Thromboprophylaxis Treatment Does Not Affect Hemoglobin and Hematocrit Levels After Elective Total Hip Arthroplasty

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ABSTRACT

Background: Postoperative anemia is a significant complication in patients undergoing total hip arthroplasty (THA). The primary objective of this study was to evaluate the prevalence of postoperative anemia in patients undergoing elective THA and to determine whether there is a relationship with the thromboprophylactic treatment used. **Materials and Methods:** This was a prospective randomized trial. A total of 358 patients who underwent elective THA between February 2019 and January 2022 were included. Patients were divided into three groups receiving daily thromboprophylaxis: rivaroxaban 10 mg, enoxaparin sodium 40 mg, or aspirin 100 mg. **Results:** No confirmed cases of thromboembolic disease or severe bleeding were reported. Hemoglobin and hematocrit levels were consistent across all treatment groups, with no statistically significant differences. There were no differences in complication rates among the groups. However, iron supplementation was significantly higher in the enoxaparin group (p = 0.041). In the ordinal regression model, the incidence of anemia was associated with age (OR 1.02, 95% CI 1.00-1.05, p = 0.04), male sex (OR 0.33, 95% CI 0.19-0.56, p < 0.01), and the presence of any comorbidity (OR 0.49, 95% CI 0.28-0.85, p = 0.012). **Conclusions:** The thromboprophylaxis treatments evaluated in this study had no impact on the development of postoperative anemia in patients undergoing THA. Male sex, age, and the presence of comorbidities appear to be the factors most negatively influencing the development of anemia. No significant differences were found in the safety profiles of the three thromboprophylaxis therapies.

Keywords: Anemia; hip; arthroplasty; thromboprophylaxis.

Level of Evidence: II

El tratamiento trombofiláctico no afecta los niveles de hemoglobina y hematocrito luego de una artroplastia total de cadera

RESUMEN

Introducción: La anemia posoperatoria es una complicación importante en pacientes sometidos a una artroplastia total de cadera (ATC). El objetivo principal de este estudio fue evaluar la prevalencia de anemia posoperatoria en pacientes sometidos a una ATC programada y determinar si está relacionada con el tratamiento tromboprofiláctico administrado. **Materiales y Métodos:** Ensayo prospectivo aleatorizado. Se incluyó a 358 pacientes sometidos a una ATC programada entre febrero de 2019 y enero de 2022, que fueron divididos en 3 grupos para recibir: rivaroxabán 10 mg, enoxaparina sódica 40 mg o aspirina 100 mg como estrategia de tromboprofilaxis diaria. **Resultados:** No hubo casos de enfermedad tromboembólica confirmada ni de hemorragia grave. Los niveles de hemoglobina y hematocrito fueron similares en todos los grupos de tratamiento, sin diferencias estadísticamente significativas. No se hallaron diferencias en la incidencia de complicaciones. La suplementación con hierro fue significativamente mayor en el grupo de enoxaparina (p = 0,041). La incidencia de anemia en el modelo de regresión ordinal se asoció con la edad (OR 1,02; IC95% 1,00-1,05; p 0,04), el sexo masculino (OR 0,33; IC95% 0,19-0,56; p <0,01) y la presencia de una comorbilidad (OR 0,49; IC95% 0,28-0,85; p 0,012). **Conclusiones:** La tromboprofilaxis utilizada no tiene impacto en el desarrollo de la anemia posoperatoria en pacientes sometidos a una ATC. El sexo masculino, la edad y la presencia de alguna comorbilidad parecen ser los factores que influyen negativamente en la anemia. No hubo diferencias significativas en el perfil de seguridad de estas tres terapias de tromboprofilaxis.

Palabras clave: Anemia; cadera; artroplastia; tromboprofilaxis.

Nivel de Evidencia: II

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INTRODUCTION

Complications following total hip arthroplasty (THA) prolong hospital stays and subsequently increase healthcare costs.[1] Postoperative anemia is a significant complication in patients undergoing THA, affecting one-third of patients, particularly those of advanced age.[2] The prevalence of preoperative anemia is estimated at 24.9% (± 9%), while postoperative anemia occurs in about 51% (± 10%).[3]

Numerous studies have demonstrated the association between anemia and an increase in postoperative complications, including infection, death, decreased function, and extended hospital stays, irrespective of patients' preexisting comorbidities. [4]

Traditionally, the treatment of postoperative anemia has focused on blood transfusions, which can result in a range of complications, including allergic reactions, circulatory overload, pulmonary thromboembolism, immunosuppression, surgical site infection, and prolonged hospitalization.[5]

THA is a major risk factor for postoperative venous thromboembolic disease (VTE); therefore, anticoagulant thromboprophylaxis is strongly recommended to prevent this serious complication. The appropriate use of thromboprophylaxis significantly reduces the risk of postoperative VTE. However, it remains unclear whether anticoagulant thromboprophylaxis can also influence the development of postoperative anemia in these patients.[6]

The primary objective of this study was to evaluate the prevalence of postoperative anemia in patients undergoing elective THA at our institutionand to explore whether there is an association between the pharmacological thromboprophylaxis strategy used and the incidence of postoperative anemia. Secondary objectives included determining whether there is a correlation between anemia and preexisting comorbidities or surgical duration, assessing the need for transfusion or other medical interventions, and identifying any increase in wound complications—such as hematoma, bleeding, surgical site infection, or VTE—based on the thromboprophylaxis administered. Furthermore, the study evaluated whether aspirin is a safe thromboprophylactic method for patients undergoing THA.

