Research Report

Evaluating the risk of post-operative abscess formation following use of hemostatic agents at time of hysterectomy

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ABSTRACT

Objective: At an academic institution in rural Virginia, we noticed a trend of increased readmissions for postoperative pelvic abscesses. The primary study objective was to determine if intraoperative use of hemostatic agents (HA) was associated with postoperative abscess formation in patients undergoing hysterectomy.

Methods: Retrospective chart review identified women who underwent hysterectomy by a Gynecologic Oncologist for any indication at a single institution from January 1, 2019 through December 31, 2019. Patient and surgical characteristics were abstracted and comparisons were made among those who received any HA and those that did not. The relationship between intraoperative HA use and postoperative pelvic abscess formation was determined using multivariate logistic regression. Secondary outcomes evaluated included the presence of other major post-operative adverse events.

Results: 428 hysterectomies were identified with a postoperative pelvic abscess rate of 3.7%. Abscesses were identified in 4 (2.2%) of cases without vs 12 (4.9%) of cases with HA use with a logistic regression model demonstrating no significant difference in the groups (OR = 2.10, p = 0.22). Data showed an increase in presentation to the Emergency Department (ED) (OR = 3.43, p = 0.002 adjusted) and higher odds of readmission within 30 days of surgery (OR = 3.19, p = 0.03) with HA use.

Conclusions: No association was found between HA use and abscess formation; however, data showed HA use was associated with increased odds of presentation to the ED and readmission to the hospital within 30 days of surgery. Given the potential negative impact on patient outcomes, use of these products at time of hysterectomy should be made with careful consideration.

1. Introduction

Nearly 600,000 women undergo hysterectomy annually in the United States. Despite a recent decline in rates, it remains the second most common surgery performed, only behind cesarean section (Whiteman et al., 2008). In fact, the Centers for Disease Control estimate that by the age of 60, one-third of all women will have had a hysterectomy (Centers for Disease Control and Prevention Website, 2015). Nearly 30% of women who undergo hysterectomy will experience at least one complication (Garry et al., 2004). These complications vary based on patient characteristics, surgical indications, the route of surgery and surgical technique. Complications include infection, injury to adjacent organs, bleeding, venous thromboembolism, vaginal cuff dehiscence, and nerve injury (Clarke-Pearson and Geller, 2013). The most common complications are infectious in nature, with rates ranging from about 9 to 13% (Clarke-Pearson and Geller, 2013). Increased blood loss is a well-documented risk factor for post-operative infection (Clarke-Pearson and Geller, 2013).

Hemostatic agents are widely used in surgery to control bleeding and prevent complications associated with intraoperative hemorrhage (Kakos et al., 2016). Use is indicated if bleeding cannot be safely controlled with electrocautery or suturing techniques particularly...
around vulnerable structures such as bladder, bowel, or large vessels (Topical hemostatic agents at time of obstetric and gynecologic surgery, 2020). Utilization has steadily increased since the 1990s. From 2000 to 2010, Wright et al identified an increase in utilization from 28.5 % to 35.2 % among all major general, gynecologic, urologic, cardiothoracic and orthopedic surgeries as a collective. Among hysterectomies, utilization essentially doubled during this period (10.1–21 %) (Wright et al., 2014).

In recent years, hemostatic agent (HA) use at the time of surgery has been identified as a possible risk factor for post-operative infection. While the primary indication for use is uncontrolled bleeding during surgery, which in and of itself is a risk factor for infection, these products also have delayed absorptive properties, which may serve as a nidus for later infection. While use has been well studied in non-gynecologic surgeries, data on gynecologic surgery is limited (Ito et al., 2018).

