Safety of perioperative subcutaneous heparin for partial nephrectomy

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WINSHIP B, PATEL N, NGUYEN L, BHALLA S, SEMERJIAN A, JARRETT T. Safety of perioperative subcutaneous heparin for partial nephrectomy. *Can J Urol* 2015;22(5):7990-7994.

Introduction: *The development of deep venous thrombosis (DVT) or pulmonary embolism (PE) following urologic surgery is a life threatening, but largely preventable complication. Patients undergoing partial nephrectomy are at increased risk for the development of DVT or PE as they often possess multiple risk factors including malignancy, advanced age, and prolonged surgical time. This risk can be significantly reduced by administration of perioperative subcutaneous heparin (SQH), however many surgeons feel this is contraindicated due to potential blood loss and related complications.*

Materials and methods: *The medical records of 293 consecutive patients undergoing planned open, laparoscopic, or robotic assisted partial nephrectomy by a single surgeon over a 7 year period were reviewed. Approximately halfway through the period, the standard DVT prevention practice was changed from sequential compression stockings and early ambulation to include 5000 units of SQH administered 30-60 minutes prior to incision and continuing every 8 hours until discharge.*

Results: *A total of 158 patients received perioperative SQH. There was no significant difference in surgical blood loss, transfusions, operative time, change in pre to postoperative hemoglobin or creatinine, conversion to radical nephrectomy, or duration of stay between the groups. There were no DVTs in either group. There was one PE in the group receiving SQH which was incidentally discovered.*

Conclusions: *Patients undergoing renal surgery for cancer are at increased risk for the development of DVT and PE. Prophylaxis against this serious complication with perioperative SQH is safe in patients undergoing partial nephrectomy despite common surgeon concerns regarding blood loss and related complications.*

Key Words: nephron sparing surgery, partial nephrectomy, thromboembolism prophylaxis

Introduction

One of the most potentially devastating complications following surgery is the development of venous thromboembolism (VTE). VTE refers to both deep venous thrombosis (DVT) and pulmonary embolus (PE) and represents the most common nonsurgical complication after urologic cancer surgery.[1] The incidence of DVT and PE after urologic cancer surgery had been reported as high as 30% and 10% respectively.[2] Fortunately, since the release and widespread implementation of recommendations for routine prophylaxis against VTE, these numbers have improved significantly.[3] Early postoperative ambulation, graduated compression stockings, intermittent pneumatic compression stockings, and perioperative administration of low molecular weight or unfractionated heparin are all methods of prophylaxis against VTE that have been employed singularly or in combination with good results. Studies have demonstrated that the combination of physical and pharmacologic prophylaxis is superior to either modality alone.[4-6]

With contemporary awareness of VTE risk and widespread use of at least some form of prophylaxis during the perioperative period, the VTE rate following radical nephrectomy has been demonstrated to be between 0.24% and 1.5%.[7-10] For patients undergoing partial nephrectomy, the incidence is likely higher. Not only do these patients share the VTE risk factors of malignancy and advanced age with those undergoing radical nephrectomy, they are also subjected to additional risk from longer operative times as the result

Accepted for publication June 2015

Abstract presented at the Mid-Atlantic Section of the AUA 72nd Annual Meeting and abstract published in *Can J Urol* 2014;21(4):7404-7428.

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of a more technically demanding surgery. Additionally, due to the increased concern for bleeding, perioperative pharmacologic DVT prophylaxis such as subcutaneous heparin (SQH) is used in less than 50% of partial nephrectomies.[11]

The purpose of this study was to evaluate a cohort of patients from a single institution undergoing partial nephrectomy in order to determine the safety of perioperative administration SQH for the prophylaxis of VTE.