MATERIALS AND METHODS

Men and women >18 years of age who underwent elective THA between February 2019 and January 2022 were included in the study. Pregnant or breastfeeding women, those with active bleeding or a high risk of bleeding, those with contraindications to enoxaparin prophylaxis, or conditions requiring an adjusted enoxaparin dose were excluded. Additional exclusion criteria included: body mass index >40, significant liver disease, severe renal dysfunction (creatinine clearance <30 ml/min), concomitant use of protease inhibitors for the treatment of HIV infection, or the need for anticoagulant therapy that could not be discontinued.

A prospective, randomized trial was conducted at two sites of a high-complexity hospital. Before surgery, patients were randomly assigned to a study group using permuted blocks via a central telephone system with a computer-generated randomization list. Patients were assigned to receive one of the following thromboprophylaxis strategies: 10 mg of oral rivaroxaban once daily, 40 mg of subcutaneous enoxaparin sodium, or 100 mg of oral aspirin. Thromboprophylactic treatment was administered to all three groups for a period of 28 days after surgery.

All participants received subarachnoid spinal anesthesia for the surgical procedure and a weight-adjusted dose of tranexamic acid (20 mg/kg) 30 minutes before the surgical incision. During the first four days, all patients received thromboprophylaxis with 40 mg of enoxaparin, after which each patient continued with the medication to which they were randomized. Enoxaparin administration began 12 hours after wound closure in patients without bleeding complications in the immediate postoperative period. Thereafter, the study drugs were administered every 24 hours (within a range of 22-26 hours) in the evening, continuing until day 28 after surgery (with the day of surgery designated as day 1).

A Doppler ultrasound of the lower limbs was ordered only if the patient exhibited clinical signs suggestive of deep vein thrombosis. Patients attended a follow-up visit 21 days (±1) after surgery to assess the surgical wound. On day 28, a telephone consultation was conducted, after which the study drug was discontinued.

The study was designed by the investigators and conducted in accordance with the Declaration of Helsinki and local regulations. The protocol was reviewed and approved by the institutional review board, and written informed consent was obtained from all patients prior to randomization.

All outcomes were evaluated by independent central adjudication committees whose members were blinded to the patients' group allocations. The primary endpoint was the appearance of deep vein thrombosis, nonfatal pulmonary embolism, or death from any cause up to 28 days after surgery.

The primary safety outcome was the incidence of major bleeding that occurred after the first dose of the study drug and up to two days after the last dose. Major bleeding was defined as bleeding that was fatal, occurred in a critical organ (e.g., retroperitoneal, intracranial, intraocular, or intraspinal), required reoperation, or occurred at a clinically evident extraoperative site and was associated with a hemoglobin drop of at least 2 g/dL or required the transfusion of 2 or more units of whole blood or packed red blood cells. Additional safety outcomes included any bleeding during treatment, non-major bleeding during treatment, hemorrhagic wound complications (such as excessive wound hematoma or reported bleeding at the surgical site), any bleeding that began after the first dose of the study drug and continued up to two days after the last dose, adverse events, and death.

Laboratory tests were performed before surgery and 24 hours after surgery to evaluate hemoglobin and hematocrit levels. Patients were classified according to the World Health Organization's severity classification: no anemia (>12 g/dL), mild anemia (10-12 g/dL), moderate anemia (8-9.9 g/dL), and severe anemia (<8 g/dL). Patients were evaluated by physicians from the Hematology Service, who determined whether anemia treatment was necessary. At 21 days postoperatively, another set of tests was performed to assess hematocrit and hemoglobin levels and their variation compared to preoperative values and those obtained 24 hours after surgery, evaluating hemoglobin recovery following THA.

Statistical analysis

Categorical variables are presented as proportions and absolute numbers, while continuous variables are expressed as mean and standard deviation or as median and interquartile range (IQR), depending on the data distribution. The Shapiro-Wilk test, histograms, and normal distribution plots were used to assess the distribution.

For bivariate analysis, numerical variables were compared using the t-test or Wilcoxon test, based on the data distribution, while categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

The effect of the randomized drugs on hemoglobin levels at day 21 was analyzed using a multiple linear regression model adjusted for sociodemographic confounders, clinical history, and surgical characteristics.

Additionally, a multivariate ordinal logistic regression model was developed to evaluate the independent effect of the assigned drugs on the presence of different degrees of anemia at day 21, also adjusted for sociodemographic confounders, clinical history, and surgical characteristics. The associations are reported with their 95% confidence intervals (95% CI). A p-value of <0.05 was considered statistically significant.

All analyses were performed using STATA 13 software (StataCorp, Texas, USA).

RESULTS

Between February 2019 and January 2022, a total of 367 patients were enrolled in the study, with 358 patients included in the modified intention-to-treat population (Figure 1). The mean age of participants was 62.73 years (standard deviation 12.25), and 59.5% were male. There were no significant differences in demographic or surgical characteristics among the three groups, except for a trend toward older age in the enoxaparin group (Table 1). The mean duration of pharmacological antithrombotic prophylaxis was 28 days in all groups.

