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Original article

**Bleeding and thromboembolism risk of standard antithrombotic
prophylaxis after hip or knee replacement within an enhanced
recovery program**

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ABSTRACT

Introduction

Prevention of venous thromboembolism (VTE) generally consists of low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) after total hip arthroplasty (THA) or total knee arthroplasty (TKA). Enhanced recovery after surgery (ERAS) protocols may reduce the VTE risk after these procedures. The aim of this study was to compare the risk of VTE and the risk of bleeding complications in a non-selected population of primary THA and TKA cases done within an ERAS protocol.

Hypothesis

The risk of postoperative VTE after primary THA and TKA is lower than the risk of bleeding complications within an ERAS protocol.

Methods

This was a prospective observational study conducted on a national scale in France. All patients who underwent primary unilateral THA or TKA at one of 11 participating hospitals between October 2016 and October 2017 were enrolled and followed for 3 months. The occurrence of a VTE or major bleeding event was recorded. No patients were lost to follow-up at 3 months.

Results

Of the 1110 THA cases, there were 5 VTE (0.4%) and 19 bleeding events (1.7%). Of the 893 TKA cases, there were 9 VTE (1.0%) and 14 bleeding events (1.7%). There was no significant difference in the VTE incidence and bleeding event incidence after THA and TKA. The overall incidence of bleeding complications (1.7%) was significantly greater than the overall incidence of VTE complications (0.7%) ($p = 0.005$). This was the case after THA ($p = 0.004$) but not after TKA.

Discussion

The primary finding of this study is that bleeding complications are significantly more common than VTE complications after THA or TKA within an ERAS protocol. Based on these findings, the cost-benefit ratio of antithrombotic prophylaxis by LMWH or DOACs in this context should be reassessed.

Level of evidence: IV; Prospective cohort study without control group

Keywords: Total hip arthroplasty; total knee arthroplasty; venous thrombosis event; prophylaxis; bleeding

1. Introduction

Venous thromboembolism (VTE) is a potentially serious complication after total hip arthroplasty (THA) and total knee arthroplasty (TKA) that justifies various prophylactic measures [1,2,3]. While international guidelines are not uniform [4,5,6], aggressive prophylaxis with low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs) is recommended in France [7]. The risk of bleeding complications is implicitly assumed but often not well evaluated [8,9]. The introduction of enhanced recovery after surgery (ERAS) protocols [10,11,12,13] may reduce the risk of VTE without altering the bleeding risk [3,14], and consequently modify the cost-benefit ratio of current recommendations [15].

The primary objective of this study was to compare the risk of VTE and bleeding events in a non-selected population of primary THA and TKA cases done within an ERAS protocol. The secondary objectives were to identify VTE or bleeding risk factors that are specific to ERAS. The hypothesis was that the risk of postoperative VTE after primary THA or TKA is lower than the risk of bleeding complications when the patient follows an ERAS protocol.

2. Methods

2.1. Study overview

This was a prospective observational study conducted on a national scale in France. It complied with the recommendations of the Helsinki declaration and was approved by the Ethics Committee of the Strasbourg University Hospital. All the participating sites were selected on a volunteer basis. These hospitals had already implemented an ERAS protocol for TKA and THA before this study; the hospitals' respective protocols were not modified for this study. The common aspects of these protocols were use of multimodal perioperative analgesia [16,17], early ambulation (within 24 hours of procedure) [14,18] and free

rehabilitation with limitations placed on the joint range of motion or weight bearing. Discharge was allowed when the patient could walk alone with their pain under control; direct discharge to home was preferred [10,17].

2.2. Patients

All patients who underwent a primary unilateral TKA or THA procedure at one of the 11 participating hospitals between October 2016 and October 2017 were eligible for this study after having provided written informed consent. All patients were included in that hospital's ERAS protocol; there were no refusals. A cohort of 1949 patients was followed prospectively. There were 1136 women (58%) and 813 men (42%) with a mean age of 70 ± 11 years (min 19, max 97) (Table 1) who had the typical indications for this type of procedure. Table 2 lists their risk factors for bleeding and VTE complications. More specifically, 1110 patients (57%) underwent a THA procedure and 839 (43%) underwent a TKA procedure. All patients followed the ERAS protocol that included getting out of bed within 24 hours of the procedure; 1559 patients (80%) were discharged to home after the surgery with a mean length of hospital stay of 3.3 ± 2.9 days (min. 1, max. 35) for THA and 4.4 ± 3.3 days (min. 1, max 30) for TKA. Antithrombotic prophylaxis consisted of LWMH or similar molecules in 1651 cases (85%) and DOACs in 298 cases (15%). This prophylaxis was initiated on the day of the procedure in 681 cases (61%) and on the next day in 429 cases (39%). Also, 1594 patients received systemic tranexamic acid injection (82%).