Materials and methods

After institutional review board approval, we reviewed the medical records of all patients undergoing a planned open, laparoscopic, or robotic-assisted laparoscopic partial nephrectomy at our institution between January 1, 2006 and December 31, 2013 by a single surgeon. Preoperative characteristics including age, gender, body mass index (BMI), previous history of VTE including DVT and/or PE, procedure type, DVT prophylaxis received, preoperative hemoglobin, preoperative serum creatinine, and largest tumor diameter on imaging were recorded for each patient, Table 1. Postoperative characteristics including operative time, warm ischemia time, final procedure type, and estimated blood loss were recorded, Table 2. The postoperative change in hemoglobin was calculated by subtracting the preoperative hemoglobin from the lowest recorded postoperative hemoglobin during the same admission. The postoperative change in serum creatinine was calculated by subtracting the serum creatinine measured on preoperative laboratory evaluation from that recorded closest to time of discharge. Postoperative outcomes recorded included length of stay, readmission within 30 days of surgery, and complications occurring within 30 days of surgery. Length of stay was calculated as the time in days from the date of surgery to discharge. Patients were recorded as having received a transfusion if they were administered any red blood cell transfusion intraoperatively, during the postoperative stay prior to discharge, or during readmission within 30 days of surgery. Number of units transfused in total for the 30-day period were recorded. A patient was considered to have a prolonged postoperative ileus if they had recovered appropriately from surgery in all aspects except lack of evidence of return of bowel function by the end of postoperative day three.

Patients undergoing partial nephrectomy prior to 6/1/2010 were treated with pneumatic compression stockings intraoperatively and postoperatively until time of discharge and were out of bed and ambulating on postoperative day one for VTE prophylaxis. Following this date, unless contraindicated by allergy or coagulation abnormality, all patients undergoing partial nephrectomy received 5000 units of unfractionated heparin 30 to 60 minutes prior to incision and then every 8 hours until time of discharge in addition to pneumatic compression stockings and early ambulation. Surgeries originally planned as partial nephrectomy in which an intraoperative conversion to radical nephrectomy was made were included in the analysis.

We used Student's 2 tailed t- test for continuous variables and x^2 test for categorical variables to assess the difference between groups based on type of DVT prophylaxis. We used Microsoft Excel (Microsoft, Redmond, WA, USA) for all statistical analysis. We considered $p < 0.05$ to be significant.

Results

A total of 293 records were identified and analyzed. One hundred and thirty-five patients did not receive perioperative SQH for VTE prophylaxis. There was no significant difference between the groups at baseline regarding BMI, previous VTE, preop hemoglobin or preop serum creatinine. The group receiving perioperative SQH was significantly older and had a larger average tumor diameter. Over 95% of partial nephrectomies performed in each group were laparoscopic with or without robotic assistance. Nearly 80% of operations in the perioperative SQH group were completed with robotic assistance, compared to only 21% in the other, Table 1.

Perioperatively there was no difference between the groups with regard to operative time, rate of conversion from partial to radical nephrectomy, rate of conversion from laparoscopic to open, estimated blood loss, or preop to postop change in hemoglobin and serum creatinine. The perioperative SQH group did have significantly less warm ischemia time by nearly 4 minutes on average, Table 2.

There were eight patients readmitted within 30 days of surgery. Three were in the SCDs only group, representing two patients with delayed bleed and one with a urine leak. Five were in the perioperative SQH group, three readmitted for delayed bleed and two for urine leak. Postoperative complications including number of patients receiving blood transfusions as well as total number of units transfused were not significantly different between groups, Table 3. Note that in this series, no patient received more than 3 units of PRBCs in the perioperative or postoperative setting. No patients were diagnosed with a DVT during the

TABLE 1. **Preoperative characteristics**

	SCDs only	Perioperative SQH	p value
Total patients	135	158	
Male (%), Female (%)	76 (56), 59 (44)	199 (63), 58 (37)	0.27
Mean +/- SD age	54.7 +/- 11.5	57.4 +/- 12.6	0.05
Mean +/- SD body mass index	30.6 +/- 10.3	29.4 +/- 6.7	0.25
No. previous VTE (%)	0	5	0.10
Mean +/- SD preop serum creatinine (mg/dL)	0.9 +/- 0.2	0.9 +/- 0.3	0.06
Mean +/- SD preop hemoglobin (gm/dL)	13.3 +/- 1.8	13.3 +/- 1.5	0.89
Mean +/- SD tumor size (cm)	2.8 +/- 1.5	3.1 +/- 1.4	0.04
No. surgical approach (%)			
Laparoscopic	100 (74)	27 (17)	
Robotic	28 (21)	125 (79)	
Open	7 (5)	6 (4)	

