Surgical Operative Time Increases the Risk of Deep Venous Thrombosis and Pulmonary Embolism in Robotic Prostatectomy

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ABSTRACT

Background and Objectives: To evaluate the effect of operative time on the risk of symptomatic venous thromboembolic events (VTEs) in patients undergoing robot-assisted radical prostatectomy (RARP).

Methods: We reviewed the records of all patients at our institution who underwent RARP by a single surgeon from January 2007 until April 2011. Clinical and pathologic information and VTE incidence were recorded for each patient and analyzed by use of logistic regression to evaluate for association with VTE risk. All patients had mechanical prophylaxis, and beginning in February 2008, a single dose of unfractionated heparin, 5000 U, was administered before surgery.

Results: A total of 549 consecutive patients were identified, with a median follow-up period of 8 months. During the initial 30 days postoperatively, 10 patients (1.8%) had a VTE (deep venous thrombosis in 7 and pulmonary embolism in 3). The median operative time was 177 minutes (range, 121–360 minutes). An increase in operative time of 30 or 60 minutes was associated with 1.6 and 2.8 times increased VTE risks. A 5-point increase in body mass index and need for blood transfusion were also associated with increased risk of VTEs (odds ratios of 2.0 and 11.8, respectively). Heparin prophylaxis was not associated with a significant VTE risk reduction but also was not associated with a significant increase in estimated blood loss ($P = .23$) or transfusion rate ($P = .37$).

Conclusion: A prolonged operative time increases the risk of symptomatic VTEs after RARP. Future studies are needed to evaluate the best VTE prophylactic approach in patients at risk.

Key Words: Robot-assisted radical prostatectomy, Prostate cancer, Deep venous thrombosis, Pulmonary embolism, Venous thromboembolic events.

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INTRODUCTION

The Agency for Healthcare Research and Quality has determined that deep venous thrombosis (DVT) and pulmonary embolism (PE) are the most common preventable causes of hospital death and that thromboprophylaxis against venous thromboembolic events (VTEs) should be the top priority for patient safety practices.[1] However, few high-quality studies have investigated venous thromboembolism prophylaxis in urologic surgery, and current prophylaxis guidelines are largely derived from other surgical specialties or retrospective data. In the American Urological Association best practice statement, the authors cite "insufficient outcomes data to support a formal meta-analysis and an evidence-based guideline on the prevention of DVT during urological surgery."[2] Historically, the reported rate of symptomatic VTEs is low in open prostatectomy series,[3] as well as robot-assisted radical prostatectomy (RARP) series.[4] As a result, it is unclear which patients are at highest risk of VTEs developing and who would benefit from medical prophylaxis, given the low incidence of VTEs and possible increase in complications with the use of heparin.[5]

Within the past decade, RARP has become an increasingly common approach for surgical treatment of localized prostate cancer.[6] The median operative time in large series at experienced centers is reportedly between 160 and 210 minutes,[4,7] but there is significant variability in operative time, with some series reporting a median operative time >300 minutes during the initial learning curve for novice surgeons performing robotic techniques.[8] Previous studies have suggested that a longer RARP operative time may lead to increased VTEs.[4] However, because surgical technique, positioning, type of prophylaxis, follow-up regimen, and clinical pathways may influence the develop-

ment of VTEs, it is difficult to evaluate the effect of prolonged operative time from multisurgeon, multi-institutional studies.

The purpose of this study was to evaluate the effect of operative time on the incidence of symptomatic VTEs in patients undergoing RARP performed by a single experienced, fellowship-trained surgeon.

METHODS

After institutional review board approval, we reviewed the records of all patients at our institution who underwent RARP by a single surgeon from January 2007 until April 2011. The surgeon was fellowship trained in urologic oncology and had significant experience in minimally invasive procedures. To account for the possibility that prolonged operative times could be caused by the learning curve or early technical changes in procedure, data from the first year for this surgeon (92 RARP patients) were not included in this analysis. Wilcoxon and t tests were used to evaluate whether there was any differences in operative time or body mass index (BMI) over the time course of the study. Clinical and pathologic information was recorded for each patient. Operative times and estimated blood loss were recorded from anesthesia records. Symptomatic DVT or PE was considered to be associated with surgery if identified within 30 days postoperatively. All RARP patients are routinely seen in the clinic for follow-up at 1 week and 6 weeks after surgery.

Before induction of anesthesia, all patients had serial compression devices and compression stockings placed. Surgery is performed in the Trendelenburg position, with standard lymph node dissection (obturator dissection) according to risk stratification and discussion with the patient and attending physician. Ambulation beginning on postoperative day 1 is encouraged in all patients, and discharge from the hospital occurs on the afternoon of postoperative day 1 for most patients. Beginning in February 2008, a single dose of 5000 U of unfractionated heparin was administered before skin incision. Patients with a history of VTEs were counseled and treated individually according to risk stratification by primary physician and cardiology consultation. Six patients with a distant history of DVT received a single dose of 5000 U of unfractionated heparin before surgery, and 3 patients received additional low–molecular weight heparin for 5 days after the procedure as VTE prophylaxis.

