MedPharmRes

Journal of University of Medicine and Pharmacy at Ho Chi Minh City
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Original article

Risk of venous thromboembolism and appropriateness of thromboprophylaxis in patients undergoing lower limb orthopedic surgery in a Vietnamese hospital

Duong Hong Nguyen[a], Kim Thai Thien Nguyen[a], Minh Lam Tuan Phan[a], Thao Huong Nguyen[ab*]

[a]*Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam;*
[b]*Department of Pharmacy, Trung Vuong Hospital, Ho Chi Minh City, Vietnam.*

Received April 18, 2022: Revised June 03, 2022: Accepted June 18, 2022

Abstract: ***Introduction:*** Patients undergoing orthopedic surgery are at high risk of venous thromboembolism (VTE), but the prophylactic practices are suboptimal. We aim to investigate the risk of VTE, the appropriateness of VTE prophylaxis and its associated factors in patients undergoing lower limb orthopedic surgery. ***Method:*** A cross-sectional study was conducted at Gia Dinh People's Hospital. Data was collected from medical records of patients aged ≥18 years undergoing lower limb orthopedic surgery between March 1st 2020 and June 30th 2020. VTE risk was stratified using the Caprini Risk Assessment Model, contraindications to anticoagulation and the appropriateness of thromboprophylaxis were evaluated according to current guidelines. Multivariate logistic regression analysis was used to determine factors associated with the appropriateness of VTE prophylaxis. ***Results:*** A total of 217 patients was included (median age 54, 57.6% male). There were 80.2% of patients at risk of VTE. Overall rate of appropriate VTE prophylaxis was 35.0%. Patients with age ≥41, BMI >25 kg/m^2, surgical duration >45 minutes, plaster cast or screw splint were less likely to receive appropriate VTE prophylaxis; patients with hospital stay >4 days after surgery got more chances to have proper VTE prophylaxis ($p < 0.05$). ***Conclusions:*** The majority of patients undergoing lower limb orthopedic surgery were at risk of VTE, but the rate of appropriate VTE prophylaxis was low. Factors associated with the appropriateness of VTE prophylaxis were age, BMI, surgical duration, plaster cast or screw splint, and length of hospital stay after surgery. Interventions are needed to improve the appropriateness of VTE prophylaxis.

Keywords: venous thromboembolism (VTE); orthopedic surgery; thromboprophylaxis.

1. INTRODUCTION

Venous thromboembolism (VTE) is one of the most frequent and severe complications after surgery, which can occur in 10-20 cases per 10,000 person-years [1,2]. In Asia, among every 100,000 patients undergoing surgeries, there were 14 to 57 cases developing post-surgical VTE [3]. In Vietnam, a multicenter study demonstrated that of 2,790,027 patients undergoing surgery, 3,608 patients were diagnosed with VTE [4]. VTE has increased the rate of hospital admission by 5.4 times and the total healthcare cost by 2.2 times [5]. Notably, the risk of VTE is 70-fold higher in individuals with orthopedic surgery compared to those with other surgeries [6]. The high prevalence and the deadly consequences of VTE have raised important implications for appropriate prevention, especially in patients undergoing orthopedic surgery.

In 2012, the American College of Chest Physicians (ACCP) and in 2016, the Vietnam National Heart Association

*Address correspondence to Thao Huong Nguyen at the Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City. 41-43 Dinh Tien Hoang Street, District 1, Ho Chi Minh City, Vietnam; E-mail: thao.nh@ump.edu.vn

DOI: 10.32895/UMP.MPR.7.1.9

(VNHA) issued guidelines on diagnosis, treatment, and prevention of VTE [7,8]. Both the ACCP 2012 and the VNHA 2016 guidelines recommended thromboprophylaxis for major orthopedic surgeries including total hip arthroplasty, total knee arthroplasty, and hip fracture surgery [7,8]. In contrast, there is a lack of consensus on the use of thromboprophylaxis for patients undergoing non-major orthopedic surgeries including upper and lower limb surgeries [7,9]. The VNHA 2016 guideline suggests that the risks of VTE in such surgeries are low and therefore, does not recommend a thromboprophylaxis [8]. Meanwhile, the National Institute for Health and Care Excellence (NICE) 2018 guideline recommends that the VTE risk of all individuals should be assessed to decide on the use of prophylaxis [9]. This discrepancy may lead to suboptimal practices. As such, patients undergoing non-major surgeries with additional risk factors of VTE may not have been indicated VTE prophylaxis properly. To our knowledge, studies thoroughly examining the risk of VTE in this population were limited and whether these patients were prescribed accordingly was not fully demonstrated. Thus, in this study, we aim to investigate (1) the risk of VTE and (2) the appropriateness of VTE prophylaxis and its associated factors in patients undergoing lower limb orthopedic surgery.