Few studies have investigated the relationship between use of hemostatic agents and development of postoperative infection, more specifically pelvic abscess formation following hysterectomy. Current literature is mixed. A large retrospective cohort study including 52 Michigan hospitals found an increased predicted rate of pelvic abscess with HA use only among robotic-assisted laparoscopic hysterectomies (Harris et al., 2017). This association was not sustained however, when all hysterectomy types were included in analysis. Anderson et al found that among women undergoing open or minimally invasive hysterectomy for gynecologic malignancy, gelatin-thrombin matrix use was associated with an increased risk of pelvic abscess (OR 7.0, 95 % CI 1.5–32.9, p = 0.013)(Anderson et al., 2014). In our own experience in a Gynecologic Oncology practice with a large percentage use of minimally invasive surgery, we noted an increased rate of post-operative pelvic abscess. Given this experience, as well as the conflicting literature findings, we sought to determine the relationship between use of hemostatic agent at time of hysterectomy and development of post-operative abscess among high volume surgeons at a rural teaching institution.

2. Methods

This study was performed as part of a quality improvement effort and therefore met the criteria for exempt review by the institutional review board at the University of Virginia. Retrospective chart review was performed using EPIC to query all hysterectomies performed by five attending gynecologic oncologists at the University of Virginia for any indication over the one-year period between January 1, 2019 and December 31, 2019. We chose to evaluate outcomes among the Gynecologic Oncology department in order to ensure data and outcomes as reflected by high volume surgeons. Furthermore, by including a robust amount of cancer cases in our cohort, we sought to identify differences in outcomes based on indication for hysterectomy. All vaginal hysterectomies were excluded from analysis.

Data were abstracted by review of all clinical documentation in the electronic medical records, including those documents sent and scanned in through outside providers and emergency departments, and data available via the Care Everywhere EPIC function. Patient characteristics included in analyses were age and body mass index (BMI) at time of procedure, race, indication for surgery, and number of prior abdominal surgeries. Abdominal surgeries were defined as any prior surgery requiring entry into the peritoneal cavity, including all laparotomies or laparoscopic/robotic procedures. Surgical characteristics included in analyses were surgical approach, uterine weight, lymph node sampling, estimated blood loss, total operating time, and intra-operative receipt of at least one hemostatic agent. Hemostatic agent use was identified in the surgeon’s operative note as well as the documented intra-operative medication list and served as the primary independent variable for our study purposes. We then compared patient and surgery characteristics among those who received any hemostatic agent to those that did not. Age 65 designates “elderly” and research suggests worse post-operative outcomes in this group, thus it was used as a cutoff for comparing characteristics (Massarweh et al., 2009). Furthermore, it is well documented that increasing BMI also increases surgical risk. Morbid obesity, defined as BMI > 40, is where the increase significantly jumps and is associated with not only increased pert-operative morbidities, but also mortality (Ri et al., 2017). Thus a BMI cutoff of 40 was used for our purposes of comparing characteristics, such that individuals with a BMI of less than 40 were compared to those whose BMI is 40 or greater.

Descriptive statistics were analyzed using the chi square test for categorical variables and confidence intervals were calculated.

The primary outcome of interest was development of pelvic abscess. Pelvic abscess was identified as a diagnosis documented in the medical record and defined as an organized pelvic fluid collection on imaging in conjunction with systemic signs of infection; including fever, chills, malaise, leukocytosis, or localized pain or tenderness. Secondary variables of interest included the presence of other major post-operative adverse events, including post-operative blood transfusion, presentation to the emergency department (ED) within 30 days of surgery, readmission within 30 days of surgery, or reoperation within 30 days of surgery. Multivariate logistic regression was used to calculate odds ratios and 95 % confidence intervals for the association between hemostatic agent use and the development of pelvic abscess and the other secondary outcome variables of interest. All models were adjusted for age, race, BMI, blood loss, uterine weight, surgical approach, number of prior surgeries and OR time. All analyses were conducted using SAS version 9.4.

3. Results

We identified 428 women who underwent hysterectomy over the one-year period. The characteristics of these women, including the indication for surgery, are shown in Table 1. The average age was 58 years (range 29–95 years) and average BMI was 34 kg/m² (range 18–64 kg/m²). The majority of women were white (n = 329, 77 %) and had 0 (n = 158, 36.9 %) or 1 (n = 156, 36.5 %) prior abdominal surgery. Endometrial cancer was the most common indication for hysterectomy (n = 188, 43.9 %) and robotic surgery was the most common surgical approach (n = 217, 50.7 %). Blood loss was less than 250 mL in 82.5 % of cases. Only 3 minimally invasive procedures required a conversion to laparotomy to complete the case. The vast majority of uteri were less than 250 g (n = 353, 82.5 %).

