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# Effectiveness of apixaban versus enoxaparin in preventing wound complications and deep venous thrombosis following total knee replacement surgery: A retrospective study

Mohannad Ali Hasan[1] | Malath Azeez Alsaadi[2] | Jameel Tahseen Mehsen[3]

[1]College of Medicine, University of Babylon, Babylon, Iraq

[2]College of Dentistry, University of Babylon, Babylon, Iraq

[3]Hammurabi Collage of Medicine, University of Babylon, Babylon, Iraq

**Correspondence**
Malath Azeez Alsaadi, College of Dentistry, University of Babylon, Hilla, Babil, Iraq.
Email: malathazeez1122@gmail.com

## Abstract

**Background:** Enoxaparin, a thromboprophylactic drug that is widely used for preventing deep venous thrombosis (DVT) and surgical wound complications after total knee replacement surgery, can only be administered subcutaneously. Apixaban, a novel factor Xa inhibitor that could be comparable to enoxaparin, is an oral formulation and thus would be easier to manage.

**Objective:** To compare the thromboprophylactic effectiveness of apixaban and enoxaparin in patients receiving total knee replacements.

**Methods:** In this retrospective, single-institution study, the records of 200 patients who underwent elective total knee replacement surgery were reviewed. Of those, 120 patients had received enoxaparin 4000 IU daily (initiated 6 hours before surgery), whereas 80 had received apixaban 2.5 mg twice daily (initiated 12 hours after surgery), for 21 days. All patients were examined for major and minor surgical wound complications and DVT incidence during their hospital stay and 7-21 days after surgery.

**Results:** No statistically significant differences ($P \geq .005$) were found between the apixaban and enoxaparin groups with regard to minor and major surgical wound complications and DVT incidence. Patients in both groups were comparable in terms of age, hospital stay, and required blood transfusion units. Two enoxaparin-treated patients and one apixaban-treated patient developed DVT (1.5%) during the study period.

**Conclusion:** Oral apixaban is an effective alternative to enoxaparin as a thromboprophylactic drug for patients undergoing elective total knee replacement surgery.

## 1 | INTRODUCTION

Deep venous thrombosis (DVT), which is the formation of a blood clot (thrombus) in the veins, is a life-threatening condition caused mainly by vascular injuries, immobility, and hypercoagulation.[1] It can complicate the outcomes of patients who have undergone orthopaedic surgeries, such as for a total knee replacement or total hip replacement, especially in elderly patients who are more prone to long periods of immobility after surgery and injury.[2,3]

Falck-Ytter et al [4] estimated a 5%-22% DVT incidence following total knee replacement surgery owing to the increasing numbers of such surgeries and the advanced age of the patients. Fortunately, DVT is a preventable complication, and many guidelines have been suggested to lower its incidence.[5]

The prevention of DVT following orthopaedic surgery is based significantly on pharmacological prophylactic treatments, such as anticoagulant drugs, the most commonly used one of which is low-molecular-weight heparin (enoxaparin).[6] Enoxaparin indirectly

  

inhibits factor Xa by accelerating the activity of the antithrombin enzyme, leading to effective thrombus inhibition. It has been proven to be effective and safe after total knee arthroplasty.[6] However, this drug can only be administered via the subcutaneous route, a limitation that necessitates efficient patient compliance and careful monitoring[7] Therefore, the need for an ideal anticoagulant alternative to enoxaparin is still a concern for many orthopaedic surgeons.

Several new oral anticoagulant drugs have been developed in recent years, such as apixaban, a direct factor Xa inhibitor that also inhibits the conversion of prothrombin to thrombin and thereby thrombus formation.[8,9] The main advantage of apixaban is that it is administered orally, thus allowing it to be prescribed outside of hospitals and negating the need for its regular laboratory monitoring. However, not much evidence is available to prove its superiority to enoxaparin as a safe postoperative prophylactic anticoagulant for preventing wound complications and DVT.[8,10]

In our national institutions, enoxaparin is the mainstay prophylactic anticoagulant in spite of the availability of apixaban. This is due to an insufficient number of local studies to compare the drugs, making the judgement of the safety and effectiveness of apixaban difficult to achieve. Accordingly, the aim of this study was to compare apixaban with enoxaparin in terms of their safety and effectiveness in preventing postoperative DVT and surgical complications in patients who have undergone total knee replacement surgery.