2. MATERIALS AND METHOD

2.1. Study design

A cross-sectional study was conducted at the Trauma and Orthopedic Department of Gia Dinh People's Hospital, a provincial general hospital in Ho Chi Minh city which facilitates 1,500 beds. We examined medical records of patients aged 18 years and above, undergoing lower limb orthopedic surgery between March 1, 2020 and June 30, 2020. Patients who were being treated for confirmed VTE and patients who were taking anticoagulants for indications other than VTE prophylaxis were excluded.

Patients' demographics characteristics, VTE risk factors, contraindications to anticoagulants, and thromboprophylactic management were collected. The risk of VTE was assessed using the Caprini Risk Assessment Model (ACCP, 2012), and was stratified into very low (0-1 score), low (2 scores), moderate (3-4 scores), high (5-8 scores), and very high (> 8 scores) [10]. The risk of haemorrhage or bleeding was evaluated through relative and absolute contraindications of anticoagulants according to the VNHA 2016 guideline [8]. Indication of thromboprophylaxis was appropriate if it was in line with current guidelines [7–10]. In particular, a routine prophylaxis is not recommended for patients with low or very low risk of VTE. For patients with moderate to high/very high risk of VTE, anticoagulant should be prescribed if there is no contraindication; otherwise, mechanical prophylaxis should be substituted [9,10]. Low-molecular-weight heparin (LMWH), fondaparinux, dabigatran, rivaroxaban, unfractionated heparin (UFH), adjusted-dose vitamin K antagonist, or aspirin is preferred for patients undergoing major orthopedic surgery. Duration of thromboprophylaxis in those patients should range from a minimum of 10-14 days post-surgery to a maximum of 35 days after being discharged from the hospital [7,8]. In contrast, LMWH is the first-line prophylaxis medication for patients undergoing non-major orthopedic surgery. Thromboprophylaxis should be maintained until individuals are able to move or discharge from the hospital; however, a maximum of 28 days after hospital discharge could be considered in very high risk patients [7].

2.2. Statistical analysis

Data were analyzed using Microsoft Excel 2016 and Statistical Package for Social Sciences (SPSS) Program version 20.0 [11]. Descriptive analyses were performed to analyze patients' demographic and clinical characteristics. Data were presented as mean ± S.D. or median (interquartile range-IQR 25%-75%) for continuous variables, and as frequency and/or percentage for categorical variables. Multivariable logistic regression analysis was applied to identify potential factors (including gender, age, BMI, type of surgery, the emergence of surgery, surgical duration, immobilization time, plaster cast or screw splint, and length of hospital stay after operation) associated with the overall appropriateness of thromboprophylaxis. All statistical tests were two-tailed and the significant level was set at $p < 0.05$.

2.3. Ethical clearance

This study was approved by the Ethics Committee of University of Medicine and Pharmacy at Ho Chi Minh City before being conducted (approval number: 786/HĐĐĐ-ĐHYD (November 2nd, 2020)).

3. RESULTS

Demographic and clinical characteristics of patients

A total of 217 patients was included. The median age of patients was 54 years (37-66) and 57.6% of patients were male. The majority of participants underwent non-major orthopedic surgeries including foot or ankle fracture surgery, arthroscopic knee surgery, surgical removal of instruments, and other types of lower extremity surgery. The median surgical duration was 80 (50-103) minutes and more than half of patients had surgical duration greater than 45 minutes. Details of demographic and clinical characteristics of patients are presented in Table 1.

