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Apixaban versus enoxaparin to prevent venous thromboembolism in post-operative patients with gynecologic cancers at an urban academic medical center

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A B S T R A C T

Objective: A recent clinical trial demonstrated that the use of apixaban was safe and equal to enoxaparin (LMWH) in post-operative gynecologic oncology patients. This study aimed to determine if these findings are applicable in a diverse patient population at a single site urban academic medical center.
Methods: This was a retrospective cohort study of patients who underwent an exploratory laparotomy for confirmed or presumed gynecologic cancer from the years 2017–2023 at a single-site urban academic medical center. Venous thromboembolism (VTE) prophylaxis with LMWH was standard practice at our institution up until January 2021 after which apixaban became standard for post-operative prophylaxis in our division. Baseline demographic and clinical characteristics of patients receiving apixaban post-operatively were compared to the population previously receiving enoxaparin. The primary outcome was a VTE event within 90 days of surgery. Secondary outcomes included major and minor bleeding events.
Results: Two hundred fifteen patients met inclusion criteria, of which 65 were discharged on enoxaparin and 150 were discharged on apixaban. Baseline characteristics in terms of age, race/ethnicity and BMI found no significant difference between the two groups. Rates of any VTE event within 90 days of surgery were similar for apixaban and LMWH (3.33 % vs. 4.61 %, p = 0.6). Secondary outcomes demonstrated that the rate of a major bleeding event in apixaban group was 1.31 % and LMWH group was 3.08 %, ($p = 0.38$). Minor bleeding events in the apixaban group were comparable to the LMWH group (10.60 % vs 10.16 %, p = 0.5).
Conclusions: In this real world, urban setting, for women undergoing laparotomy for gynecologic cancer, apixaban as post-operative VTE prophylaxis showed no increase in VTE events and appeared safe with no increase in bleeding events compared to LMWH. This study adds to the literature demonstrating that apixaban is safe and effective for VTE prophylaxis in our gynecologic oncology patients.

1. Background

Gynecologic cancers make up a significant proportion of all cancers with an estimated 100,000 new cases in the United States each year (American Cancer Society. Cancer facts and figures, 2018). These cancers, including uterine, ovarian, cervical, vulvar, and vaginal cancers, accounted for approximately 32,120 documented deaths in the US in 2018 (American Cancer Society. Cancer facts and figures, 2018). Although the treatment for each type of cancer varies, the majority of women with gynecologic cancer will have surgery at some point in their cancer care. Often, this is a laparotomy including surgical debulking of visible disease. Many of these debulking procedures can be quite extensive, requiring long operative times and length of post-operative immobility. Abdominal surgery alone poses a high risk of venous thromboembolism, and that risk increases in those patients with an underlying malignancy (Barber and Clarke-Pearson, 2017).

Previous studies have shown that VTE occurs in up to 25–38 % of patients with gynecologic cancer (Carrier et al., 2019; Gressel et al., 2021; Gunderson et al., 2014). For women with epithelial ovarian cancer, VTE events are associated with a lower survival (Guntupalli et al., 2020). Additionally, in these women, as disease burden increases, so does the risk for VTE (Barber and Clarke-Pearson, 2017). One study of 2373 patients undergoing surgery for cancer reported an overall death rate of 1.7 % within 30 days of surgery, with 46.3 % of the deaths attributable to venous thromboembolism (Carrier et al., 2019).

There are many potential adverse events to consider in post-operative patients with a presumed malignancy. VTEs pose an increased risk of morbidity and mortality but are a highly preventable

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outcome. Currently, there are numerous interventions and strategies that can be employed to decrease the risk of post-operative VTE including: mechanical prophylaxis, pre-operative pharmacological prophylaxis, post-operative inpatient pharmacologic prophylaxis, and extended duration pharmacologic prophylaxis after hospital discharge (Carrier et al., 2019).

While there are many studies regarding VTE prophylaxis recommendations in post-operative patients, the data specific to those patients with gynecologic malignancies is limited. The current recommendation for women undergoing laparotomy includes 28 days of postoperative prophylaxis with low-molecular weight heparin administered daily (Gressel et al., 2021). While effective, low-molecular weight heparin, enoxaparin, poses some challenges for patient adherence. In addition to a high cost, as the drug is administered subcutaneously, many studies note patient concerns including injection site reactions, pain and bruising (Gressel et al., 2021). Other disadvantages of LMWH which limit its broad use in this population include cost and being contraindicated in patients with renal impairment (Carrier et al., 2019).

Apixaban is a direct oral anticoagulant, (DOAC) which targets Xa as an antagonist. DOACs have important advantages including adherence, oral administration, and convenience (Morimoto et al., 2014 Jul). This drug has been well studied in patients undergoing orthopedic surgery, but only one prior study has prospectively investigated apixaban in this specific patient population of post-operative patients with gynecologic malignancies (Gressel et al., 2021).

