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Venous thromboembolism following minimally invasive surgery among women with endometrial cancer☆

Alexandra H. Freeman [a], Allison Barrie [a], Liisa Lyon [b], Ramey D. Littell [c], Christine Garcia [d], Carol Conell [b], C. Bethan Powell [b,c,*]

[a] Kaiser Permanente San Francisco Medical Center, CA, USA
[b] Kaiser Permanente Northern California, Division of Research, Oakland, CA, USA
[c] Northern California Kaiser Permanente Gynecologic Cancer Program, Kaiser Permanente Northern California, CA, USA
[d] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Virginia, Charlottesville, VA, USA

HIGHLIGHTS

- In contrast to laparotomy, venous thromboembolism (VTE) among women after minimally invasive surgery for endometrial cancer is rare.
- VTE rate after minimally invasive surgery did not differ by mode of thromboprophylaxis received
- Pharmacologic prophylaxis may not be warranted for women undergoing minimally invasive surgery for endometrial cancer

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ABSTRACT

Objective. To determine the rate of venous thromboembolism (VTE) among women undergoing minimally invasive surgery (MIS) for endometrial cancer.

Methods. Women undergoing robotic or laparoscopic hysterectomy for endometrial carcinoma or complex hyperplasia with atypia were identified between January 2009 and 2014 in a community based health care system. Patient data including age, race, cancer stage, grade, procedure type, length of hospital stay, use of prophylaxis, and diagnosis of VTE were collected retrospectively. The primary outcome was the rate of VTE within 30 days following surgery. Fischer's exact tests were performed to evaluate factors associated with VTE.

Results. During the study period, 1433 patients underwent MIS for endometrial cancer, with 20 excluded due to known thrombophilia, VTE history, or long-term anticoagulation. A total of 1413 patients were included (739 robotic and 674 laparoscopic cases). All women received mechanical prophylaxis per hospital policy and 61% had additional pharmacologic prophylaxis. The rate of VTE was 0.35% (5/1413), which did not differ among those who received pharmacologic compared to mechanical prophylaxis (0.23% [2/865] versus 0.55% [3/548] respectively, $p = 0.38$). No factors were associated with increased risk of VTE due to the low event rate.

Conclusion. VTE in patients undergoing MIS for endometrial cancer was very low irrespective of the mode of prophylaxis received in this large cohort. National guidelines for VTE prophylaxis need to differentiate the low risk associated with MIS surgery from the risk associated with laparotomy for endometrial cancer. We recommend mechanical prophylaxis is sufficient for these women undergoing MIS.

1. Introduction

Venous thromboembolism (VTE) is a well-known complication of surgical intervention and accounts for the most preventable cause of hospital-related mortality in the United States [1–3]. Risk factors for the development of deep vein thrombosis (DVT) and pulmonary embolus (PE) among women undergoing gynecologic surgery include: malignancy, advanced age, history of prior VTE, varicose veins, race, obesity, type of surgery, and prior pelvic radiation [4]. Mechanical prophylaxis (sequential compression devices [SCDs] and graduated compression stockings [TEDs]) as well as pharmacologic modalities (low molecular weight heparin and low-dose unfractionated heparin) have been utilized to reduce perioperative clot formation after cancer surgery [1,5,6].

Endometrial cancer is the most common gynecologic malignancy with an estimated 54,870 new cases and 10,170 deaths due to disease

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* Corresponding author at: 2350 Geary Blvd (1st floor), San Francisco, CA 94115, USA.
E-mail address: Bethan.Powell@kp.org (C.B. Powell).

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among women in the United States in 2015 [7]. Women with endometrial cancer often have multiple risk factors for the development of thromboembolic disease, including malignancy, obesity, advanced age, and surgical intervention. While open laparotomy remained the gold standard for endometrial cancer staging for many years, laparoscopy and robotic-assisted surgery has evolved such that minimally invasive surgery (MIS) is considered the standard surgical approach for endometrial cancer staging. Compared to laparotomy, MIS has demonstrated fewer complications, lower estimated blood loss, shorter hospital stay, faster return to daily activity, and increased patient satisfaction during the recovery period [8,9]. Further, for oncology patients, robotic surgery compared to traditional laparoscopy has exhibited lower minor complication rates, decreased rate of conversion to laparotomy, less estimated blood loss coupled with shorter operating times and similar length of hospital days [10–12].

The incidence of VTE after MIS compared to laparotomy has not been well established due to the relative paucity of these events. Studies from the general surgery literature suggest that the laparoscopic approach is associated with a lower incidence of clinically relevant thromboembolic events compared to laparotomy [13]. Various publications from the 1980s and 1990s quote a range of VTE events of 17%–40% among gynecologic patients undergoing major laparotomy using noninvasive fibrinogen uptake tests without prophylaxis [1,6,14,15]. The diagnosis by fibrinogen uptake tests, however, exaggerates clinically significant VTE events. When relying on clinically apparent VTE, Clarke-Pearson reported on an overall incidence of 8.4% among women undergoing abdominal surgery for endometrial cancer and 4.2% in those not receiving heparin, most using just TEDs [16]. The more recent Gynecologic Oncology Group randomized trial of laparoscopy versus laparotomy for uterine cancer surgical staging found the combined rate of thrombophlebitis and PE to be 2.7% (14/886) after laparotomy and 2.1% (34/1630) following laparoscopy [8].