VTE risk stratification

There were 80.2% of patients having moderate to high/very high risk of VTE (see details in Table 2). Prolonged surgical duration (> 45 minutes) was the most common risk factor (78.8%). Other common risk factors included age of 41 and above (71.9%), confined to bed more than 72 hours (24.4%), and undergoing minor surgery (21.2%). Details of VTE risk factors are presented in Table 3.

Moderate to high/very risk of VTE encourages a prescription of pharmacological prophylaxis but only after excluding the risk of major post operative bleeding. In our study, six patients were contraindicated to anticoagulant due to their concurrent medication use (platelet aggregation inhibitors such as aspirin or clopidogrel), platelet below 100,000/µL, or haemorrhage. Relative contraindications were found in 4 patients while absolute contraindications were found in 2 patients.

The appropriateness of VTE prophylaxis

Of 217 patients, pharmacological prophylaxis was indicated in 76 patients (35.0%). We found no patient

indicated with mechanical prophylaxis. Notably, while there were 174 patients (80.2%) having moderate to high/very high VTE risk, the majority of them (141 patients) did not receive any prophylaxis. In total, an appropriate thromboprophylactic (pharmacological or mechanical) method was indicated in 53% of patients. Table 4 presented the discrepancy between the number of patients who are recommended to/not to receive a specific prophylaxis method and the actual number of prophylaxis performed.

Table 1. Demographic and surgical characteristics of patients

Characteristics		Number (N = 217)	Percentage (%)
Demographic characteristics			
Gender	Male	125	57.6
	Female	92	42.4
Age (year)	Median (IQR1 - IQR3)	54 (37 - 66)	
BMI		32	14.7
Comorbidity	None	115	53.0
	At least 1 comorbidity	102	47.0
Platelet count (10^3/µL)	< 100	3	1.4
	100 - 400	195	89.8
	> 400	19	8.8
Creatinine clearance (mL/min)	< 30	3	1.4
	≥ 30	214	98.6
Surgical characteristics			
Type of surgery	Major orthopedics	80	36.9
	Total hip arthroplasty	36	16.6
	Total knee arthroplasty	3	1.4
	Hip fracture surgery	41	18.9
	Non-major orthopedics*	137	63.1
Planned/unplanned surgery	Planned	154	71.0
	Unplanned (urgent)	63	29.0
Method of operation	Open	202	93.1
	Endoscopy	14	6.4
	Open and endoscopy	1	0.5
Past surgical history	None	193	88.9
	≥ 1	24	11.1
Type of anesthesia	Endotracheal anesthesia	132	60.8
	Laryngeal mask anesthesia	25	11.5
	Spinal anesthesia	58	26.7
	Local anesthesia	2	1.0
Surgical duration	Median (IQR1 - IQR3)	80 (50 - 103)	
	≤ 45 min	46	21.2
	> 45 min	171	78.8
Length of hospital stay after surgery	Median (IQR1 - IQR3)	4 (3 - 6)	
Total length of hospital stay	Median (IQR1 - IQR3)	9 (5 - 13)	

**including foot/ankle fracture surgery, arthroscopic knee surgery, surgical removal of instruments and other types of lower extremity musculoskeletal system surgery*

Table 2. VTE risk stratification

Risk stratification	Caprini score	Non-major surgery (n =137)	Major surgery (n = 80)	All sample (N = 217)
Very low	0 - 1	11 (8.0%)	-	11 (5.1%)
Low	2	32 (23.4%)	-	32 (14.7%)
Moderate	3 - 4	56 (40.9%)	-	56 (25.8%)
High	5 - 8	35 (25.5%)	11 (13.8%)	46 (21.2%)
Very high	> 8	3 (2.2%)	69 (86.2%)	72 (33.2%)