**What's known**

- The thromboprophylactic drugs enoxaparin and apixaban are used after major surgeries (eg, total knee replacement) to reduce the incidence of deep venous thrombosis.
- Apixaban is a newly introduced oral anticoagulant drug, but its effectiveness and safety compared with those of enoxaparin have not yet been confirmed in Iraq.

**What's new**

- Apixaban is a safe and acceptable alternative to enoxaparin for patients undergoing total knee replacement surgery, showing equivalent reductions in surgical wound complications and incidence of deep venous thrombosis.

## 2 | METHODS

This retrospective study was conducted at a single hospital (Al-Salam Private Hospital, Hilla city, Iraq), where the records of 200 patients who had undergone total knee replacement surgery at this hospital between October 2018 and March 2020 were reviewed. All surgeries were performed by two surgeons. This study was reviewed and approved by the Institutional Review Board of Al-Salam Private Hospital.

### 2.1 | Patients

Based on the request of the Institutional Review Board, the records of patients who had undergone total knee replacement between October 2018 and March 2020 were reviewed. The records included detailed information about the postoperative wound examinations. Among all the records reviewed, we found that two surgeons had prescribed enoxaparin and apixaban, and their records contained the information we needed for the study. Accordingly, 200 patient records were included for the analysis.

### 2.2 | Exclusion criteria

Patients were excluded if they had a history of bleeding tendency, baseline persistent blood pressure of ≥160 mm Hg systolic and/or ≥100 mm Hg diastolic, a history of recent myocardial infarction or cerebrovascular accident, renal impairment with a creatinine clearance of <60 mL/min, and coagulopathy associated with hepatic failure. Patents with records that had inadequate history details or postoperative examination results were also excluded.

### 2.3 | Treatments and assessment of the effectiveness outcomes

In total, 120 patients had received a single subcutaneous dose of enoxaparin 4000 IU (40 mg) daily for 21 days, starting 6 hours prior to surgery. The other 80 patients had received apixaban (2.5 mg) twice daily for 21 days, starting 12 hours after surgery. The effectiveness assessment was based on the incidence of DVT, which was evaluated routinely using duplex Doppler ultrasonography at 7-21 days after surgery.

### 2.4 | Assessment of the safety outcomes

All assessments were performed by surgeons or their residents and were recorded in the patients' record files. The principal safety outcome was the combined incidence of major and minor postoperative wound complications that occurred 48 hours after the last dose of prophylactic medication administered. Major wound complications were defined as haematomas necessitating interventions such as surgery or aspiration, superficial or deep wound infections, periprosthetic infections, increased wound bleeding requiring prolonged hospitalisation for more than 1 week, anaemia requiring ≥6 units of packed red blood cells to treat, or hypotension necessitating medical intervention.[10] Surgical wounds were evaluated as four criteria (swelling, drainage, erythema, and oozing) according to the categories “as expected,” “better than expected,” or “worse than expected”[11] (Table 1).

### 2.5 | Surgical procedures

The surgery involved a 10-cm midline incision and a medial parapatellar approach to the knee. Two suction drains and deep and superficial dressings were placed. Patients started passive and active exercises immediately, while partial weight bearing was started 21 days later. The drains were removed at 48-72 hours after the surgery.

### 2.6 | Statistical analysis

The sample size of this study was determined according to the records of patients found in the study institution that met the inclusion criteria. Statistical analysis was performed using the independent sample *t* test and one-way analysis of variance for continuous data and the chi-square test for categorical data to compare between groups. The level of statistical significance was set at a *P* value of ≤.05.

## 3 | RESULTS

In total, 130 of the 200 patients included in the study were female, and the average age and weight were comparable for both treatment groups (Table 2).