Efficacy endpoints

VTE was suspected in six patients: one in the enoxaparin group, two in the rivaroxaban group, and three in the aspirin group. However, Doppler ultrasound ruled out all cases, meaning no confirmed VTE occurred during the follow-up period.

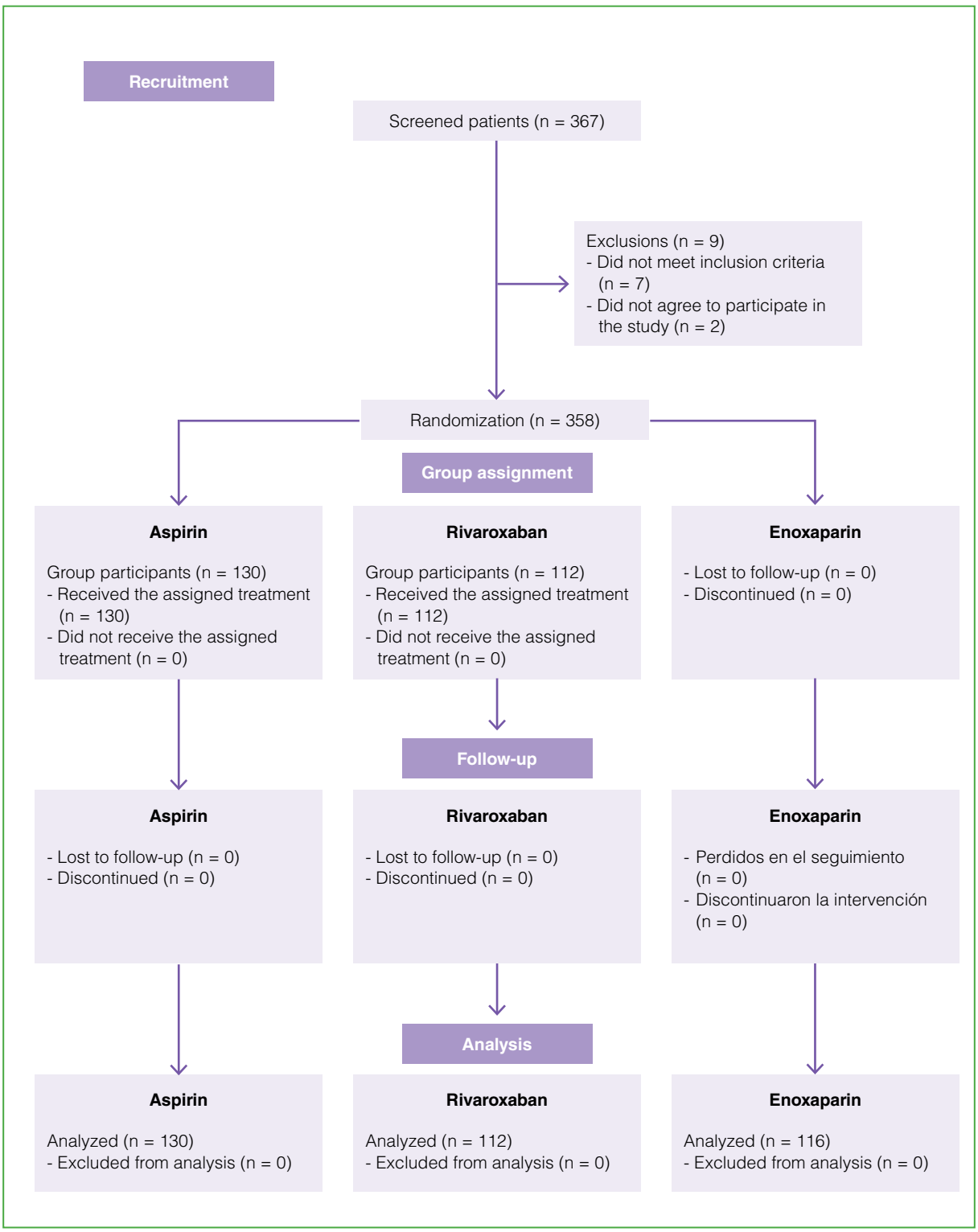

Figure 1. Elective total hip arthroplasty: anemia and thromboprophylaxis. Flow chart.

Table 1. Characteristics of the 358 patients included in the study.