Table 3. Caprini score for VTE risk factors

Score	Risk factors	Frequency	Percentage %
1	Age 41 – 60 years	36	34.6
	Minor surgery planned	46	21.2
	History of prior major surgery	2	1.0
	BMI > 25 kg/m^2	32	14.8
	Swollen legs (current)	1	0.5
	Varicose veins	6	2.8
	Sepsis (< 1 month)	3	1.4
	Abnormal pulmonary function (COPD)	1	0.5
	Congestive heart failure (< 1 month)	1	0.5
	History of inflammatory bowel disease	5	2.3
2	Aged 61 – 74 years	55	25.3
	Laparoscopic surgery (> 45 min)	10	4.6
	Major open surgery (> 45 min)	161	74.2
	Prior or present malignant diseases	4	1.8
	Confined to bed (> 72 hours)	53	24.4
	Immobilizing plaster cast (< 1 month)	36	16.6
	Central venous catheter access	1	0.5
3	Aged ≥ 75 years	36	12.0
	History of VTE	1	0.5
5	Elective major lower extremity arthroplasty	39	18.0
	Hip, pelvic fracture (< 1 month)	41	18.9
	Multiple traumas	7	3.2

Table 4. The appropriateness of VTE prophylaxis

VTE risk	Frequency	Recommended method	Performed method	No. of appropriate cases
Very low/ low	43	No prophylaxis	43 patients received no prophylaxis	43
Moderate to high/very high	6	Mechanical prophylaxis*	4 patients received anticoagulants	0
	168	Pharmacological prophylaxis	72 patients received anticoagulants	72
Total	217			115 (53.0%)

**Patients were contraindicated to anticoagulant*

Table 5. Factors associated with the appropriate VTE prophylaxis

Factor		OR	95% CI	P value
Gender	Female*			
	Male	0.550	0.253 - 1.196	0.132
Age group	18 - 40*			
	41 - 60	**0.129**	**0.050 - 0.331**	**< 0.001**
	61 - 74	**0.161**	**0.054 - 0.483**	**0.001**
	≥ 75	**0.204**	**0.054 - 0.769**	**0.019**
Type of surgery	Non-major orthopedics*			
	Major orthopedics	0.865	0.345 - 2.169	0.757
Planned/unplanned surgery	Planned*			
	Unplanned (urgent)	1.262	0.559 - 2.848	0.576
Surgical duration > 45 min	No*			
	Yes	**0.211**	**0.089 - 0.504**	**< 0.001**
BMI > 25 kg/m^2	No*			
	Yes	**0.239**	**0.072 - 0.791**	**0.019**
Confined to bed (> 72 hours)	No*			
	Yes	1.866	0.234 - 1.226	0.536
Plaster cast or screw splint	No*			
	Yes	**0.061**	**0.015 - 0.246**	**< 0.001**
Length of hospital stay after surgery	≤ 4 days*			
	> 4 days	**3.205**	**1.396 - 7.361**	**0.006**

**Reference category*

Regarding pharmacological prophylaxis, enoxaparin alone or a combination of enoxaparin and rivaroxaban was indicated in 76 patients. In which, 43.4% of them (33 patients) received a proper medication at the right dose and were administered timely in relevant duration. The inappropriate anticoagulant prescriptions included improper choice of medication (29%), wrong dosage (31.6%), wrong administration time (6.6%), and insufficient duration (26.3%). For instance, there were 13 patients prescribed excessive doses of rivaroxaban (15-20 mg/day). Improper choice of rivaroxaban was found in 4 patients with hip fracture and the other 6 patients with lower limb orthopedic surgery. Notably, rivaroxaban was prescribed in 4 patients who were contraindicated.

Forty-three patients with low to very low risk of VTE were not indicated any prophylaxis, which we appraised as appropriate (see Table 4). Of 174 patients with moderate to high/very high risk of VTE, only 33 patients received appropriate prophylaxis (proper method, appropriate choice of anticoagulant, dosage, and duration). Overall, there were only 76 patients (35%) got an appropriate indication of whether receiving or not receiving a thromboprophylaxis.

Factors associated with the appropriateness of VTE prophylaxis

Multivariable logistic regression analysis demonstrated that patients aged 41 years and above (OR = 0.129, $p < 0.001$), having BMI > 25 kg/m^2 (OR = 0.239, $p = 0.019$), prolonged surgical duration (> 45 minutes) (OR = 0.211, $p < 0.001$), or plaster cast or screw splint (OR = 0.061, $p < 0.001$) were less likely to receive appropriate VTE prophylaxis. On the contrary, patients stayed in the hospital longer than 4 days were more likely to receive appropriate prophylaxis (OR = 3.205, $p = 0.006$) (see Table 5).