The Fisher exact test was used to evaluate differences in incidences of VTEs among groups. Univariate and multi-

variate logistic regression analysis was performed to evaluate for an association of clinical and pathologic factors and VTE development within 30 days of surgery. A two-sided $P < .05$ was considered statistically significant. All analyses were performed with SAS statistical software, version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 549 consecutive patients were identified for inclusion in our study. The clinical and pathologic characteristics are summarized in **Table 1**. The median follow-up duration was 8 months (range, 1–48 months). Pelvic lymph node dissection was performed in 71 of 549 patients (12.9%). Blood transfusions were required in 6 patients (1.1%) intraoperatively or while hospitalized after surgery.

During the initial 30 days postoperatively, 10 patients (1.8%) had a VTE (DVT in 7 and PE in 3). DVT was diagnosed by duplex ultrasonography, and PE was diagnosed by computed tomography angiography for all patients. All VTE patients were treated initially with low–molecular weight heparin and transitioned to oral anticoagulation when appropriate. During their initial hospitalization, 4 patients were diagnosed with a symptomatic VTE whereas 6 patients were diagnosed as outpatients. No patients died as a result of VTEs.

Univariate and multivariate predictors of symptomatic VTEs are shown in **Table 2**. Operative time and BMI were significantly associated being diagnosed with symptomatic VTEs ($P = .03$ and $P = .02$, respectively). The median operative time was 177 minutes (range, 121–360 minutes). An increase in operative time of 30 minutes and 60 minutes was associated with 1.6 times (confidence interval [CI], 1.1–2.4) and 2.8 times (CI, 1.3–5.9) increased VTE risks, respectively. The median BMI was 28.9 (range, 20.1–46.3). Patients who had 5- and 10-point increases in BMI had 2.0 times (CI, 1.1–3.6) and 4.0 times (CI, 1.2–13.0) increased risks of VTEs developing, respectively.

There was no significant difference in operative time over the time of the study when we compared the first and fourth quartiles ($P = .55$) or when we compared patients who had surgery in 2007 versus 2011 ($P = .52$). In addition, BMI was not different in the first versus fourth quartiles ($P = .45$) or patients who had surgery in 2007 versus 2011 ($P = .26$). There was no association of DVT/PE events with positive surgical margins ($P = .61$).

To stratify a patient's risk for symptomatic VTEs, we considered the following 3 risk factors: blood transfusion, top

Table 1.
Clinical and Pathologic Characteristics

	No VTE	VTE
No. of patients (%)	539 (98.2)	10 (1.8)
Age [median (range)] (y)	59.4 (40.2–77.1)	59.8 (54.4–68.1)
Prior history of DVT/PE [n (%)]	8 (1.5)	1 (10.0)
EBL[a] [median (IQR[a])] (mL)	150 (100–150)	125 (100–150)
Smoking history [n (%)]		
Never	304 (56.4)	4 (40.0)
Current	64 (11.9)	0 (0)
Past	171 (31.7)	6 (60.0)
ASA[a] score [n (%)]		
1	39 (7.2)	0 (0)
2	448 (83.1)	10 (100.0)
3	50 (9.3)	0 (0)
4	2 (0.4)	0 (0)
Clinical stage [n (%)]		
T1c	470 (87.2)	9 (90.0)
T2a	63 (11.7)	0 (0)
T2b	3 (0.6)	0 (0)
T2c	3 (0.6)	1 (10.0)
T3	0 (0)	0 (0)
T1a	0 (0)	0 (0)
Pathologic stage [n (%)]		
T1c	0 (0)	0 (0)
T2a	79 (14.7)	1 (10.0)
T2b	4 (0.7)	1 (10.0)
T2c	377 (69.9)	7 (70.0)
T3a	60 (11.1)	1 (10.0)
T3b	18 (3.3)	0 (0)
T4	1 (0.2)	0 (0)
Gleason score on biopsy [n (%)]		
6	310 (57.6)	6 (60.0)
3 + 4	146 (27.1)	2 (20.0)
4 + 3	35 (6.5)	1 (10.0)
8	34 (6.3)	1 (10.0)
9	12 (2.2)	0 (0)
10	2 (0.4)	0 (0)
Pathologic Gleason score [n (%)]		
6	168 (31.2)	7 (70.0)
3 + 4	265 (49.2)	2 (20.0)

Table 1. (continued)
Clinical and Pathologic Characteristics

	No VTE	VTE
4 + 3	64 (11.9)	0 (0)
8	23 (4.3)	1(10.0)
9	18 (3.3)	0 (0)
10	1 (0.2)	0 (0)

[a]ASA = American Society of Anesthesiologists; EBL = estimated blood loss; IQR = interquartile range.

quartile of operative time, and BMI. Most patients, 321 of 547 patients (58.7%), had no risk factors, with an incidence of symptomatic VTEs of 1 in 321 (0.3%) compared with 226 of 547 patients (41.3%) who had at least one identified risk factor, corresponding to a symptomatic VTE incidence of 9 in 226 (4.0%).

