Original Article

Apixaban vs Enoxaparin for Preventing Postoperative Thromboembolic events in Women Undergoing Surgery for Gynecologic Cancers: A Randomized Clinical Trial Study

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Abstract

Background: Venous thromboembolism (VTE), encompassing deep venous thrombosis and pulmonary embolism, presents a significant clinical risk for women undergoing surgical intervention for gynecologic malignancies. Enhanced prophylactic strategies are vital to mitigating these complications. This study evaluates the efficacy and safety of oral apixaban compared to subcutaneous enoxaparin for postoperative VTE prevention in this high-risk population. **Materials and Methods:** This randomized clinical trial was conducted from March 2022 to March 2023. One hundred eligible patients undergoing gynecologic cancer surgery were randomized to receive either oral apixaban (2.5 mg twice daily) or subcutaneous enoxaparin (40 mg daily). The primary endpoints included the incidence of thromboembolic events and bleeding complications, monitored up to 12 weeks postoperatively. **Results:** This cohort consisted of 48 patients in the apixaban group and 52 in the enoxaparin group. Postoperative complications included vaginal bleeding (8.32% apixaban vs. 3.85% enoxaparin), hematoma (2.15% apixaban vs. 3.85% enoxaparin), and ecchymosis (6.37% apixaban vs. 9.62% enoxaparin). None of these differences achieved statistical significance ($p > 0.05$). Both groups demonstrated comparably high levels of treatment adherence and patient satisfaction. **Conclusions:** Apixaban and enoxaparin demonstrated comparable efficacy and safety profiles in preventing postoperative VTE following gynecologic cancer surgery. Given its oral administration route, apixaban may serve as a feasible alternative to enoxaparin, potentially enhancing patient compliance. Further large-scale studies are warranted to validate these findings.

Keywords: *Apixaban, enoxaparin, gynecology, venous thromboembolism*

Introduction

Venous Thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a critical complication in women undergoing surgery for gynecologic cancers. The presence of gynecologic tumors in the pelvis affects lymphatic drainage, closely linked to the vessels of the lower extremities, resulting in significantly elevated VTE rates compared to those with other types of cancers.[1,2] Incidences of DVT can reach up to 26% in women not receiving treatment, and postoperative PE can occur in as many as 9% of cases.[3] PE is a major contributor to mortality and can lead to death in approximately 18–20% of affected individuals.[4] Additionally, the extensive dissections common in gynecologic surgeries pose a substantial risk for major bleeding.[5]

The financial burden of VTE complications on the healthcare system is considerable, necessitating prolonged anticoagulation treatment and ongoing monitoring for 6 months post-treatment. Recurrent events may require lifelong anticoagulation.[6] Extended periods of anticoagulation therapy create significant strain on healthcare resources due to the need for continuous monitoring and imaging to manage VTE risks. The American Society of Clinical Oncology, supported by the CHEST 2016 guidelines, has set forth guidelines to mitigate these burdens through effective postoperative VTE prophylaxis in oncology patients. These guidelines recommend preoperative heparin, the use of sequential compression devices during surgery, and postoperative thromboprophylaxis with heparin and low-molecular-weight heparin (LMWH), specifically recommending a

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Access this article online

Website: https://journals.lww.com/jnmr

DOI: 10.4103/ijnmr.ijnmr_205_24

Quick Response Code:

How to cite this article: Behnamfar F, Khalili T, Sajjadieh A, Movahedi M, Anaei Z. Apixaban vs enoxaparin for preventing postoperative thromboembolic events in women undergoing surgery for gynecologic cancers: A randomized clinical trial study. Iran J Nurs Midwifery Res 2026;31:725-9.

Submitted: 23-Jun-2024. **Revised:** 25-May-2026. **Accepted:** 26-May-2026. **Published:** 16-Jul-2026.

28-day postoperative regimen with LMWH (enoxaparin 40 mg subcutaneously daily).[7-9]

Despite its benefits in reducing VTE, the application of subcutaneous LMWH has faced challenges, particularly in adherence. Patient grievances often include reactions at the injection site, pain, bruising, bleeding, nausea, vomiting, and costs. Adherence rates to outpatient postoperative thromboprophylaxis are notably low.[10] The inefficacy in adherence to enoxaparin suggests a need for more cost-effective and user-friendly alternatives that could improve VTE outcomes. Oral anticoagulants, like apixaban, could eliminate many adverse effects linked to the subcutaneous administration route.