4. DISCUSSION

Our investigation on 217 patients undergoing lower limb orthopedic surgeries, in which 57.6% were male and the median age was 54 (37-66), found that 80.2% of patients were at risk of VTE; however, less than half of patients had a proper pharmacological prophylaxis indication and the overall rate of appropriate VTE prophylaxis remained low (35%). Age ≥ 41, BMI > 25 kg/m2, surgical duration > 45 minutes, plaster cast or screw splint, and length of hospital stay > 4 days after surgery were associated with the appropriateness of VTE prophylaxis ($p < 0.05$).

In the present study, the proportion of patients with moderate to high/very high risk of VTE was 80.2%. This was higher than the finding in ENDORSE study (2008) (64.4%) [12]. However, both studies agree that the majority of patients with orthopedic surgery are at increased risk of VTE. Notably, more than two-thirds of patients undergoing non-major orthopedic surgery were categorized as moderate to high/very high risk of VTE. This finding has clinically important implications since non-major surgery had long been asserted as low risk of VTE and thus, to date, a routine prophylaxis has not been recommended in the ACCP 2012 and the VNHA 2016 guideline [8]. The lack of guidance on VTE prevention in non-major orthopedic surgery could possibly result in the low appropriateness of prophylaxis in our study (35%). This suggests that VTE risk stratification should be considered in patients with non-major surgery.

By using the Caprini model, we found that prolonged surgical duration (> 45 minutes), age 41-60, and being confined to bed for more than 72 hours were the most common VTE risk factors. In this study, prolonged surgeries were found in 78.8% of patients, which was in line with results reported in a study by Zhai et al. [13]. Other common risk factors included age 41-60 and confined to bed more than 72 hours. Older age is associated with a higher risk of VTE after surgery [1]. Moreover, an elderly patient confined to bed more than 72 hours would have their VTE risk increased by 15 folds [14]. Thus, a comprehensive VTE prevention strategy should be utilized for these patients and an early mobilization or mechanical prophylaxis should be encouraged in addition to pharmacological approach.

On the other hand, we also evaluated the risk of bleeding in our participants. Predicting the risk of bleeding is as important as predicting the risk of VTE, acknowledged that improper use of anticoagulants may, reversely, induce the risk of bleeding in some patients. As far as we are concerned, there was insufficient guidance on assessing the risk of bleeding in surgical patients. The ACCP 2012 guideline has described certain factors that could increase the bleeding risk including previous major bleeding, severe renal impairment, concurrent use of antiplatelet, and several surgical characteristics [7]. However, no specific threshold for using mechanical prophylaxis (as a substitute method) was demonstrated. This discrepancy possibly explained why all 6 patients with increased risk of bleeding did not receive appropriate prophylaxis. They either received anticoagulants (4 patients) or did not receive any prophylaxis at all (2 patients).

The overall rate of appropriate thromboprophylaxis was low (35%). This finding is consistent with a previous study by Zhai et al. which showed insufficient prophylaxis for both surgical and medical patients [13]. The poor overall rate of appropriate prophylaxis in the present study could possibly be explained by two main reasons: the low rates of proper prophylaxis method (53%) and the low rates of proper anticoagulant prescription (43.4%).

First, the low rate (53%) of proper prophylaxis method (pharmacological or mechanical method) is mainly due to the under-prescription of anticoagulant in patients with moderate to high/very high VTE risk. This rate is lower than the finding in the ENDORSE study (2008) (63.5%) [12]. Underestimate of the VTE risk may be the underlying reason, as mentioned above in the case of non-major surgeries. In major surgeries, the low rate may be explained by the lack of mechanical prophylatic devices (elastic compression or intermittent pneumatic compression (IPC)), or the overestimation of patients' bleeding risk. Thus, to prompt the use of appropriate VTE prophylaxis, both VTE and bleeding risk stratifications should be considered.