In the patients who received unfractionated heparin before surgery, there was no significant increase in estimated blood loss ($P = .23$) or transfusion rate ($P = .37$). Heparin prophylaxis was not associated with a significant risk reduction in VTE rate.

DISCUSSION

This study has identified longer operative time, increased BMI, and receiving a blood transfusion as risk factors associated with the development of symptomatic VTEs. In an attempt to minimize the confounding effect of different techniques or clinical pathways associated with VTE development, we have performed our study using data from a single fellowship-trained urologic oncologist and excluded his initial 100 RARPs. Although the incidence of VTEs in patients undergoing RARP appears low and heparin prophylaxis may not advisable for all patients,[4] physicians performing RARP should take into account the patient risk factors to consider individual prophylaxis.

Over the past decade, RARP has become the dominant approach for radical prostatectomy in the United States, and it is increasing in popularity worldwide.[9] There is considerable variability in the length of operative time among patients and among surgeons, especially early in the surgeon's RARP experience.[8,10] Although increased operative time is known to increase the overall cost and risk of complications,[11,12] less is known about how operative time increases the risk for VTE development. In a multi-institutional series of 5951 patients undergoing laparoscopic radical prostatectomy or RARP, the incidence of symptomatic VTEs was low overall, at 0.5%, but variable

Table 2.
Univariate and Multivariate Predictors of Symptomatic VTEs

	Univariate Analysis		Multivariate Analysis	
	OR[a] (CI[a])	*P* Value	OR (CI)	*P* Value
Age	1.0 (0.9–1.1)	.82		
ASA[a] score	0.8 (0.2–3.8)	.84		
Race	0.3 (0.0–2.3)			
BMI (per patient)	1.1 (1.0–1.3)	.02	1.1 (1.0–1.3)	.03
History of smoking	1.94 (0.5–7.0)	.62		
Prior history of DVT/PE	7.4 (0.8–65.3)	.07		
Heparin prophylaxis	0.4 (0.1–1.4)	.15		
Statin preoperatively	1.1 (0.3–4.0)	.85		
Transfusion	11.8 (1.2–112.1)	.03	32.2 (2.8–364.1)	.0005
EBL[a]	1.0 (0.97–1.0)	.17		
Increased operative time (30 min)	1.6 (1.1–2.2)	.02	1.6 (1.1–2.2)	.02
Clinical stage	1.3 (0.2–10.6)	.80		
Pathologic stage	0.6 (0.1–5.2)	.69		
Lymph node dissection performed	1.2 (0.1–9.4)	.9		
Cancer recurrence	0.3 (0.1–1.6)	.15		

[a]ASA = American Society of Anesthesiologists; CI = confidence interval; EBL = estimated blood loss; OR = odds ratio.

Table 3.
Selected Series Reporting Symptomatic VTE Risk in Patients Undergoing Prostatectomy

	Approach	No. of Patients	Type	Overall VTE Rate (%)	Associated Factors
Kundu et al,[3] 2004	RRP	3477	Multi-institution, single surgeon	1.3	NR[a]
Beyer et al,[13] 2009	RRP	415	Single institution, multisurgeon	1.9	Prior VTE, blood transfusion, lymphoceles/pelvic vein flow impairment
Secin et al,[4] 2008	RARP, LRP[a]	5951	Multi-institution, multisurgeon	0.5	Operating time, prostate volume, length of stay, prior DVT, reoperation
Eifler et al,[15] 2011	LRP	773	Single institution, single surgeon	0.9	Pelvic lymph node dissection, BMI
Agarwal et al,[7] 2011	RARP	3317	Single institution, multisurgeon	0.2	NR
Patel et al,[18] 2011	RARP	307	Single institution, multisurgeon	0.6	NR
Current series	RARP	549	Single institution, single surgeon	1.8	Operative time, BMI, blood transfusion

[a]LRP = laparoscopic radical prostatectomy; NR = not reported.

among surgeons (0.2%–6.2%) and operative time was associated with increased VTE risk. However, in this study across 13 institutions, it is difficult to exclude the confounding effects of how variables were reported or the effects of multiple different clinical pathways.[4] In our series we have included one surgeon to limit confounding our risk assessment.