All patients underwent elective total knee replacement surgery carried out by the two surgeons, and their operation times were not significantly different ($P \geq .05$). The patients required one blood transfusion unit on average during surgery, and their hospital stays were approximately 4-5 days, with no statistically significant difference between the enoxaparin and apixaban groups (Table 2).

Up to 21 days after surgery, there were no incidences of major surgical complications in any of the patients in either group, as shown in Table 3. Furthermore, with regard to minor surgical complications, there were no significant differences found in the degrees of swelling, drainage, oozing, and erythema between the two treatment groups during the hospital stay and at 21 days after surgery (Table 3).

Other complications, such as major organ bleeding, were not recorded for both treatment groups.

### 3.1 | Deep venous thrombosis events

In total, three patients (3/200, 1.5%) were confirmed by duplex Doppler ultrasonography to have developed DVT and were symptomatic, with swelling of the leg and pain in the calf. Two of those patients were receiving enoxaparin, whereas the third patient was receiving apixaban. The patients were sent to a specialist to complete treatment by increasing the dose of enoxaparin from 6000 to 8000 twice daily for 5 days and then continuing with a warfarin tablet for 3-6 months.

## 4 | DISCUSSION

This retrospective study was performed to meet the urgent need for assessing the safety and effectiveness of apixaban in comparison with enoxaparin, the latter of which is used widely in our national health institutions for the prevention of postoperative DVT. The results of the study were based on records obtained of patients treated by two orthopaedic surgeons at a single hospital according to the Institutional Review Board demands to set the best treatment for their patients.

Of the 200 patients included in the study, 120 were treated with enoxaparin and 80 with apixaban. This variation in patient number for the analysis itself was due to the time restriction set for the study and the availability of records meeting our inclusion criteria.

The results of this study confirmed the safety and effectiveness of enoxaparin and apixaban as prophylactic anticoagulants for the prevention of postoperative thrombotic events such as DVT and revealed that the two drugs were comparable in effects, without statistically significant differences between them. These results are consistent with those of the study by Russell and Huo,[12] where patients administered with either apixaban or enoxaparin showed no differences in postoperative wound complications. This finding highlights the benefit of prescribing apixaban as an alternative to enoxaparin, especially when the feasibility and simplicity of the oral route for patients are considered.

Boyd et al[13] found that the therapeutic index of oral anticoagulants (including apixaban) was better than that of enoxaparin. By contrast, we did not find significant differences between the treatments with regard to recorded events of DVT or surgical wound complications, indicating that both drugs had comparable effectiveness.

**TABLE 1** Surgical wound assessment criteria

| | Better than expected | As expected | Worse than expected |
|---|---|---|---|
| Swelling | Between 2 and 5 cm | ≥5 cm with or without tenderness and induration | >5 cm with tenderness and induration |
| Erythema | ≤10 cm margins only | ≥10 cm around the wound | >10 cm diffuse |
| Drainage | ≤300 and 800 mL | >300 and ≤800 mL | ≥800 mL |
| Oozing | <2.65 cm (no oozing), 2 d | <2.65 cm, 4 d | >2.65 cm, more than 4 d |

**TABLE 2** Baseline demographic data (expressed as the mean ± standard deviation of the mean)

| Criteria | Enoxaparin group (120 patients) | Apixaban group (80 patients) | *P* value |
|---|---|---|---|
| Gender[a] | 70 (58.3%) female, 50 (41.6%) male | 60 (75%) female, 20 (25%) male | .00 |
| Age (y) | 58.94 ± 9.56 | 60.64 ± 10.20 | 1.98 |
| Weight (kg) | 77.34 ± 10.3 | 77.25 ± 10.0 | .746 |
| Operation time (min) | 95.92 ± 7.79 | 94.87 ± 6.8 | .737 |
| Blood transfusion units | 1.0 ± 1.3 | 1.0 ± 1.4 | .82 |
| Hospital stay (d) | 3.99 ± 0.72 | 3.96 ± 0.73 | .744 |

[a]Values are the number of patients, with the percentage in parentheses.