While the use of extended post-operative thromboprophylaxis in gynecologic oncology patients is well established, there is a lack of literature comparing LMWH versus DOACs. In this study, we sought to compare the safety and efficacy of low molecular weight heparin with apixaban in our diverse, real world, patient population.

2. Methods

This was a retrospective cohort study of patients who underwent an exploratory laparotomy for suspected gynecologic cancer from 2017 to 2023 at an urban academic medical center. Venous thromboembolism (VTE) extended prophylaxis with LMWH (enoxaparin, 40 mg, SQ, daily) for 28 days after surgery was standard practice at our institution up until January 2021 after which apixaban became our standard. In addition to extended thromboprophylaxis after discharge, all patients received pre- and post-operative subcutaneous heparin and sequential compression devices throughout their hospital admission.

Study approval was granted by the institutional review board. All patients who underwent exploratory laparotomy between January 2017 to June 2023 by a gynecologic oncologist were reviewed. Two cohorts were created, those that were discharged home on LMWH for post-operative venous thromboprophylaxis versus those discharged on apixaban. Exclusion criteria included those previously on apixaban or LMWH at baseline.

Baseline demographic and clinical characteristics of patients receiving apixaban post-operatively were compared to the population previously receiving enoxaparin. Age, BMI, weight and race/ethnicity were characterized. The primary outcome was VTE event within 90 days of surgery. VTE events included deep vein thrombosis (DVT), stroke, and pulmonary embolism (PE). Secondary outcomes included major bleeding event, defined as symptomatic bleeding in a critical area or organ or bleeding that requires transfusion of two units of packed red blood cells, and minor bleeding event, including vaginal bleeding, epistaxis, hematoma or significant bruising. Baseline patient characteristic and outcomes were compared using *t*-test for continuous variables, and chi-square testing or fishers exact test as appropriate for categorical variables.

3. Results

Two hundred fifteen patients met inclusion criteria, of which 65 were placed upon enoxaparin upon discharge and 150 were discharged on apixaban. Exclusion criteria included those previously on apixaban or LMWH prior to surgery. Baseline characteristics in terms of age, race/ethnicity, BMI and types of cancer were similar between the two groups. (Table 1). The majority of patients were treated for uterine or ovarian cancer. (Table 2).

Rates of any VTE event within 90 days of surgery were low, and were similar for apixaban and LMWH (3.33 % vs. 4.61 %, $p = 0.6$) (Table 3). Major bleeding events were similarly rare, occurring in 1.31 % of the apixaban group and 3.08 % of the LMWH ($p = 0.38$) (Table 4). Minor bleeding events in the apixaban group were also comparable to the LMWH group (10.60 % vs 10.16 %, $p = 0.5$). As shown in Table 4, hematomas were found to be more common in the LMWH group (2 % vs 9.23 %, $p = 0.017$), however overall both major and minor bleeding events were similar between the two groups.

4. Discussion

In this real world, urban setting, for women undergoing laparotomy for gynecologic cancer, apixaban as post-operative VTE prophylaxis showed no increase in VTE events compared to LMWH. Additionally, apixaban appeared safe with no increase in major bleeding events compared to the standard of care. There was one significant difference in minor bleeding events with a higher rate of hematomas in the LMWH group compared to the apixaban group. However, the rate was overall very low for both groups. It is unclear whether this difference in minor bleeding is clinically significant.

When reviewing the surgical procedures, this study focused on exploratory laparotomies performed by a gynecologic oncologist at an urban academic center. While most of the procedures were for gynecologic malignancies, there were many with benign final pathology or even other malignant conditions including lymphomas. We acknowledge there are a significant number of benign cases in our study. However, we believe that this case mix reflects the broader population of patients that are seen by a typical gynecologic oncologist in an urban, low-resource setting. These patients are often surgically complex and therefore may also have a higher risk of VTE event. Additionally, this study is limited by further detailing the extent of each surgical procedure and the cancer by histology type, which may be confounding factors.

Our study is strengthened by its diverse population and characteristics such as mean BMI in the obese range, further reflecting the typical American population. There are many risk factors that exist for venous thromboembolism including increasing age, cancer, African American race, personal history of venous thromboembolism, prior pelvic radiation, blood loss and prolonged immobility after surgery (Carrier et al., 2019; Rauh-Hain et al., 2015). This study's patient population had an average BMI was 30 while the original study comparing LMWH and apixaban had an average BMI of 27. Additionally, our study represents a diverse population that is reflective of this city's community.

Recently, Knisley et al from MD Anderson and Floyd et al at University of Colorado, published important studies which validate the safety and efficacy of apixaban in gynecologic oncology. Our study

Table 1
Baseline demographics and clinical characteristics.