	All n = 358	Enoxaparin n = 116	Rivaroxaban n = 112	Aspirin n = 130	p
Sex Female Male	 145 (40.5%) 213 (59.5%)	 52 (44.8%) 64 (55%)	 42 (37.5%) 70 (62.5%)	 51 (39.2%) 79 (60.8%)	0.49
Age, mean (SD)	62.7 (12.3)	65.2 (11.4)	61.5 (13.5)	61.6 (11.6)	0.032
Weight (kg), mean (SD)	83.5 (13.1)	84.3 (13.1)	83.4 (14.1)	82.9 (12.1)	0.69
BMI, mean (SD)	27.9 (3.7)	28.5 (4.0)	27.6 (3.4)	27.7 (3.6)	0.12
Operated side Right Left Bilateral	 192 (53.6%) 162 (45.3%) 4 (1.1%)	 60 (51.7%) 54 (46.6%) 1 (0.9%)	 60 (53.6%) 51 (45.5%) 2 (1.7%)	 72 (55.4%) 57 (43.8%) 1 (0.8%)	0.93
Hypertension	141 (39.4%)	43 (37.1%)	43 (38.4%)	55 (42.3%)	0.68
Diabetes	10 (2.8%)	5 (4.3%)	3 (2.7%)	2 (1.5%)	0.42
Dyslipemia	30 (8.4%)	12 (10.3%)	4 (3.6%)	14 (10.8%)	0.085
Heart disease	32 (8.9%)	15 (12.9%)	11 (9.8%)	6 (4.6%)	0.068
Obesity	7 (2.0%)	5 (4.3%)	1 (0.9%)	1 (0.8%)	0.083
Number of comorbidities None One Two	 117 (32.7%) 220 (61.5%) 21 (5.9%)	 29 (25.0%) 80 (69.0%) 7 (6.0%)	 46 (41.1%) 62 (55.4%) 4 (3.6%)	 42 (32.3%) 78 (60.0%) 10 (7.7%)	0.09
ASA Score 1 2 3	 34 (9.5%) 313 (87.7%) 10 (2.8%)	 7 (6.0%) 102 (87.9%) 7 (6.0%)	 17 (15.3%) 93 (83.8%) 1 (0.9%)	 10 (7.7%) 118 (90.8%) 2 (1.5%)	0.013
Type of prosthesis Uncemented Hybrid Cemented	 228 (63.7%) 126 (35.2%) 4 (1.1%)	 65 (56.0%) 49 (42.2%) 2 (1.7%)	 72 (64.3%) 40 (35.7%) 0 (0.0%)	 91 (70.0%) 37 (28.5%) 2 (1.5%)	0.13
Duration of surgery, mean (SD) (min)	97.5 (16.1)	99.0 (17.3)	97.1 (14.9)	96.5 (16.2)	0.45
Duration of hospitalization, mean (SD) (days)	1.7 (0.6)	1.9 (0.6)	1.8 (0.5)	1.6 (0.7)	<0.001

SD = standard deviation; BMI = body mass index; ASA = *American Society of Anesthesiologists*.

Safety outcomes

No cases of major bleeding were reported during follow-up. Six patients (1.67%) required transfusions in the immediate postoperative period before receiving the study-specific medication. Of these, three were in the enoxaparin group and three were in the rivaroxaban group. However, the bleeding did not meet the criteria for major bleeding.

No significant differences were found in mean pre- and postoperative hemoglobin or hematocrit levels between the groups. Hemoglobin and hematocrit values were similar across all treatment groups, with no significant differences in their progression. Across the three groups, a mean decrease of 3 g/dL in hemoglobin was observed in the first postoperative control compared to preoperative values. The greatest decrease in hemoglobin and hematocrit occurred on day 2, with hemoglobin dropping by approximately 3 g/dL in all groups (Table 2, Figures 2 and 3).

Table 2. Comparison of hemoglobin levels throughout follow-up.

	Preoperative period	Day 1	Day 2	Day 21
Enoxaparin	13.95	11.50	11.14	12.30
Rivaroxaban	14.08	11.25	10.94	12.53
Aspirin	14.13	11.57	11.36	12.61
p	0.64	0.25	0.13	0.33