SCD = sequential compression devices; SQH = perioperative subcutaneous heparin; VTE = venous thromboembolism

TABLE 2. **Postoperative characteristics**

	SCDs only	Perioperative SQH	p value
Operative time +/- SD (mins)	245.1 +/- 55.6	245.6 +/- 57.2	0.97
Warm ischemia time +/- SD (mins)	27.2 +/- 9.1	23.4 +/- 7.9	0.002
No. converted to radical nephrectomy (%)	2 (1.5)	6 (3.8)	0.39
No. converted lap/rob to open (%)	0	1 (0.6)	0.36
Blood loss +/- SD (cc)	162.1 +/- 158.6	173 +/- 162.5	0.51
Postop change at discharge (range)			
Hemoglobin (gm/dL)	2.2 (-0.8-5.4)	2.2 (-0.5-5.8)	0.76
Serum creatinine (mg/dL)	-0.1 (-0.6-0.4)	-0.1 (-0.9-0.4)	0.68

SCD = sequential compression devices; SQH = perioperative subcutaneous heparin

TABLE 3. **Postoperative outcomes**

	SCDs only	Perioperative SQH	p value
Mean +/- SD hospital stay (days)	3.3 +/- 1.3	3.6 +/- 2.3	0.15
No. readmissions – 30 day (%)	3 (2.2)	5 (3.2)	0.62
No. complication (%)	22 (16.3)	32 (20.2)	0.38
Transfusion – pts	12 (8.9)	12 (7.6)	0.69
Transfusion – units PRBCs	20	22	0.87
Pulmonary embolus	0	1 (0.6)	0.32
Urine leak	2 (1.5)	1 (0.6)	0.49
Perinephric hematom	1 (0.7)	3 (1.9)	0.38
Delayed bleed/pseudonaneurysm	3 (2.2)	5 (3.2)	0.62
Atrial fibrillation	0	1 (0.6)	0.32
Ileus	3 (2.2)	9 (5.7)	0.19

SCD = sequential compression devices; SQH = perioperative subcutaneous heparin; PRBCs = packed red blood cells

30-day postoperative period. There was one patient in the perioperative SQH group who was incidentally diagnosed with a pulmonary embolus after undergoing diagnostic axial imaging on postoperative day six to investigate new onset flank pain and hematuria. He was asymptomatic from the PE, but did require endovascular embolization of a renal pseudoaneurysm and ureteral stent placement. Three patients, one in the perioperative SQH group, developed postoperative urine leak requiring placement of a ureteral stent. There were three perinephric hematomas in the perioperative SQH group which required placement of a drain, compared to only one in the no SQH group. A total of eight patients were found to have delayed bleeding (occurring postoperative day five or greater) requiring urgent intervention by interventional radiology for embolization. Five of these were patients who received perioperative SQH and all but one of those were found to have a pseudoaneurysm on angiography. One patient in the SQH group developed new onset atrial fibrillation, which was effectively rate-controlled by the day of discharge with consultation from cardiology. Nine patients in the SQH group had prolonged postoperative ileus which increased the length of their hospital stay. Of note, all the complications experienced in both groups were successfully managed with either conservative, endoscopic or endovascular techniques.

Discussion

We report on the issue of safety of partial nephrectomy in patients receiving preoperative pharmacologic venous thromboembolism prophylaxis. Although heparin is a potent anticoagulant and it is intuitive to avoid such agents prior to a procedure with the potential for large blood loss, this series demonstrates SQH can be administered safely prior to partial nephrectomy. Despite a significantly larger average tumor size and thus a larger nephrectomy bed defect, there was no difference in intraoperative blood loss, postoperative hemoglobin change, units of blood transfused, or transfusion rate between patients receiving no pharmacologic prophylaxis and those receiving SQH. There are numerically greater numbers of perinephric hematomas, delayed bleed, and ileus in the perioperative SQH group, however these are not statistically significant relative to the mechanical prophylaxis only group and any difference is likely related more to the significantly larger tumor size between the groups than heparin anticoagulation effect. Overall, postoperative complications were rare and not significantly different between groups. This mirrors similar data from a study of radical prostatectomies demonstrating preoperative administration of 5000u of SQH has no significant impact on intraoperative blood loss.[12] In addition, a recent report by Kefer and colleagues[13] demonstrated no difference in postoperative transfusion or complication rates following partial nephrectomy between patients on chronic anticoagulation bridged with enoxaparin for the perioperative period and patients receiving no form of perioperative anticoagulation.