2.3. Assessment methods

All patients were evaluated after 3 months; none were lost to follow-up (Fig. 1). The following complications were recorded:

VTE:

- deep or distal vein thrombosis with clinical symptoms and ultrasonography confirmation
- pulmonary embolism with clinical symptoms and CT or MRI confirmation

Major bleeding event:

- hematoma at surgical site requiring therapeutic modification (strengthening of analgesic treatment, modification to rehabilitation protocol, modification to anticoagulant or anti-platelet treatment, aspiration, percutaneous drainage, surgical draining)
- external bleeding at the surgical site requiring a therapeutic modification (see above)
- wound drainage that does not dry up spontaneously after 5 days
- bleeding at another site (digestive, ocular, cerebral, etc.)
- need for homologous transfusion no matter the reason.

The treatment applied to the complication and its effect on the outcome were also collected.

2.4. Statistical analysis

The statistical calculations were done using an Excel™ spreadsheet (Microsoft, Issy-les-Moulineaux, France) with the XLSTAT™ add-on (Addinsoft, Bordeaux, France). The sample size was calculated using the following basic information: α risk = 0.05, β risk = 0.20, expected frequency of bleeding events = 4%, minimum clinically significant difference = 1%. This calculation pointed to a minimum of 798 observations needed. The VTE and major bleeding events were compared using a Chi-square test on the entire cohort then separately on the THA and TKA cases. The effect of potential prognostic variables identified before the study (listed in Tables 1 and 2) and the effect of the type of thromboprophylaxis administered were analyzed. The data were compared between the different hospitals to identify any center

effects. Categorical data were analyzed using the Chi-square test. All statistical tests were done with a 5% threshold.

3. Results

Of the 1110 THA, there were 5 VTE (0.4%) (2 non-fatal pulmonary embolism and 3 deep vein thrombosis). All were treated conservatively with no impact on the outcome. There were 19 major bleeding events (1.7%): 10 significant hematomas (of which five required surgical drainage and 3 were followed by an infection) and 9 cases of anemia (4 required transfusion).

Of the 839 TKA, there were 9 VTE (1.0%): 4 non-fatal pulmonary embolism and 5 deep vein thrombosis. All were treated conservatively with no impact on the outcomes. There were 14 major bleeding events (1.7%): 8 hematoma (of which 4 required surgical draining and 2 were followed by an infection) and 6 cases of anemia (5 required transfusion).

The overall incidence of bleeding complications (1.7%) was significantly greater than the overall incidence of VTE complications (0.7%) ($p = 0.005$). This was also the case for THA in isolation ($p = 0.004$) but not TKA. There was no significant difference in the VTE rate and bleeding event rate after THA and TKA.

None of the risk factors analyzed had a significant impact on the risk of VTE (Table 3) or major bleeding events (Table 4), except for the effect of taking antiplatelet or anticoagulant agent before the procedure on the bleeding risk (Table 4). In particular, the type of thromboprophylaxis administered and use of tranexamic acid had no significant effect (Tables 3 and 4). There was also no significant difference in the percentage of VTE and major bleeding events between the various participating hospitals (Table 5).

4. Discussion

Our study hypothesis was confirmed: the risk of postoperative VTE after primary THA or

TKA was significantly lower than the risk of bleeding events when the patient follows an ERAS protocol. One takeaway from this study is that symptomatic VTE after THA or TKA within an ERAS protocol are now rare, with an incidence of 0.7%. This very low level is clearly lower than the one published after standard rehabilitation protocols [8,20,21,22,23] for comparable populations who received similar prophylactic treatment (Table 6). In particular, a French study on a similar population with standard thromboprophylaxis found a VTE incidence of 1.3% after THA and 2.8% after TKA [24]. Other studies have reported comparable results after similar ERAS protocols [25], sometimes even after simplified [26] or shortened prophylactic protocols [27] (Table 3). Lastly, aspirin may have a role in prophylactic antithrombotic treatment [26].