		Apixaban (N = 150)	LMWH (N = 65)	p-value
Age (years)		59	63	0.03
Weight (kg)		79.9	79.6	0.85
BMI (kg/m^2)		30.1	30.4	0.79
Race/Ethnicity N (%)	White	83 (55.3)	38 (58.4)	0.69
	African American	57 (38)	21 (32.3)	0.69
	Hispanic	6 (4.0)	1 (1.54)	0.69
	Asian	5 (3.33)	4 (6.15)	0.69
	Other	2 (1.33)	1 (1.53)	0.69

Table 2
Indication for surgery.

Type of cancer N (%)		Apixaban (N = 150)	LMWH (N = 65)
	Uterine	35 (23.3)	31 (47.7)
	Ovarian	53 (35.5)	25 (38.5)
	Cervical	14 (9.3)	0 (0)
Other Gynecologic Malignancies N (%)		14 (9.3)	4 (6.2)
Benign Condition (Suspected Malignancy Pre-operatively) N (%)		34 (22.7)	5 (7.7)

Table 3
VTE events in patients discharged on apixaban versus LMWH.

		Apixaban (N = 150)	LMWH (N = 65)	p-value
VTE Event N (%)	All	5 (3.3)	3 (4.61)	0.6
	DVT	1 (0.006)	1 (1.52)	0.67
	PE	4 (0.0267)	2 (3.08)	0.67
	Stroke	0 (0)	0 (0)	–

Table 4
Bleeding events in patients discharged on apixaban versus LMWH.

		Apixaban (N = 150)	LMWH (N = 65)	p-value
Major Bleeding Events N (%)		2 (1.31)	2 (3.08)	0.38
Minor Bleeding Events N (%)	All	16 (10.6)	9 (10.16)	0.50
	Vaginal Bleeding	10 (6.67)	2 (3.07)	0.53
	Hematoma	3 (2.0)	6 (9.23)	0.017
	Epistaxis	0 (0)	0 (0)	–-
	Significant Bruising	0 (0)	1 (1.53)	0.174

continues to add to the gynecologic oncology literature on this important subject. However, it is important to point out that these two studies demonstrated a predominately Caucasian population, with a range of 73–75 % and 79–89 % in each study respectively, while this paper demonstrates a population that is only about half Caucasian. Our patient population accurately reflects the broader, diverse American population with a focus on inner city community. Additionally, the average BMI of patients in our study is about 30, which is also the average of that in the U.S.. These real-world population statistics are a major strength of this study and underscore its importance and applicability.

VTEs pose an increased risk of morbidity and mortality in gynecologic oncology patients undergoing surgical debulking and are a highly preventable outcome. The recommendation for extended prophylaxis of 28 days post-operatively can pose many challenges to patients, and oral agents such as DOACs may be more practical for many clinical situations. This study adds to the growing literature in gynecologic oncology that apixaban is equally safe and effective compared to LMWH, and may be a more attractive option for patients. The study does have some limitations including the retrospective design and that all patients are from a single institution. Given that our study is retrospective, medication compliance was not able to be measure and reported, but this again speaks to the real-world applicability of our study as in usual clinical practice, medication compliance is not routinely measured. The small sample size also limits our power to detect potential statistically significant yet small differences in this relatively rare outcome. However, despite the potential statistical limitations, our results are reassuring that there is no clinical significance given the small absolute difference in outcomes.

These findings suggest that in our patient population at a single cite urban medical center, apixaban is a safe and efficacious alternative for extended post-operative thromboprophylaxis in patients undergoing exploratory laparotomy for suspected gynecologic malignancy. This data adds to the very limited, yet growing, literature regarding this topic in gynecologic oncology. While extremely well studied in other surgical populations, direct oral anti-coagulants should continue to be further explored in gynecologic oncology. Additionally, further research may explore a standardization of pre-op and post-op risk stratification in this patient population.

5. Conclusion

Apixaban as an extended 28-day thromboprophylaxis for post-operative gynecologic oncology patients appears to be a safe and effective option for our patient population. This study adds to the limited literature regarding thromboprophylaxis in gynecologic oncology. More prospective and retrospective studies are needed to create a culture change in this field, yet apixaban should be strongly considered for this patient population. Shared decision making between providers and patients should be utilized using a cost effective, patient centered approach.

CRediT authorship contribution statement

Victoria Diamond: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Katherine Gerber:** Investigation, Data curation. **Geno Merli:** Writing – review & editing, Conceptualization. **Rebecca Mercier:** Formal analysis, Data curation. **Aaron Shafer:** Writing – review & editing, Supervision, Conceptualization. **Norman Rosenblum:** Writing – review & editing, Supervision, Conceptualization.

Author contribution

All authors made individual contributions to authorship. VD performed the original study design, IRB approval, and draft preparation. KG assisted in data curation and investigation. RM was involved in the original study design as well as the data analysis. GM and NR helped with conceptualization, supervision, and editing. AS helped with formal analysis, final draft review and editing. All authors reviewed and approved the final manuscript.

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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