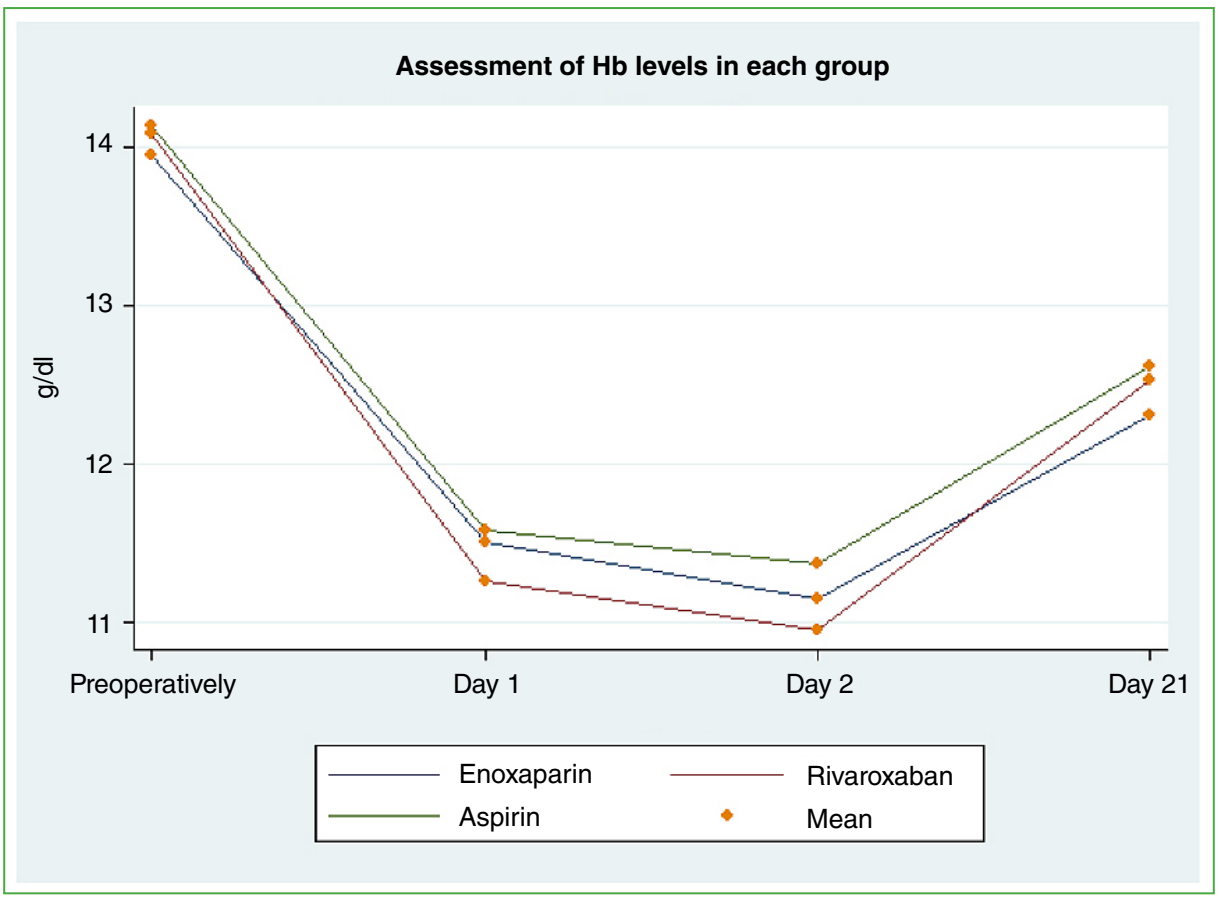

Figure 2. Assessment of hemoglobin (Hb) levels based on the assigned thromboprophylaxis treatment.

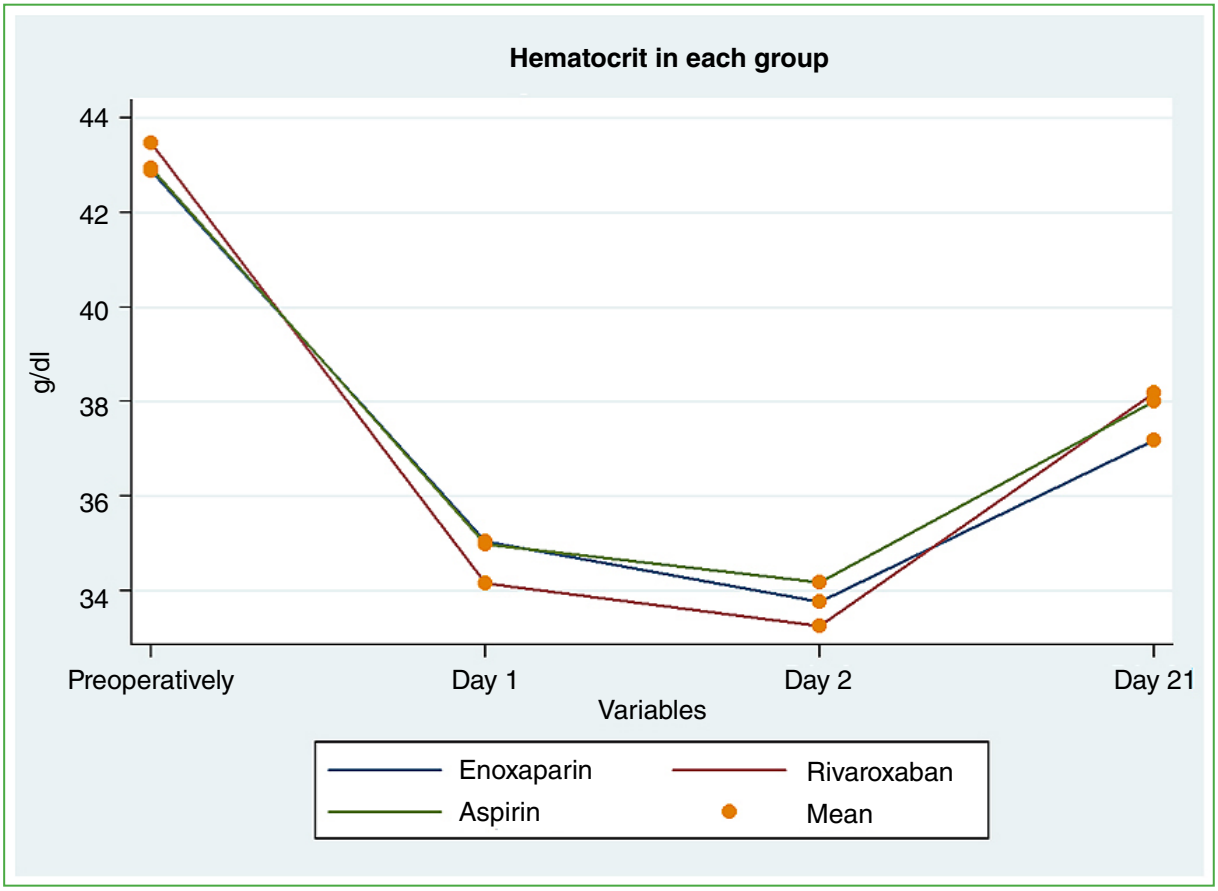

Figure 3. Assessment of hematocrit levels based on the assigned thromboprophylaxis treatment.