A hemostatic agent was used in the majority of cases, n = 246, 57.5 %. The most commonly used agent was Surgicel powder (n = 160, 37.4 %), followed by Surgicel snow (n = 28, 6.5 %), and Surgiflo (n = 27, 6.31 %). More than one agent was used in 3.3 % of cases (n = 14). Among the full study cohort, patients who received hemostatic agents were more likely to be non-White (66 % vs 55 % p = 0.04), to have undergone open surgery (67 % vs 54 %, p = 0.01), and to experience an estimated blood loss of at least 250 mL (67 % vs 53 %, p < 0.0001) (Table 2).

The overall prevalence of post-operative abscess was 3.7 % (n = 16) within 30 days of surgery. Pelvic abscesses occurred in 2.2 % of women who did not receive a hemostatic agent intra-operatively compared to 4.9 % of women who did receive a hemostatic agent (OR = 2.28, p = 0.16). The logistic regression model demonstrated no association between the use of hemostatic agents and development of pelvic abscess (OR = 2.10, p = 0.22) (Table 3). Similarly, neither blood transfusion nor reoperation within 30 days were associated with use of hemostatic agents (OR = 1.26, p = 0.62 and OR = 0.47, p = 0.54, respectively). However, presentation to the Emergency Department (ED) and readmission within 30 days of surgery were both associated with use of hemostatic agents. The overall prevalence of ED visits was 10.7 % (n = 46). Nine (4.9 %) women who did not receive a hemostatic agent intra-operatively were seen in the ED within 30 days of surgery compared to 37 (15 %) of women who did receive a hemostatic agent (OR = 3.43, p-0.002 adjusted).
Similarly, hemostatic agent use was associated with a three times higher odds of readmission within 30 days (OR = 3.19, p = 0.03). The most common re-admission diagnosis was abscess, n = 16 (61.5 %), followed by gastrointestinal (GI) complications including small bowel obstruction (SBO) or ileus (n = 5, 31.2 %). Other indications for re-admission include pleural effusion, vulvar edema, post-operative anemia requiring transfusion, surgical site infection, and vaginal cuff dehiscence, each with an n = 1.

Four patients required a return to the operating room (OR). Two required surgery during the immediate postoperative period for acute intra-abdominal bleed. No hemostatic agents were used during either of these initial surgeries. For the remaining two return surgeries, one woman was found to have a vaginal cuff dehiscence on exam on post-operative day (POD) #21 from a robotic hysterectomy, and one woman was admitted on POD #10 following robotic hysterectomy with a 7 cm vaginal cuff abscess as well as a sub-umbilical abscess from prior laparoscopic incision site. Given the extent of the umbilical abscess, she was taken to the OR for incision, drainage and debridement of sub-umbilical abscess as well as incision and drainage of vaginal cuff abscess with placement of Penrose drain. Surgicel powder was used at her initial surgery.

### 4. Discussion

In this small study of women undergoing hysterectomy with a high volume surgical practice, we found a significant association between the use of hemostatic agent at the time of surgery and both ED visits and readmission within 30 days, with a three times higher odds of both within 30 days (OR = 3.43 and OR = 3.19, respectively) for those patients who had HA use at the time of surgery. This increase in 30-day readmission is significant in that it represents a definition of poor quality of care, and is deserving of further investigation. While our data did not support our primary hypothesis, that the use of HA would be associated with development of post-operative abscess, it is likely that a review of one year of data was not sufficiently powered to demonstrate a difference. Indeed, we did see a doubling of the abscess rate, though this was not statistically significant in this small series (2.2 % vs 4.9 %, OR = 2.28, p = 0.16).