Apixaban, an oral factor Xa inhibitor, has been investigated for VTE prevention in patients undergoing hip and knee replacement surgeries.[11-13] Its safety and efficacy in both preventing initial VTE and recurrent events in surgical and high-risk cancer patients in outpatient settings have been validated.[14,15] Moreover, apixaban has been identified as a promising substitute for subcutaneous enoxaparin in thromboprophylaxis for women undergoing gynecologic cancer surgery.[16] Yet, studies comparing apixaban with subcutaneous enoxaparin specifically for VTE prophylaxis in abdominal surgeries with gynecologic cancers are lacking.

This study aimed to evaluate the efficacy of apixaban versus subcutaneous enoxaparin in preventing postoperative VTE among women treated for malignant gynecologic neoplasms.

Materials and Methods

This randomized clinical trial (IRCT20231026059897N1) study was conducted from March 2022 to March 2023. Due to the different administration methods (injection vs. oral) and the nature of the surgical intervention, blinding was not feasible. During the perioperative period, patients were approached and provided written informed consent. Participants were randomly assigned in a 1:1 ratio to either oral apixaban (2.5 mg twice daily) or subcutaneous enoxaparin (40 mg daily), using an online randomization tool.[17] Patient evaluations occurred on day 1 (initial dose), day 14 (±3 days), day 42 (±4 days), and day 85 (±10 days) to monitor outcomes. Adherence was tracked through self-reports, study diaries, and checks of pill bottles or syringes. An independent, blinded reviewer—a non-affiliated oncologist—assessed treatment outcomes.

Eligible participants included those with a suspected or confirmed diagnosis of gynecologic cancer undergoing laparotomy. This included individuals with conditions such as pelvic masses, precancerous gynecologic lesions, elevated cancer antigen 125 levels, and vulvar or cervical abnormalities. Confirmed cases had a histological diagnosis validated by pathological review of ovarian, uterine, cervical, or vulvar cancers. Women aged 20–80 years, medically cleared for surgery and able to attend a 12-week follow-up at one of the cancer centers during the enrollment period, were included. Exclusion criteria included a nongynecologic cancer diagnosis prior to surgery, a history of VTE, long-term nonsteroidal anti-inflammatory drug use, concurrent serotonin modulation therapy, severe renal or hepatic conditions, bleeding disorders, or hypercoagulability predispositions.

The endpoint was the occurrence of thromboembolic events, bleeding events, hematoma, and ecchymosis incidents during treatment and at 2, 6, and 12-week follow-ups comparing oral apixaban and subcutaneous enoxaparin. Major bleeding was defined by the International Society on Thrombosis and Hemostasis criteria[18] and included severe scenarios requiring intensive medical intervention. Screening for VTE was conducted using the Wells criteria for DVT[19] and modified Wells criteria for PE assessment tools, with high-risk cases confirmed by venous Doppler ultrasonography and chest computed tomography.[20]

A modified intent-to-treat analysis was performed based on participants who commenced treatment on the first day. For continuous variables, nonparametric median tests or *t*-tests were applied, while Fisher's exact tests or Chi-square tests were used for categorical data. Descriptive statistics and tests for normality were conducted on continuous variables. All analyses used a significance threshold of $p < .05$ and were performed using SPSS software version 22 (IBM Corp, Chicago, USA).

Ethical considerations

This study was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1400.468) Ethical considerations, including confidentiality of participants 'information, getting informed consent of the participants, explanation of the research goals, voluntary participation in the research, permission to leave the study at any time, and trust in using the texts, were taken into consideration. This manuscript has no plagiarism. The results of the analysis were completely honest. Any data fabrication has been avoided.

Results

Between March 2022 and March 2023, a total of 115 patients were considered for the study; however, nine were excluded. Additionally, six patients consented but were not randomized due to reasons such as surgeon's choice, patient preference, inability to follow up, or immediate postoperative complications. Consequently, 100 patients were ultimately included in the study: 48 were administered apixaban and 52 were given enoxaparin. Figure 1 illustrates the selection process for the cohort of women who underwent surgical procedures for gynecologic cancers and participated in the treatment aspect of the study.