Other outcomes

The median hospitalization time for the study population was 2 days (IQR 1-2), with no significant differences between groups regarding the incidence of infection, hematoma, or wound bleeding.

The requirement for iron supplementation was significantly higher in the enoxaparin group (6 cases, 5.2%) compared to the rivaroxaban group (4 cases, 3.6%) and the aspirin group (0 cases, 0.0%) (p = 0.041) (Table 3).

Table 3. Comparative outcomes between arms.

	Enoxaparin (n = 116)	Rivaroxaban (n = 112)	Aspirin (n = 130)	p
21-day DVT symptoms	1 (0.9%)	2 (1.8%)	3 (2.3%)	0.67
Confirmed DVT	0 (0%)	0 (0%)	0 (0%)	-
Hemoglobin on day 21	12.3 (1.7)	12.5 (1.6)	12.6 (1.6)	0.34
transfusions	3 (2.6%)	3 (2.7%)	1 (0.8%)	0.47
Iron	6 (5.2%)	4 (3.6%)	0 (0.0%)	0.041
Bruising or bleeding	3 (2.6%)	6 (5.4%)	4 (3.1%)	0.49
Infections	2 (1.7%)	1 (0.9%)	2 (1.5%)	0.85

DVT = deep vein thrombosis.

In the model evaluating the effect of the treatment arms on hemoglobin levels at day 21 (Figure 4), men were found to have, on average, 1.04 g/dL more hemoglobin than women (95% CI 0.65-1.43; $p < 0.01$), a result expected due to physiological gender differences. Aside from this gender-based difference, no significant variation in hemoglobin levels at day 21 was observed between the three treatment arms, nor were there differences between the medication arms or other confounding factors studied (Table 4).

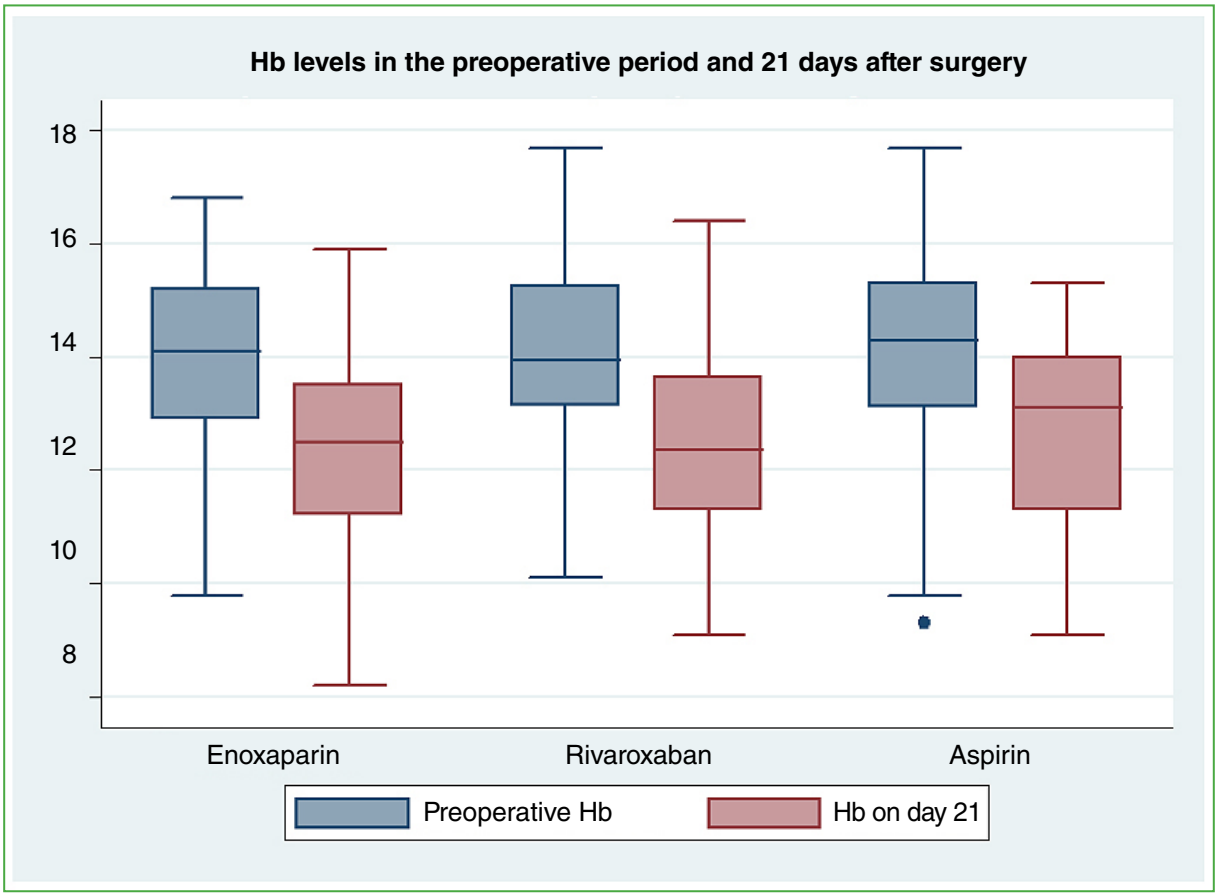

Figure 4. Box plot comparing hemoglobin (Hb) levels in the preoperative period and 21 days after surgery based on the assigned thromboprophylaxis treatment.