All of these findings suggest that ERAS protocols themselves help to reduce the risk of VTE complications [14,25] – probably because getting the patient out of bed early on reactivates the muscular pump [14] – since the other components of ERAS protocols, especially non-opioid multimodal analgesia are not known to affect the postoperative risk of VTE. We hypothesize that doing these procedures on an outpatient basis, which is still rare in France but likely coming up, could further reduce this risk [28,29], although this possibility could not be analyzed in our study. In any case, given the absence of any complications specific to ERAS protocols [25], together, these elements confirm these procedures should now be the standard postoperative treatment after primary THA and TKA. The difficulties with implementing these procedures, mainly due to organizational issues, but also related to the psychological obstacles to change, should not hinder this progress [30].

The other takeaway is that bleeding complications were significantly more frequent than VTE, with an incidence of 1.7%. This incidence, in absolute numbers, is not totally unacceptable, and is similar to other recent publications [8,20,22,31]. Thus, we cannot expect an alteration to the bleeding risk because of ERAS protocols. However, this reduction in

number of VTE complications alters the cost-effectiveness ratio of LMWH or DOAC prophylaxis, as these complications very often require specific treatment, and sometimes re-operation [32], which have an effect on the speed of recovery and potentially on the procedure's outcome. We must also mention wound healing disturbances with prolonged discharge, which are more likely with anticoagulant treatments, and set the stage for surgical site infections, with its well-documented treatment challenges [33]. We must also cite the difficulties with treatment compliance, especially with DOAC prescriptions, which may increase the risk of iatrogenic complications [34]. The results of this study suggest that the cost-benefit ratio of antithrombotic prophylaxis by LMWH or DOACs after THA or TKA within an ERAS protocol should be reassessed. [21]. It seems desirable to personalize the postoperative antithrombotic prophylaxis based on the individual risk of VTE or postoperative bleeding [6,20,35]. The use of aspirin may be an acceptable compromise in patients without major risk factors for thrombosis [6,22,26,28,36]. But since the literature does not provide any specific protocol [27,28,37], this decision must be made on a case-by-case basis by analyzing the risks related to the procedure and those related to the patient [6]. However, these selection criteria have not been validated.

We did not identify any risk factors for the occurrence of VTE or bleeding event specific to ERAS protocols. Multiple risk factors for VTE have been suggested in the literature: higher age, female sex, obesity, personal or family history of VTE, advanced cancer, tourniquet time, duration of procedure [38-40]. In parallel, multiple risk factors for major bleeding events have been described: advanced age, high or low weight, kidney failure [40,41]. However, none of these factors had a significant effect on the VTE or major bleeding percentage in this study. But this is not surprising given the low incidence of these complications. A much larger sample size would be needed, although this does not seem feasible except in a meta-analysis.

Our current study has several limitations. 1) This was a purely observational multicenter study; thus, some potential biases were not controlled for. For example, the ERAS protocols could vary between hospitals, and the observed complication rates may have reflected these different practices instead of the application of the ERAS protocol itself. Nevertheless, the guiding principles were the same and applied in a consistent manner at all sites. 2) The complications were compiled, and their severity evaluated differently in the participating hospitals; however, a univocal endpoint or one determined by a single rater was not realistic. Nevertheless, this study is a true analysis of the practices of the participating teams, with university and private-practice recruitment in large or medium-sized cities, which paint an acceptable picture of the national practices in France. 3) The sample size was small for analyzing the occurrence of low probability events, although our power calculation pointed to it being enough to detect the expected effect. This does not bring into question the significant nature of the difference observed and would only be a drawback if no differences had been found. However, the small sample size may explain why no risk factors were identified for VTE or major bleeding events.

5. Conclusion

The prescription of LMWH or DOAC after primary THA or TKA within an ERAS protocol could significantly increase the risk of bleeding events over VTE events. Personalization of antithrombotic prophylaxis in the context of ERAS is desirable, although the criteria must still be defined [6].