In addition to no increase in blood loss related complications, there was also no difference between groups with regard to operative time, rate of conversion to radical nephrectomy or open procedure, or postoperative length of stay. We did find a significantly shortened warm ischemia time in the SQH group. This is likely related to the surgical approach. Seventy-four percent of the mechanical prophylaxis only group had a partial nephrectomy completed in a purely laparoscopic fashion, while 79% of the SQH group had procedures with robotic assistance. It is our experience that the increased ease of laparoscopic suturing afforded by the surgical robot significantly decreases the time which renal vessel clamping is required and this is reflected in the decreased warm ischemia time. This finding is supported in studies comparing laparoscopic and robotic assisted partial nephrectomy.[14,15]

Warm ischemia time for a purely laparoscopic approach may be longer relative to one with robotic assistance, however in our study this does not translate into a clinically significant effect on postoperative renal function. There is no significant difference in preop to postoperative creatinine between the groups. In fact, we demonstrate an average decrease in creatinine level from preop to postop in both groups. However, we do not suggest that partial nephrectomy results in improved renal function. This phenomenon likely represents the effects of postoperative hydration, but does support the minimal impact of a partial nephrectomy on renal function regardless of approach.

The greater proportion of robotic cases in the group receiving SQH draws into question the ability to fairly draw conclusions relative to the group receiving mechanical prophylaxis only. However, it is our opinion that the addition of robotic assistance only modestly changes the procedure relative to a purely laparoscopic approach. At our center both techniques are started in the same fashion with laparoscopic mobilization of the colon and dissection of the renal hilum without robotic assistance. The robot is docked with the patient only just before application of the vascular clamps in preparation for removal of the tumor and repair of the nephrectomy bed. Laparoscopic suturing is significantly enhanced with robotic assistance and results in decreased average

warm ischemia time as discussed above. The current study demonstrates no significant difference in blood loss between groups. Some studies have suggested faster repair of the tumor bed leads to decreased intraoperative blood loss.[14,15] However, the renal vessels remain clamped during this portion of the case and there is relatively little blood loss. Benway and colleagues demonstrated the blood loss difference between the robotic and laparoscopic approaches to be statistically significant, however this was an average of only 46 cc and there was no significant difference in postoperative hematocrit change.[14] Although the greater proportion of robotic assisted cases in the SQH group may mask a greater blood loss relative to the mechanical prophylaxis group, this is not likely to be clinically significant.

There was no significant difference in VTE events between the two groups with no diagnosed DVTs and only one PE. This translates to an overall VTE event rate of 0.3%. Although this fits within the published range of VTE following radical nephrectomy, we recognize that both the published and our own data demonstrate some degree of under-diagnosis of VTE. Many patients are asymptomatic, especially in the immediate post-operative setting, only develop symptoms long after discharge, and may seek care though another provider at another institution for an issue seen as unrelated to their renal surgery. It is not surprising that the only PE in our series was diagnosed incidentally on imaging obtained for another purpose. We cannot demonstrate the efficacy of SQH as a prophylactic strategy against VTE relative to mechanical interventions only given our sample size. However, numerous studies across multiple surgical disciplines have established that the addition of pharmacologic prophylaxis to mechanical interventions is superior to mechanical interventions alone.[4-6]

Conclusion

Deep venous thrombosis and pulmonary embolus are serious but potentially preventable post-surgical complications. The safest and most efficacious method of VTE prophylaxis should be employed throughout the perioperative period, especially in patients undergoing surgery for urologic malignancy. For partial nephrectomy this should include not only mechanical prophylaxis, but pharmacologic prophylaxis as well. □

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