Table 4. Linear regression between demographic and clinical predictors and hemoglobin level 21 days after surgery.

	Coefficient	95%CI	p
Treatment arms			
Enoxaparin	Ref.	-	-
Rivaroxaban	0.098	(from -0.29 to 0.49)	0.62
Aspirin	0.17	(from -0.21 to 0.55)	0.38
Age	-0.009	(from -0.02 to 0.007)	0.25
Sex			
Female	Ref.	-	-
Male	1.04	(0.65-1.43)	**0.0001**
Comorbidities			
none	Ref.	-	-
1	-0.12	(from -0.52 to 0.27)	0.55
2 or more	-0.51	(from -1.26 to 0.23)	0.18
ASA Score			
1	Ref.	-	-
2	0.42	(from -0.18 to 1.02)	0.17
3	0.84	(from -0.29 to 1.99)	0.15
Type of prosthesis			
Uncemented	Ref.	-	-
Hybrid	-0.44	(from -0.89 to 0.01)	0.058
cemented	-0.73	(from -2.27 to 0.81)	0.35
Duration of Surgery	0.0004	from -0.009 to 0.10	0.93

ASA = *American Society of Anesthesiologists*; 95%CI = 95% confidence interval.

In the ordinal regression model analyzing the factors associated with the incidence and severity of anemia, the following characteristics were found to be significant: age (odds ratio [OR] 1.02; 95% CI 1.00-1.05; p = 0.04), male sex (OR 0.33; 95% CI 0.19-0.56; p < 0.01), and the presence of comorbidities (OR 0.49; 95% CI 0.28-0.85) (Figure 5, Table 5).

DISCUSSION

The development of anemia after scheduled total hip arthroplasty (THA) is a frequent complication associated with increased morbidity, prolonged hospital stay, higher health care costs, and a greater need for blood transfusion or iron supplementation. The occurrence of anemia may be influenced by the type of antithrombotic prophylaxis administered.

Postoperative anemia can be easily explained by acute blood loss and the inflammatory response triggered by the surgery, which disrupts erythropoiesis and iron metabolism, reducing iron availability as the body tries to compensate.[5] The incidence of postoperative anemia in our study population was similar to that reported by Sphan et al.[3] In our cohort, male sex, advanced age, and the presence of comorbidities were associated with a higher incidence or greater severity of anemia.

No statistically significant differences were observed in the decrease in hemoglobin after surgery among patients receiving enoxaparin, rivaroxaban, or aspirin as VTE prophylaxis. All three treatment options showed a similar safety profile in this regard. However, it is worth noting that laboratory follow-up was only extended until day 21 post-surgery, at which point hemoglobin and hematocrit levels had shown favorable recovery. In contrast, Bala et al.[7] reported differences in anemia rates among four drugs (factor Xa inhibitors, aspirin, low-molecular-weight heparin, and warfarin), with these differences persisting even up to 90 days post-surgery.

