of the cases were fatal. In this survey, patients received thromboprophylaxis in about 71% of the cases. The most important risk factors for thromboembolic complications were history of previous VTE (OR 6.0), anesthesia > 2h (OR 4.5), postoperative bed-rest > 4 days (OR 4.4) and age ≥ 60 years (OR 2.6).

Data on thromboprophylaxis in urologic surgery are scarce (6); therefore, the optimal approach to thromboprophylaxis in these patients is not known (1). The use of mechanical methods, both graduated compression stockings and intermittent pneumatic compression (IPC), are likely to be efficacious (7). Heparins, both unfractioned and low-molecular weight, have been demonstrated to be efficacious in patients undergoing urologic surgery (8). However, bleeding complication has been a matter of concern in urologic patients receiving pharmacological thromboprophylaxis (9).

In this issue of the Journal, Nakamura et al. reported a retrospective single Centre experience of combination strategy for thromboprophylaxis with both IPC and enoxaparin 4000 U o.d. Although the study presented several limitations due to the retrospective design, to the low number of patients recruited, and to the absence of a control group, it is interesting to note that bleeding complications was limited to one case, so confirming that pharmacological prophylaxis is safe. Another aspect outlined in the study is the difficulty related to the use of IPC. These devices are poorly tolerated by patients, requires an intense nursing care, and their diffusion is limited to few hospitals. Instead, the subcutaneous administration of heparin is easy to manage and well tolerated by patients. Unfractioned heparin (UH) should be administered 2 to 3 times daily and low-molecular weigh heparins (LMWH) once daily. The once daily administration profile and the lower risk of heparin induced thrombocytopenia with respect to UH, have contributed to the diffusion of the use of LMWH.

Radical cancer operations are being performed more frequently than in the past, consequently, the number of patients at high risk of VTE is growing in urologic departments and specific guidelines for thromboprophylaxis should be used in every hospital (1). It is recommended that (1) in patients undergoing major, open urologic surgery prophylaxis with UH 5000 U 2-3 times daily or LMWH > 3400 U once daily should be used. For patients at high risk of VTE such as cancer patients or patients with history of previous VTE, prophylaxis should be continued for 3-4 weeks after hospital discharge (10). For patients with active bleeding or at high risk for bleeding, mechanical prophylaxis should be used until the bleeding risk de-
creases. The combination of mechanical and pharmacological prophylaxis may be more effective than either alone, and should be limited to patients with multiple risk factors of VTE (1). Instead, there is no specific need for thromboprophylaxis other than early mobilization in patients undergoing transurethral prostatectomy (1, 4).

There is good evidence that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective (1), providing an opportunity both to improve patients outcome and to reduce hospital costs.

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Dr. Daniela Poli
Department of Critical Care Medicine
Thrombosis Center
Azienda Ospedaliera Universitaria Careggi
Florence, Italy
E-mail: polida@ao-careggi.toscana.it