Additionally, the majority of ED visits were for post-operative fever. Furthermore, the most common indication for admission was for patient management of post-operative abscess. While no association with use of hemostatic agent and abscess formation in particular was identified, our data does support previous studies that have identified a positive association between HA use and an increase in other post-operative adverse events.
Table 3
Estimated risk of post-operative adverse events with use of hemostatic agent.

| Post-operative adverse event | N(%)/w/o HA | N(%)/w/ HA | Odds ratio (95 % CI) – unadjusted | p-value | Odds ratio (95 % CI) adjusted \* | p-value |
|-----------------------------|------------|------------|---------------------------------|--------|------------------------------|--------|
| Pelvic abscess              | 4 (2.2)    | 12 (4.9)   | 2.28 (0.72, 7.19)                | 0.16   | 2.10 (0.63, 6.97)            | 0.22   |
| Blood transfusion           | 8 (4.4)    | 22 (8.9)   | 2.14 (0.93, 4.91)               | 0.07   | 1.26 (0.50, 3.13)            | 0.62   |
| ER within 30d               | 9 (4.9)    | 37 (15.0)  | 3.40 (1.60, 7.25)               | 0.0015 | 3.43 (1.56, 7.56)            | 0.0022 |
| Readmission (30d)           | 5 (2.7)    | 21 (8.5)   | 3.30 (1.22, 8.94)               | 0.02   | 3.19 (1.13, 9.07)            | 0.03   |
| Resorption (30d)            | 3 (1.6)    | 1 (0.4)    | 0.24 (0.02, 2.36)               | 0.23   | 0.47 (0.04, 5.48)            | 0.54   |

*Adjusted for age, race BMI, blood loss, uterine weight, surgical approach, prior surgeries, and OR time.

Harris et al identified an increased predicted rate of hospital readmission as well as an increased predicted rate of re-operation (Harris et al., 2017). Similar to our cohort, the authors note the causes for readmission were frequently for fever and infection. To this effect, with regard to pelvic abscess diagnosis, there is likely some degree of both over- and under-attributed causes of readmission. There are data to suggest that physical hemostatic agents may mimic an abscess on imaging, even in the absence of infection (Behbehani and Tulandi, 2013). Typical presentation of a postoperative abscess includes fever, tachycardia, tachypnea, and abdominal or pelvic pain greater than anticipated in the postoperative period. Abscesses are diagnosed with computed tomography scan or pelvic ultrasound and treated with antibiotics and drain placement if the collection is amenable (Jaiyeoba, 2012). Given the relatively high frequency of other infectious causes of fever, namely urinary tract infection or superficial wound infection, there could certainly be an under-reporting of post-operative abscess in the absence of appropriate imaging.

We must acknowledge that the use of HA in this study was quite high, documented in almost 60 % of cases, a higher rate than seen in prior studies. This increased utilization could potentially be a reflection of the complexity of surgeries performed among Gynecologic Oncologists, or the relatively high percentage of minimally invasive surgeries performed. Wright et al found that individuals undergoing gynecologic and urologic surgery with cancer (OR = 1.42), and those treated by intermediate (OR = 1.09) and high volume (OR = 1.23) surgeons were more likely to receive a hemostatic agent (Wright et al., 2014). Despite this, only 18 % of hysterectomies in our cohort experienced a blood loss of over 250 mL and only 26 % required over three hours of operating time. Stachowitz et al found that physician preference is a central predictor for use of these products rather than documented clinical necessity (Stachowicz and Whiteside, 2020). Utilization of HA in over half of our cohort suggests likely a high frequency of prophylactic use. At this time there is insufficient research to support prophylactic use of HA in gynecologic surgery, and is discouraged by ACOG due to potential risks associated (Topical hemostatic agents at time of obstetric and gynecologic surgery, 2020). As a study aimed at quality improvement noting this rate of HA use offers an area for improving patient directed care.