Conflict of interest:

Jean-Yves Jenny: Royalties from B-Braun, paid consultant for FH Orthopedics, board member for CAOS-International and ISTA and GECO. Aymar de Ladoucette : Board of

SFHG, and outside the current study is consultant for Microport outside of this study. Patrice Mertl is current president of SFHG and consultant for Stryker and Depuy, has educational support from Stryker, Depuy and perceives royalties from X-Nov and Adler. Marc-Pierre Henry is consultant for Medacta. Nicolas Bonin perceives royalties from Dedienné Santé and is consultant for Stryker and Conmed. Philippe Tracol perceives royalties from Stryker. Philippe Boisrenoult, Cyril Courtin, Yacine Bulaid and Pierre Henky Julien Chouteau declare no conflict related or outside the current study.

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Author contributions: JYJ – study design, data collection, data analysis, writing of manuscript

ADL – study design, data collection, data analysis, edition of manuscript. Pm, YB, MPH, NB, PT, CC, JC, PH, PB, CS surgery data collection and manuscript redaction

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Table 1: Study population

	THA (N = 1110)	TKA (N = 839)	Total (N = 1949)
Age (mean \pm standard deviation, min/max)	65 \pm 12 years (16; 94)	70 \pm 9 years (12; 97)	69 \pm 11 years (12; 97)
Sex: men / women (count, percentage)	499 (45%) / 611 (55%)	314 (37%) / 525 (63%)	813 (42%) / 1.136 (58%)
BMI (mean \pm standard deviation, min/max)	27.7 \pm 5.4 kg/m ² (12.9; 60.2)	29.9 \pm 5.6 kg/m ² (17.6; 56.5)	28.7 \pm 5.6 kg/m ² (12.9; 60.2)
Length of hospital stay (mean \pm standard deviation, min/max)	3.3 \pm 2.9 days (1; 35)	4.4 \pm 3.3 days (1; 30)	3.8 \pm 3.1 days (1; 35)
Home discharge (count, percentage)	903 (81%)	584 (70%)	1.487 (76%)
LMWH / DOAC (count, percentage)	910; 200 (82%; 18%)	741; 98 (88%; 12%)	1651; 298 (85%; 15%)
Thromboprophylaxis started on D0 (count, percentage)	681; 429 (61%; 39%)	527; 312 (63%; 37%)	1208; 741 (62%; 38%)
Administration of tranexamic acid (count, percentage)	848 (76%)	746 (89%)	1.612 (83%)

THA: total hip arthroplasty, TKA: Total knee arthroplasty, BMI: Body Mass Index LMWH:

Low molecular weight heparin DOAC: Direct oral anticoagulants

Table 2: Significant comorbidities

	THA (N = 1110)	TKA (N = 839)	Total (N = 1949)
Age > 75 years (count, percentage)	300 (27%)	261 (31%)	561 (29%)
Female sex (count, percentage)	611 (55%)	525 (63%)	1.136 (58%)
BMI > 25 kg/m ² (count, percentage)	743 (67%)	666 (79%)	1.409 (72%)
Weight < 40 kg or > 120 kg (count, percentage)	24 (2%)	20 (2%)	44 (2%)
Advanced cancer (count, percentage)	0 (0%)	0 (0%)	0 (0%)
ASA 1-2-3 (count, percentage)	228; 667; 215 (21%; 60%; 19%)	90; 551; 198 (11%; 66%; 23%)	318; 1.218; 413 (16%; 63%; 21%)
History of VTE (count, percentage)	17 (2%)	9 (1%)	26 (1%)
Tourniquet use (count, percentage)	Not applicable	321 (38%)	321 (29%)
Standard anticoagulant or antiplatelet treatment (count, percentage)	258 (23%)	104 (12%)	362 (19%)