The incidence of VTEs in historical series of radical retropubic prostatectomy (RRP) is low, but it appears that the incidence with RARP may be lower (**Table 3**). Possible explanations include increased mobility as a result of less postoperative pain or a lower incidence of lymphoceles because lymphadenectomy is less commonly performed and most RARPs are performed in a transperitoneal fash-

ion. Lymphoceles have been significantly associated with VTE risk in patients undergoing RRP, especially when pelvic vein flow was impaired.[13] In addition, the incidence of reported VTEs with RRP may be higher because many series reporting complications from RRP are reported from periods when the use of mechanical or chemical VTE prophylaxis was not widespread. Furthermore, VTEs are underreported in retrospective series because most events are asymptomatic.[14] For radical prostatectomy, published rates of symptomatic VTEs are generally <2%,[3,4,7,15] which is consistent with our study. These rates are also consistent with the only randomized prospective study, by Beyer et al,[13] who studied 415 patients undergoing RRP with lymph node dissection using duplex sonography preoperatively and at days 8 and 21 postoperatively. The rate of symptomatic VTEs of 1.9% corresponded to a total VTE rate of 7.2%. Interestingly, most developed between days 8 and 21 postoperatively. Although these data confirm the small risk of VTEs after prostatectomy, they also suggest that proper prophylactic treatment of VTEs for RARP would include prolonged treatment for a minority of patients who are at risk. Treatment of VTEs is costly, with some estimates of acute treatment of VTEs in cancer patients >$20,000.[16] Studies have shown cost savings when using prophylactic heparin according to American College of Chest Physicians guidelines,[17] but these recommendations are based on data from other surgical specialties, which may not be applicable to urologic surgery patients.

The risk factors identified from our study include prolonged operative time, BMI, or receiving a blood transfusion, consistent with other series.[4,15,18] Although only 1% of patients in our series required transfusions, we observed that blood transfusion and not simply blood loss appeared to increase the risk of VTEs. This observation is similar to observations in studies of other cancer types that have noted this relationship and found increased risk per unit transfused, suggesting a mechanism from the transfusion itself.[19] Another possible explanation may be that increased bleeding consumes coagulation factors in patients who become symptomatic and undergo transfusion. Other commonly cited risk factors include a history of a VTE, which approached significance on univariate analysis ($P = .07$), but this may have been limited by the number of patients with a prior VTE in this study. Performing pelvic lymphadenectomy was not associated with an increased risk of VTEs—a finding that may be affected by the low numbers of patients undergoing lymph node dissection in this series. Finally, the use of statin medications did not statistically decrease the development of VTEs, as has been suggested in other studies.[20]

Given the low incidence and the large numbers of patients needed to show a risk reduction for symptomatic VTEs, the best method for VTE prophylaxis after RARP remains unknown. However, prolonged treatment of the highest-risk patients may be the most efficacious approach because the risk of VTEs appears to continue for weeks after surgery.[13,21] We did not find a significant reduction in symptomatic VTE rates after treatment of patients with a single dose of unfractionated heparin preoperatively, similar to other series,[13] but heparin use was also not associated with increased blood loss or an increased transfusion rate. Using a simple risk stratification method by grouping patients together if they had a blood transfusion or were in the upper quartile for operative time or BMI, we can identify a group with 9 of the 10 symptomatic VTEs. In addition, for the 321 patients who did not have any of these risk factors, only 1 VTE was identified, which may justify minimal prophylaxis for selected RARP patients. Although these and other risk factors must be validated before acceptance, the findings demonstrate a principle that may allow surgeons to identify which patients are at highest risk for VTEs and treat them accordingly.

Our series is a single-surgeon series from an experienced center but may have several limitations, including the typical biases associated with retrospective studies. Although we did not include the first 100 RARPs in this study, it is probable that the surgeon's technique was still evolving. However, we have shown that there was no difference in operative times from the first patients in this series to the last. In addition, BMI did not change significantly over the period studied, suggesting that there was minimal bias from evolving patient selection. Our incidence is marginally higher than that in other RARP/laparoscopic radical prostatectomy series reporting VTEs, which may reflect differences in risk among populations or improved detection of VTEs because of the stability of our population base, as compared with very large centers. In addition, the low incidence of symptomatic VTEs in RARP patients may affect the results of multivariate analysis and overestimate the effect of certain variables, similar to other studies.[4,15,18] We believe that using a single-surgeon series may help limit the variables that may also affect analyses of multi-institutional series, with different clinical pathways and data collection methods.

CONCLUSION

We have identified prolonged operative time as an important risk factor for VTEs after RARP. Prospective studies are needed and should consider this risk factor to deter-

mine the best risk stratification methods for prophylaxis before RARP.

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