Hemostatic agents are divided into two main groups according to mechanism of action (Topical hemostatic agents at time of obstetric and gynecologic surgery, 2020). Active agents use human plasma components like thrombin and fibrin and can be used in coagulopathies. As such, they tend to be more expensive. Surgiflo is an active, or biologic agent containing thrombin to activate a local clotting cascade. On the other hand, passive, or mechanical agents are that which promote blood absorption, increase in volume, and creates pressure on the site of the bleeding. Surgicel products are an example of this. They create a mechanical hemostasis with expansion of scaffolding at the tissue level (Cullifer et al., 2020). Different agents vary substantially in cost based on region and hospital contracts, but mechanical agents have the benefit of decreased cost compared to other agents (Cullifer et al., 2020; Pereira et al., 2018). Among our cohort, Surgicel powder was the most commonly used product in 37.4 % of cases, with Surgiflo and Surgicel snow having similar rates of use at 6.3 % and 6.5 %, respectively. Interestingly, at our institution, Surgicel powder is more expensive than Surgiflo by $40-$60 per usage. Cost was therefore an unlikely driving factor in HA choice. In recent literature, costs for mechanical agents range from $20-$400, with porcine gelatin products as the least expensive options (Cullifer et al., 2020). Price-per-use for biologic agent ranges from $100-$500 with the same factors influencing price point by institution (Cullifer et al., 2020). While cost should not influence surgeons’ choice alone, it should be factored into decisions relating to cost conscious care. This study suggests that use of these products could be associated with significant downstream healthcare spending due to ED evaluation and readmission. Cost analysis was not performed in this study related to HA use and postoperative outcomes; however, could be an area of further clinical interest for studies related to quality improvement in patient care.

The authors recognize a number of limitations in our study. The relatively low number of cases when evaluating a relatively rare outcome serves as the major limitation. Pelvic abscesses were identified in 2.2 % of women who did not receive a hemostatic agent intra-operatively compared to 4.9 % of women who did receive a hemostatic agent (OR = 2.10, p = 0.22). Unfortunately, our study was not sufficiently powered to show a significant difference in postoperative abscesses with hemostatic agent use. Based on Mahdi et al. (2014) the overall incidence of post-op abscess (within 30 days of surgery) following hysterectomy for benign disease is about 0.7 % (Mahdi et al., 2014). So using 1 % as the expected incidence of abscesses for non-exposed group, to be powered (80 %) to detect a 3 times increased incidence (3 % in exposed group), we would need N = 1536 (if 1:1 ratio, at least N = 768 in each group). Using the actual ratio of no HA to HA is 1:1.35, we would need N = 1614 total, including N = 927 in HA group and N = 687 in no HA group. Furthermore, degree of surgical difficulty cannot necessarily be accounted for by the variables included alone. An individual’s pelvic anatomy, location and degree of prior scar tissue or adhesions, and ease of uterine extraction are each difficult to capture in a statistical analysis, but could certainly impact outcomes. Also, while use of HA was documented in the operative report, we cannot make assumptions on the quantity that was used and/or left behind for that matter. ACOG recommends using the minimum required amount needed and removing any excess once hemostasis is achieved. It would be quite difficult to determine whether this recommendation was followed. Given the relatively expensive nature of HA, it is reasonable to expect 100 % utilization once a particular agent is opened. Lastly, as in all single institution studies, our cohort was formed from an Academic institution in rural Virginia, and as such could limit the generalizability to other institutions and geographic regions of the country.

In summary, we found that the use of hemostatic agent at time of hysterectomy is associated with an increase in 30-day presentation to the ED and readmission. The study did not find a statistically significant difference in postoperative abscess formation with the use of hemostatic agents, although was insufficiently powered to do so. While there was no difference in abscess rate, hemostatic agent use was associated with other adverse outcomes. As such, use of these products at time of hysterectomy should be made with careful consideration given the potential negative impact on patient outcomes. An evaluation of adherence to appropriate usage, including using the minimum required amount needed and removal of excess product once hemostasis is achieved would be beneficial to determine trends and also allow for educational interventions. With increasing use of hemostatic agents in gynecologic surgery, it would be beneficial to determine trends and also allow for educational interventions.
surgery and the potential for adverse patient outcomes further research is needed to determine implications for patient care. Further large randomized controlled trials should be undertaken to analyze hemostatic agent use in gynecologic surgery.

CRediT authorship contribution statement

Megan Howard: Data curation, Writing – original draft, Writing – review & editing. Jeanine N. Staples: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Samhita Nela-mangala: Data curation, Writing – review & editing. Connell Kling: Data curation, Writing – review & editing. Linda R. Duska: Data curation, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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