Second, only 43.4% of patients in the study received an appropriate anticoagulant. This poor rate is primarily due to inappropriate choice of medication and/or dosage. In our study, enoxaparin was indicated for all patients after surgeries. When patients were ready to be discharged from the hospital, rivaroxaban was prescribed. The indication of enoxaparin is in line with the ACCP 2012 and the NICE 2018 guidelines which recommend LMWH as first-line thromboprophylaxis

in major- and several non-major orthopedic surgeries [7,9]. LMWH has a superior efficacy profile, lower risk of heparin induced thrombocytopenia (HIT) and it could be administered subcutaneously without monitoring or dose adjustment [7]. Improper choice of anticoagulant agents in our study mainly related to the use of rivaroxaban. Rivaroxaban is only officially approved for VTE prevention in hip or knee replacement surgeries [7]. Improper choice of medication was evident if patients were indicated rivaroxaban for hip fracture or non-major surgeries. However, studies have demonstrated the efficacy and safety profile of rivaroxaban for lower limb surgeries including hip fracture [15,16]. Rivaroxaban is also approved for such surgeries in certain countries [15]. Compared to anti-vitamin K oral anticoagulant, which is recommended by the ACCP 2012 guideline, rivaroxaban requires no therapeutic monitoring or frequent dose adjustment [7]. This may suggest further investigations on the efficacy and safety of rivaroxaban for VTE prevention in lower limb surgeries. In the meantime, indication of rivaroxaban for thromboprophylaxis should be limited to patients with hip and knee arthroplasty. Regarding rivaroxaban dose, 10 mg per day is recommended [7]. Inappropriate dosage such as exceed dose of rivaroxaban (15-20 mg) may exaggerate the risk of bleeding.

Regarding factors associated with the appropriateness of VTE prophylaxis, we found that patients who aged 41 years and above, having BMI > 25 kg/m2, prolonged surgical duration (> 45 minutes) and plaster cast or screw splint were less likely to receive appropriate VTE prophylaxis; while a prolonged hospital stay (> 4 days) after surgery increased the likelihood of receiving a proper VTE prophylaxis. Under-prescription in elderly patients and those with prolonged surgery duration is probably due to the overestimation or the fear of bleeding risk in such populations. Meanwhile, older age (≥ 41 years old) and prolonged surgical duration were predominantly associated with increased risk of VTE [1], [10]. In general, the benefits of VTE prophylaxis should outweigh the risk of bleeding in these patients and therefore, a prophylaxis plan should be considered [17]. BMI > 25 kg/m2 increases the risk of VTE after surgery [1,10]; however, the lack of guidance on adjusting anticoagulant dosages possibly deterred obese patients from receiving appropriate thromboprophylaxis. Despite immobilizing plaster cast is a predominant risk factor of VTE, the ACCP 2012 guideline suggests no thromboprophylaxis for individuals with plaster cast or screw splint [7]. This inconsistency has probably discouraged physicians from prescribing anticoagulants for these patients. In contrast, we found that patients who stayed in the hospital for more than 4 days after surgery were more likely to receive appropriate prophylaxis compared to those who stayed in a shorter time. Patients with complicated surgeries may require longer hospital stay and more attention to their VTE risk, resulted in a higher chance of receiving appropriate VTE prevention.

To our knowledge, this is one of the first studies that determined the risk of VTE and the appropriateness of thromboprophylaxis in patients with lower limb orthopedic surgery. While a thromboprophylaxis for patients undergoing non-major surgeries are not recommended in current guidelines, comprehensive risk stratification using Caprini score in our study demonstrated an elevated risk of VTE and the clinical need to prescribe prophylaxis for these patients. Nevertheless, this study also had certain limitations. First, we conducted the study in just one hospital and employed convenient sampling method to collect patients' medical record in a relatively short time, so the results cannot be extrapolated to other hospitals. Second, the observational study design may under-detect some VTE risk factors related to the patient's medical history.

Conclusion

The majority of patients undergoing lower limb orthopedic surgery were at increased risk of VTE. However, the overall rate of appropriate VTE prophylaxis was low. Factors associated with the appropriateness of VTE prophylaxis were age, BMI, surgical duration, plaster cast or screw splint, and length of hospital stay after surgery. Intervention measures should be taken to enhance/support the application of VTE prevention especially for patients with non-major surgeries.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to gratefully thank Gia Dinh People's hospital and Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh city that supported and facilitated the authors to complete this study.

ORCID ID

Kim Thai Thien Nguyen https://orcid.org/0000-0002-5548-0588
Thao Huong Nguyen https://orcid.org/0000-0002-5272-6298

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