The median age of the participants was 54.54 years, with an age range of 20–80 years. Among them, 5 women (5.00%)

were diagnosed with high-stage cancer (stages III and IV), and 45 women (45.00%) had low-stage cancer (stages I and II). There were no significant differences in demographic data between the two treatment groups. In the apixaban group, the median age was 53.00 years (range, 21–80 years) compared to 58.51 years (range, 20–77 years) in the enoxaparin group. Regarding cancer staging, 4.16% (two patients) in the apixaban group and 5.76% (three patients) in the enoxaparin group had high-stage cancers. The median body mass index (BMI), which is the weight in kilograms divided by the square of height in meters, was 26.00 (range, 18.0–30.0) for both groups.

Participants were categorized by the site of confirmed cancer, including uterine, ovarian/fallopian, cervical, vulvar/vaginal, and other types. The distribution of these categories was fairly similar between the two groups, with no statistically significant differences, as indicated by *p* values all above 0.05. Underlying diseases included conditions such as hypertension, diabetes mellitus, hyperlipidemia, hypothyroidism, and other unspecified conditions. Again, the distribution of these conditions was similar between the two groups, with no significant differences indicated by *p* values. Overall, Table 1 suggests that the two groups were well-matched in terms of baseline characteristics, indicating that any differences in outcomes observed in Table 2 are more likely due to the treatment effects rather than differences in initial participant characteristics.

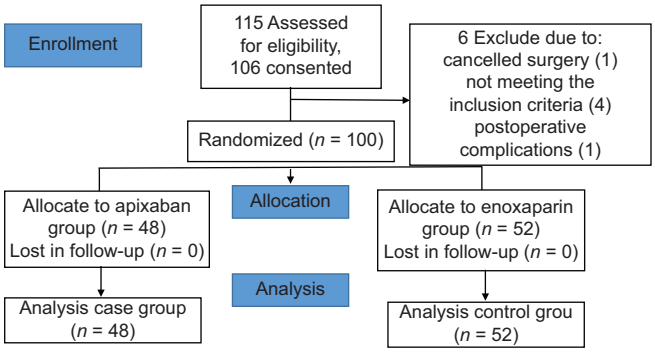

Figure 1: Diagram of patient enrollment, randomization process

Table 2 summarizes the primary and secondary outcomes measured in terms of incidence of venous thromboembolic events, major bleeding, and other clinically relevant nonmajor bleeding events. The incidence of hematomas, ecchymosis, and vaginal bleeding or discharge was higher in the Enoxaparin group than in the Apixaban group, but none of these differences reach statistical significance (all *p* values > 0.5). Overall, Table 2 demonstrates that while there are some differences in the rates of various events between the Apixaban and Enoxaparin groups, none of these differences are statistically significant.

Discussion

Anticoagulants for VTE prevention include novel oral alternatives (e.g., dabigatran, apixaban, rivaroxaban),[21] injectables such as LMWH, and straightforward oral agents such as aspirin. Notably, aspirin is appreciated for its excellent safety profile, ease of administration, affordability, and the absence of a need for blood monitoring.[22] Currently, in both the United Kingdom and the United States, aspirin is used off-label for VTE prevention. However, concerns persist regarding newer, pricier anticoagulants due to their association with higher risks of bleeding and wound complications.[22,23] Consequently, there is an ongoing debate about which medications should be prioritized to effectively balance clinical benefits against costs and bleeding risks.

Our research indicates that oral apixaban could serve as a safe alternative to subcutaneous enoxaparin concerning bleeding risks in women undergoing gynecologic cancer

Table 1: Baseline characteristics of participants

Characteristic	Participants, No. (%)			*p* value
	Apixaban (*n*=48)	Enoxaparin (*n*=52)	Total (*N*=100)	
Age, y*	53.00 (21.00-80.00)	58.51 (20.00-77.00)	54.54 (20.00-80.00)	0.198
Body mass index*	26.00 (18.00-30.00)	26.00 (18.00-30.00)	26.00 (18.00-30.00)	0.617
Confirmed cancer site**				
Uterine	29 (60.41)	33 (63.46)	62 (62.00)	0.753
Ovarian or fallopian	12 (25.00)	11 (21.15)	23 (23.00)	0.647
Cervical	3 (6.25)	2 (3.84)	5 (5.00)	0.581
Vulvar or vaginal	1 (2.08)	2 (3.84)	3 (3.00)	0.605
Other	3 (6.25)	4 (7.69)	7 (7.00)	0.777
Underlying diseases**				
Hypertension	14 (29.16)	11 (21.15)	25 (25.00)	0.355
Diabetes mellitus	9 (18.75)	10 (19.23)	19 (19.00)	0.951
Hyperlipidemia	6 (12.50)	5 (9.61)	11 (11.00)	0.645
Hypothyroid	6 (12.50)	5 (9.61)	11 (11.00)	0.645
Other	1 (2.08)	3 (5.76)	4 (4.00)	0.687