THA: total hip arthroplasty, TKA: total knee arthroplasty, BMI: body mass index

Table 3: Risk factors for venous thromboembolism

	VTE complication	No complication	Significance
Age \geq 75 years	4 (1%)	610 (99%)	NS
Age < 75 years	10 (1%)	1325 (99%)	
Female	11 (1%)	1125 (99%)	NS
Male	3 (0.4%)	810 (99.6%)	
BMI \geq 25 kg/m ²	11 (1%)	1427 (99%)	NS
BMI < 25 kg/m ²	3 (1%)	508 (99%)	
Advanced cancer	0	0	NS
No advanced cancer	14 (1%)	1935 (99%)	
History of VTE	0 (0%)	15 (100%)	NS
No history of VTE	14 (1%)	1920 (99%)	
Tourniquet (TKA)	4 (1%)	263 (99%)	NS
No tourniquet used (TKA)	5 (1%)	567 (99%)	
Prior antiplatelet / anticoagulant treatment	0	362 (100%)	NS
No prior antiplatelet / anticoagulant treatment	14 (0.9%)	1573 (99.1%)	
LMWH prophylaxis	12 (0.7%)	1639 (99.3%)	NS
DOAC prophylaxis	2 (0.7%)	296 (99.3%)	
Administration of tranexamic acid	11 (0.7%)	1583 (99.3%)	NS
No administration of tranexamic acid	3 (0.8%)	352 (99.2%)	

TKA: Total knee arthroplasty, BMI: Body Mass Index LMWH: Low molecular weight heparin, DOAC: Direct oral anticoagulants

Table 4: Risk factors for major bleeding events

	Major bleeding event	No major bleeding event	Significance
Age \geq 75 years	15 (2%)	599 (98%)	NS
Age < 75 years	18 (1%)	1317 (99%)	
Weight \leq 40 kg or \geq 120 kg	0	61 (100%)	NS
40 kg < Weight < 120 kg	33 (2%)	1855 (98%)	
Kidney failure	1 (%)	66 (99%)	NS
No kidney failure	32 (2%)	1850 (98%)	
Previous procedure	3 (3%)	91 (97%)	NS
No previous procedure	29 (2%)	1826 (98%)	
Prior antiplatelet / anticoagulant treatment	11 (3.0%)	351 (97.0%)	p = 0.03
No prior antiplatelet / anticoagulant treatment	22 (1.4%)	1565 (98.6%)	
LMWH prophylaxis	27 (1.6%)	1624 (98.4%)	NS
DOAC prophylaxis	6 (1.7%)	349 (98.3%)	
Administration of tranexamic acid	28 (1.8%)	1566 (98.2%)	NS
No administration of tranexamic acid	5 (1.4%)	350 (98.6%)	

LMWH: Low molecular weight heparin, DOAC: Direct oral anticoagulants

Table 5: Comparison of venous thromboembolism and major bleeding events in the participating sites

Site	Number of cases included	VTE (count, percentage)	Bleeding (count, percentage)
Amiens	638	4 (0.6%)	8 (1.3%)
Annecy	111	0	0
Brest	36	0	0
Cavaillon	161	4 (2.5%)	5 (3.1%)
Lyon	192	2 (1.0%)	1 (0.5%)
Lyon CHU	42	0	0
Saint-Louis	31	0	0
Strasbourg	183	0	1 (0.5%)
Strasbourg CHU	124	0	4 (3.2%)
Toulouse	165	0	5 (3.0%)
Versailles	266	4 (1.5%)	9 (3.4%)
Total	1949	14 (0.7%)	33 (1.7%)
Significance		NS	NS

Table 6: Comparisons to key published studies on the same topic

Authors	Year of publication	Procedure	VTE	Major bleeding event	Comments
Samama et al. [24]	2007	Standard	1.8%	1.0%	1080 cases THA + TKA
Kulshrestha et Kumar [20]	2013	Standard	2.1%	6.4%	900 cases TKA
Aynardi et al. [21]	2014	Ambulatory vs Standard	0		197 cases THA
Colwell et al. [23]	2014	Standard	0.9%		3060 cases THA + TKA
Odeh et al. [22]	2016	Standard	1.5%	0.5%	2611 cases THA + TKA
Jørgensen et al. [27]	2013	ERAS	0.4%		4924 cases THA + TKA
Anderson et al. [23]	2018	ERAS	0.7%	0.4%	3424 cases THA + TKA
Grosso et al. [25]	2019	ERAS	0.4%		86,099 cases THA
Current study	2020	ERAS	0.4%	1.7%	1949 cases THA + TKA

THA: total hip arthroplasty, TKA: Total knee arthroplasty, BMI: Body Mass Index, ERAS: enhanced recovery after surgery protocol

FIGURE LEGENDS

Figure 1: Study design

1949

Patients eligible



1949

Patients included



1949

Patients operated



1949

Patients reviewed at 3 months



1949

Records analyzed