While VTE prophylaxis for open surgery is well established, recommendations for VTE prophylaxis for MIS remain controversial. The American College of Obstetricians & Gynecologists (ACOG) recommends that gynecologic patients undergoing MIS should be risk stratified and provided VTE prophylaxis according to those receiving laparotomy [2,5]. Similarly, the most recent 2012 American College of Chest Physicians (ACCP) guidelines risk stratify patients to receive prophylaxis with laparoscopy >45 min and laparotomy >45 min, conferring the same risk classification among these two groups [17]. Given that MIS has become the standard of care for endometrial cancer, understanding the risk of VTE in this patient population is paramount. The aim of this study is to evaluate the rate of VTE within 30 days following robotic-assisted or traditional laparoscopic surgery for endometrial carcinoma.

2. Materials and methods

A retrospective cohort study was conducted among consecutive women who underwent MIS for endometrial cancer between January 2009 and January 2014. Participants were identified by an electronic medical record extraction of all robotic and laparoscopic hysterectomies performed by the twelve gynecologic oncology surgeons at six Kaiser Permanente Northern California (KPNC) centers, including four robotic centers. KPNC is an integrated, closed, community based health care system with all surgical and follow up events captured in the patient's electronic record.

Inclusion criteria were as follows: women undergoing robotic or laparoscopic hysterectomy during the study period for the indication of complex hyperplasia with atypia (CAH) or endometrial carcinoma. KPNC policy requires that all women with CAH or endometrial cancer be referred for gynecologic oncology surgical management. A prior publication demonstrated that 48% of cases in our health care system with a diagnosis of CAH on initial sampling are found to have cancer at hysterectomy and 25% have uterine wall invasion [18]. Due to these findings, all cases of CAH are managed identically to grade 1 endometrial cancer and were included in this analysis. Exclusion criteria were women with known thrombophilia, a personal history of VTE, and those receiving long-term anticoagulation. All women had 30 day follow up so there were no exclusions because of incomplete data. This was an intent to treat analysis of MIS: those patients with conversion to exploratory laparotomy or mini-laparotomy for removal of specimen were included in the final analysis.

The decision regarding the mode of MIS (robotic or laparoscopic) was made by the individual gynecologic oncology surgeon. For those with a preoperative diagnosis of CAH or low grade endometrial cancer, intraoperative frozen section assessment of grade, tumor size >2 cm, and depth of myometrial wall invasion >50% was used to determine whether or not to proceed with lymph node dissection. Among those with high grade lesions or high risk histology such as serous, clear cell or carcinosarcoma, lymph node dissection was routinely performed.

Baseline characteristics including age, race, body mass index (BMI), American Society of Anesthesiologists (ASA) class, surgery type, Federation of International Gynecology and Obstetrics (FIGO) stage, histology, and surgical time were extracted electronically. Operative time was defined as the time of incision to skin closure. Length of stay was defined as same date discharge or date beyond date of admission. Chart review of the integrated electronic health record system was used to collect perioperative data including lymph node counts, conversion to laparotomy or mini-laparotomy, type of perioperative thromboprophylaxis used, estimated blood loss (EBL), blood transfusion, length of hospital stay, and VTE within 30 days following surgery.

Patients were categorized into four prophylactic groups: mechanical prophylaxis with SCDs only, preoperative prophylaxis, preoperative and postoperative prophylaxis, and postoperative prophylaxis only. It is KPNC hospital policy that all patients undergoing surgery receive mechanical prophylaxis with SCDs. Therefore, all patients in this cohort received mechanical prophylaxis at baseline. The placement of SCDs is confirmed during a timeout procedure prior to the beginning of all surgical cases and SCDs remain in place throughout the duration of the procedure and until the patient is ambulatory as per hospital policy. Perioperative decision making regarding the addition and duration of pharmacologic prophylaxis was per surgeon discretion. Preoperative prophylaxis was defined as the receipt of a single dose of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) received prior to surgery. In this group, patients received Enoxaparin 30 mg or 40 mg subcutaneously 1 h prior to the procedure or UFH 5000 units subcutaneously within 1 h of surgery per physician preference. Postoperative prophylaxis was defined as prophylaxis received after surgery and only given during the hospital stay. These patients received Enoxaparin 40 mg once daily or UFH 5000 units subcutaneously every 12 h for the duration of their hospital stay. Extended prophylaxis was defined as LMWH pharmacologic treatment received after surgery that extended beyond the hospitalization. Intraoperative SCD placement and receipt of perioperative pharmacologic prophylaxis was confirmed by chart review on each patient.

The primary outcome was clinical VTE within 30 days of surgery confirmed by Doppler ultrasound, computed tomography, or ventilation-perfusion scan. The VTE rate was calculated with a 95% confidence interval (CI). Demographic and clinical characteristics were tested for association with the development of postoperative VTE. Categorical variables were evaluated using frequencies and proportions and associations were tested with Chi-square and Fisher's exact test where appropriate. Continuous variables were evaluated using means and *t*-test. Medians and quartiles [Q1, Q3] were used to describe continuous but non-normally distributed data and Mann-Whitney U-tests were used for comparisons. The analysis was repeated on a high-risk group, as defined by Sandadi et al., with both BMI >40 mg/kg^2 and surgical time >180 min [19]. Multivariable analysis was not performed due to the low number of VTE events in the cohort. To adjust for nonrandomized treatment groups, a propensity score analysis using