**TABLE 3** Minor and major surgical complications associated with anticoagulant treatment

| | Enoxaparin group (120 patients) | Apixaban group (80 patients) | *P* value |
|---|---|---|---|
| Major complications | | | |
| Haematoma requiring intervention | 0 | 0 | |
| Superficial wound infection | 0 | 0 | |
| Deep periprosthetic infection | 0 | 0 | |
| Minor complications | | | |
| Swelling[a] | | | .167 |
| Better than expected | 100 (83.3%) | 72 (90%) | |
| As expected | 18 (15%) | 7 (8.7%) | |
| Worse than expected | 2 (1.6%) | 2 (2.5%) | |
| Drainage[a] | | | .165 |
| Better than expected | 55 (45.8%) | 33 (41.25%) | |
| As expected | 60 (50%) | 45 (56.25%) | |
| Worse than expected | 5 (4.1%) | 2 (2.5%) | |
| Erythema[a] | | | .168 |
| Better than expected | 90 (75%) | 73 (91.25%) | |
| As expected | 28 (23.3%) | 6 (7.5%) | |
| Worse than expected | 2 (1.6%) | 1 (1.25%) | |
| Oozing[a] | | | .157 |
| Better than expected | 110 (91.66%) | 75 (93.75%) | |
| As expected | 8 (6.66%) | 4 (5%) | |
| Worse than expected | 2 (1.6%) | 1 (1.25%) | |

[a]Values are the number of patients, with the percentage in parentheses.

However, further prospective multicentre studies are required to confirm whether apixaban is indeed more effective than enoxaparin.

Recent studies have highlighted the concerns over the postoperative safety of apixaban versus enoxaparin or other factor Xa inhibitors with regard to wound complications.[8,14,15] Accordingly, this study focused on the records of postoperative wound complications to evaluate the safety of oral apixaban.

The reviewed data of major and minor postoperative complications recorded revealed that apixaban was not inferior to enoxaparin in terms of its safety and prevention of major bleeding. This finding confirms that of the study by Wang et al,[16] which concluded that apixaban was a reliable prophylaxis for thromboembolism, being able to reduce the clinical incidence of major bleeding events.

### 4.1 | Limitations of this study

This was a retrospective study conducted at a single institution; thus, 200 patients cannot be representative of the national institutions. However, the results were similar to those of previous studies with larger sample sizes that had compared the effectiveness and safety of enoxaparin and apixaban in preventing postoperative complications and support their findings.

Lassen et al[17] conducted a multicentre, randomised, double-blind phase 3 study and found that apixaban 2-5 mg twice daily, initiated after elective total knee replacement surgery, was a convenient and safe alternative to enoxaparin. However, to the best of our knowledge, there are to date no other published national or local studies

on the effectiveness and safety of enoxaparin and apixaban that our results can be compared against.

## 5 | CONCLUSION

Our retrospective study comparing apixaban with enoxaparin for thromboprophylaxis in patients who had undergone elective total knee replacement surgery revealed no significant differences in major and minor wound complications and DVT incidence between the two groups of treated patients. Therefore, apixaban is as safe and effective as enoxaparin and would even be a better alternative given it can be administered orally.

### DISCLOSURE

Authors declared no conflict of interest.

### AUTHORS' CONTRIBUTIONS

AAM, HM, and MTJ conceived and designed the study, conducted research, provided research materials, and collected and organised data. AAM analysed and interpreted data. AAM wrote the initial and final draft of the article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

### ETHICAL APPROVAL

This study was conducted retrospectively using data obtained for clinical purposes. We consulted the Ethics Committee of the College of Medicine, University of Babylon and the Institutional Review Board of Al-Salam Private Hospital, which determined that our study did not require ethical approval.

### DATA AVAILABILITY STATEMENT

Research data are not shared. The data are not publicly available because of privacy or ethical restrictions.

### ORCID

*Mohannad Ali Hasan* https://orcid.org/0000-0001-9801-3245
*Malath Azeez Alsaadi* https://orcid.org/0000-0001-6312-1115
*Jameel Tahseen Mehsen* https://orcid.org/0000-0003-1810-2278

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