*Median (range), **Number (percentage)

Table 2: Primary and secondary outcomes

Event*	Participants, No. (%)		*p* value
	Apixaban (*n*=48)	Enoxaparin (*n*=52)	
Hematoma	1 (2.08)	2 (3.84)	0.605
Ecchymosis	3 (6.25)	5 (9.61)	0.535
Vaginal bleeding	4 (8.33)	2 (3.84)	0.345

surgery. In this randomized clinical trial, there was no notable difference in major or clinically relevant nonmajor bleeding events between the two groups. Both treatment modalities had comparable adherence rates and adverse event profiles, with participants receiving apixaban reporting significantly higher satisfaction.

Earlier research[1] highlights the necessity of anticoagulation in women undergoing surgical treatment for gynecologic cancers. Contemporary guidelines recommend subcutaneous enoxaparin to mitigate VTE risk; however, issues with adherence due to injection site pain, bruising, and cost have been reported.[24] Given the severe risk that VTE poses to this demographic, it is crucial to employ effective and manageable prophylactic measures to mitigate this risk.

Apixaban is a direct oral anti-coagulant (DOAC) that specifically inhibits factor Xa, which is crucial in the coagulation cascade. Enoxaparin, on the other hand, is a LMWH that also acts on factor Xa but requires subcutaneous administration. Both drugs are effective for thromboprophylaxis.[13,25] Studies in general populations have shown that DOACs such as apixaban may offer comparable or even superior protection against VTE compared to LMWHs, with a similar or reduced risk of bleeding. However, the specific comparative effectiveness in the context of gynecologic cancer surgery is less extensively documented. The differences in patient populations (e.g., cancer patients vs. general surgery patients) may affect both the efficacy and safety profiles of these drugs.[4,12]

Both drugs have risks of bleeding, but DOACs, including apixaban, generally have a more predictable pharmacologic profile, which may reduce the frequency of monitoring compared to enoxaparin. However, in patients with cancer, there is an inherently increased risk of both thrombosis and bleeding, making careful monitoring essential.[13,24]

Apixaban's oral administration can be more convenient for patients compared to the subcutaneous administration of enoxaparin. This might improve compliance, an important factor in long-term prophylaxis. Decisions regarding the use of apixaban vs. enoxaparin should also consider patient-specific factors such as kidney function, potential drug interactions, the patient's ability to comply with treatment, and personal preferences.[24]

Overall, the choice between apixaban and enoxaparin for thromboprophylaxis in women undergoing surgery for gynecologic cancers should be made based on a comprehensive evaluation of the individual patient's risk factors, the specific cancer type and stage, surgical procedure details, and the overall clinical context. In scenarios where clinical trial data are limited, best practice guidelines and expert opinions become particularly valuable.[12,13,24]

This study benefits from its randomized design, which significantly diminishes potential biases and ensures an even distribution of variables such as disease sites, comorbidities, true cancer diagnoses, and median BMI across both intervention groups. Furthermore, the study's methodology, involving a 12-week in-person postoperative follow-up, revealed insight into medication adherence, suggesting potentially higher compliance rates with oral medication compared to those reported for subcutaneous enoxaparin. Moreover, the focus on the safety outcome related to bleeding provides preliminary evidence supporting the effectiveness of apixaban. However, these findings would require validation through a larger randomized controlled trial to be confirmed. A key limitation of this study is the inability to blind participants to their assigned medication, due to the distinctly different administration methods of the drugs, which could introduce bias. This was deemed a necessary compromise to minimize and justify patient risk.

Conclusion

This study indicates that oral apixaban could be a feasible and safer option than subcutaneous enoxaparin for thromboprophylaxis in women undergoing gynecologic surgery. Significantly, patients in the apixaban group reported higher satisfaction levels, and adherence rates were similar between the two treatment approaches within the confines of the controlled trial. Surgeons are advised to maintain the use of effective postoperative VTE prophylaxis in patients at high risk of surgical oncology complications and may consider different thromboprophylaxis options based on their safety profiles at their discretion.

Acknowledgments

Authors would like to thank all participants.

Financial support and sponsorship

Nil.

Conflicts of interest

Nothing to declare.

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