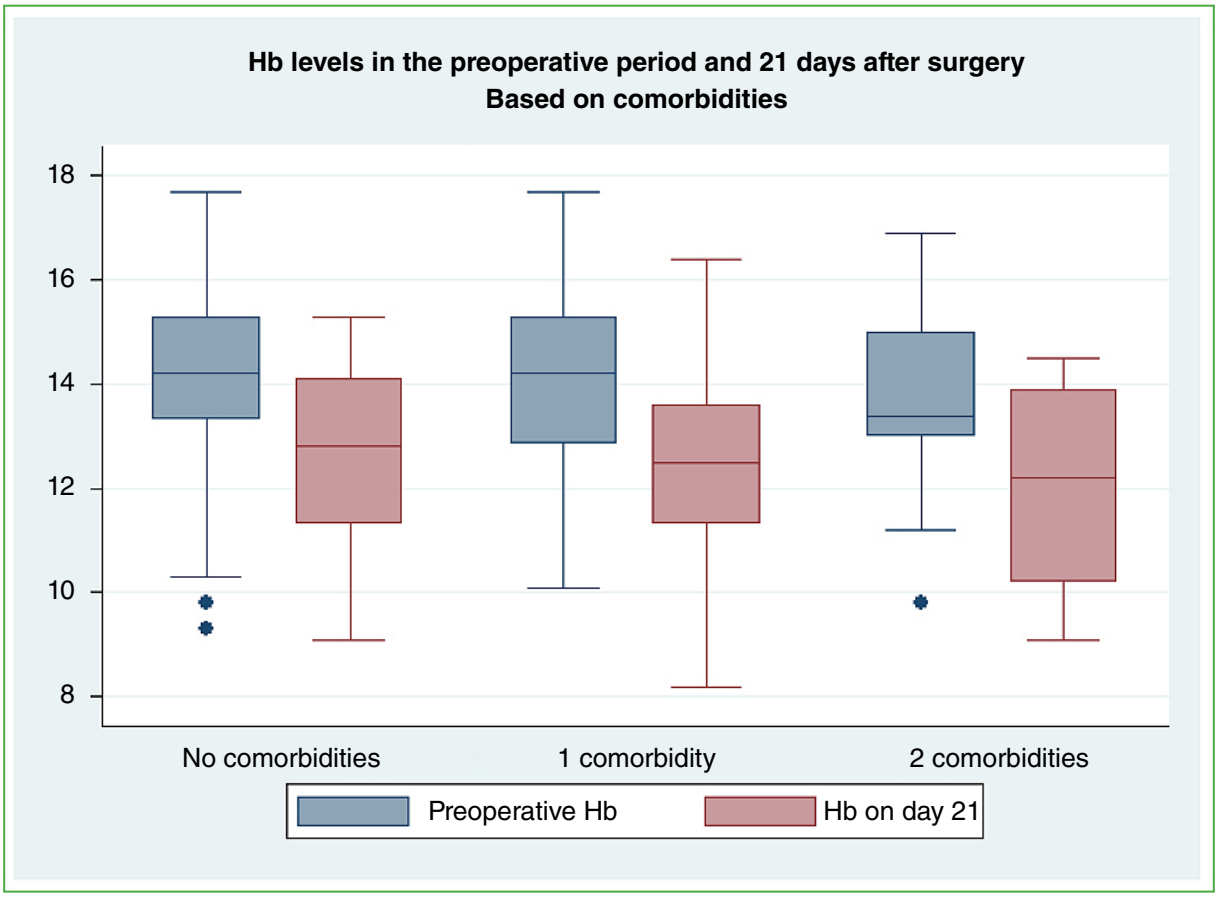

Figure 5. Box plot comparing hemoglobin (Hb) levels in the preoperative period and 21 days after surgery based on the presence or absence of comorbidities.

Traditionally, the correction of postoperative anemia has focused on blood transfusions, with the initial hemoglobin level consistently predicting the need for transfusion.[2] In our study, only six patients (1.67%)—three in the enoxaparin group and three in the rivaroxaban group—required a transfusion. This contrasts with the findings of Chen et al,[8] who reported that 38.5% of patients undergoing THA in a large hospital network required red blood cell transfusions immediately postoperatively, though with significant variation between surgeons.

Regarding the safety of the three VTE prophylactic therapies in our study, no thromboembolic events were observed. Thromboembolism was clinically suspected in six patients, but all cases were ruled out via Doppler ultrasound. A study by Tan et al.,[9] which compared the potency of anticoagulants (warfarin, low-molecular-weight heparin, and aspirin) for VTE prevention in 60,467 patients, found that aspirin was as effective as more potent anticoagulants. Our results align with those of a 2008 multicenter randomized clinical trial,[10] which concluded that rivaroxaban has a safety profile comparable to that of enoxaparin in the prevention of VTE after THA. Similarly, Matharu et al,[11] in their systematic review and meta-analysis of randomized controlled trials, found no significant differences in clinical efficacy and safety when comparing aspirin with other oral anticoagulants after joint replacement.

Our findings support the use of aspirin for VTE prophylaxis, as no patients in our series experienced thromboembolic events. These results are consistent with those of Muscatelli et al.[12] and Matharu et al.,[13] both of whom concluded that aspirin is not inferior to other anticoagulants in preventing VTE and related bleeding complications.

Table 5. Ordinal regression between demographic and clinical predictors and the level of anemia severity 21 days post-surgery

	OR	95%CI	p
Treatment arms			
Enoxaparin	Ref.	-	-
Rivaroxaban	1.00	(0.58-1.73)	0.98
Aspirin	0.73	(0.42-1.25)	0.25
Age	1.02	(1.00-1.05)	**0.04**
Sex			
Female	Ref.		-
Male	0.33	-(0.19-0.56)	**0.0001**
Comorbidities			
None	Ref.	-	-
1	0.49	(0.28-0.85)	**0.012**
2 or more	0.82	(0.30-2.26)	0.70
ASA Score			
1	Ref.	-	-
2	0.92	(0.39-2.13)	0.84
3	0.79	(0.16-3.81)	0.77
Type of prosthesis			
Uncemented	Ref.	-	-
Hybrid	1.26	(0.68-2.34)	0.46
Cemented	2.45	(0.35-17.31)	0.37
Duration of surgery	1.00	(0.99-1.02)	0.87

OR (*odds ratio*) = odds ratio; 95%CI = 95% confidence interval; ASA = *American Society of Anesthesiologists.*

A limitation of our study is that thrombotic events may have been underestimated due to the size of our cohort, as a larger study population would be needed to fully assess the efficacy of these three thromboprophylactic therapies. Randomized controlled trials or retrospective studies based on large administrative databases often lack the clinical observation, patient-specific data, and accurate complication reporting necessary for a thorough analysis. A strength of our study is that it was conducted in a single medical institution, allowing for detailed reporting of each of these factors.

CONCLUSIONS

The selection of a thromboprophylaxis agent following primary total hip arthroplasty (THA) remains a critical issue, as the ideal drug has yet to be identified. Based on our analysis of the three therapeutic options studied in our cohort—enoxaparin, rivaroxaban, and aspirin—for VTE prophylaxis after THA, we can conclude that the thromboprophylactic treatment administered does not influence the development of postoperative anemia. The factors that appear to negatively impact anemia outcomes are male sex, advanced age, and the presence of comorbidities. Additionally, no significant differences were observed in the safety profile of these three thromboprophylactic therapies with respect to thrombotic events following elective THA.

Conflict of interest: The authors declare no conflicts of interest.

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