Bridging anticoagulation in patients treated with vitamin K antagonists prior to trochanteric and hip fracture surgeries: The current practice

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Abstract

Background. The strategies of perioperative bridging anticoagulation in orthopedic surgical patients during oral anticoagulation (OAC) therapy with vitamin K antagonists (VKA) vary from center to center.

Objectives. The aim of this single-center study was to assess the risk of bleeding and thromboembolic events (TEs) in bridged patients on VKA who underwent orthopedic surgery due to trochanteric or hip fracture.

Material and methods. The retrospective study included 64 patients (mean age: 80 years) who received VKA for at least 3 months prior to orthopedic procedure. All subjects were bridged with enoxaparin (40 mg once a day). The control group (n = 69) comprised of age-, sex- and procedure-matched patients operated on for the same indications, but with neither a history of VKA therapy nor perioperative bridging anticoagulation.

Results. Severe postoperative bleeding occurred in 19 (29.7%) patients from the VKA group and in 13 (18.8%) controls (p = 0.16). Within the VKA group, intertrochanteric fractures (52.6%) and femoral neck fractures (47.4%) occurred more often in patients with bleeding than other lower extremity fractures (0%; p = 0.03). Severe adverse events (SAEs) were more common in the VKA group than in the controls (12.5% vs 1.5%; p = 0.01). Patients from the VKA group did not differ from the controls in the incidence of TEs (6.3% vs 8.9%; p = 0.31). No intrahospital mortality was documented.

Conclusions. Prophylactic administration of enoxaparin is a common strategy of bridging anticoagulation in a hospital setting. This approach does not seem to be associated with an increase in thromboembolic risk nor higher risk of bleeding in orthopedic patients who received VKA preoperatively.

Key words: anticoagulation, low molecular weight heparin, vitamin K antagonists, bridging therapy, trochanteric and hip neck fracture surgery

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Introduction

A large proportion of older persons from many countries receive oral anticoagulation (OAC) with vitamin K antagonists (VKA); one example is the UK, where VKA are prescribed to approx. 1% of older patients.[1,2] Noticeably, such individuals are more prone to osteoporosis, an established risk factor for femoral neck fracture.

Fixation of femoral neck and trochanteric fractures is a relatively common surgical procedure in older patients, associated with high comorbidity and mortality rates.[3–5] According to the literature, hip and trochanteric surgeries carry a 4% risk of perioperative mortality and a 3.2% risk of thromboembolism.[6] Despite the implementation of thromboprophylaxis, pulmonary embolism (PE) is still a common cause of perioperative mortality, accounting for approx. 10% of deaths among older orthopedic inpatients.[7] A retrospective analysis including a total of 3,082 patients who underwent hip, knee or spine surgeries documented major perioperative bleeding in 5.3% of the cases.[8] In another study, the incidence of thromboembolic events (TEs) and mortality rates in patients undergoing total hip or knee arthroplasties were estimated at 4% and approx. 0.7%, respectively.[9] A large proportion of patients being referred to an orthopedic treatment are at increased risk of venous thromboembolism (VTE), stroke or systemic embolism, due to the presence of atrial fibrillation (AF), mechanical heart valves or recurrent VTE; such individuals require long-term OAC therapy with VKA or new generation anticoagulants.

Appropriate anticoagulation treatment can be challenging in patients operated on in an emergency setting; while discontinuation of OAC may increase the risk of TEs, its maintenance may predispose to bleeding-related complications.[10] In a study of 1,884 patients with AF, in whom VKA treatment has been interrupted prior to an elective surgery or other invasive procedure, forgoing bridging anticoagulation was not inferior to perioperative bridging with low-molecular-weight-heparin (LMWH) in the prevention of arterial thromboembolism, while it decreased the risk of major bleeding.[11] Nevertheless, bridging therapy with LMWH should be applied to minimize thromboembolic risk during the anticoagulation-free interval, and in line with current guidelines, LMWH at a therapeutic dose is preferred in surgical patients at increased risk of bleeding and thromboembolic complications.[12] Perioperative administration of LMWH as a component of bridging anticoagulation may be associated with an increased risk of bleeding and severe adverse events (SAEs), such as intracranial hemorrhage with subsequent major disability or even death.[13–17] The ORBIT-AF study included a total 7,372 patients receiving OAC therapy; among them 665 individuals were given a short-acting anticoagulant to reduce the risk of TEs during a temporary discontinuation of OAC. In this study, bridging anticoagulation was associated with an increased risk of bleeding and other adverse events after the interruption of OAC.[18] A meta-analysis including a total of 7,118 bridged and 5,160 nonbridged patients demonstrated unequivocally that heparin bridging is associated with a 3–4% risk of major bleeding and 13–15% risk of overall bleeding complications in the perioperative period.[17]

To the best of our knowledge, bridging anticoagulation and its outcomes in Polish orthopedic inpatients receiving a long-term treatment with VKA has been a subject of only a few previous studies. The aim of this single-center study was to assess the risk of bleeding and TEs and the impact of bridging anticoagulation in patients on VKA who underwent orthopedic surgery due to trochanteric or hip fracture.

Material and methods

Patients

The retrospective study included all consecutive patients receiving VKA, who underwent surgical fixation of trochanteric or femoral neck fracture at the Department of Orthopedics, St. Lucas Hospital in Tarnów, Poland, in the period of 2012–2014. The study received the approval of the bioethics committee. A total of 4,453 patients were treated surgically for trochanteric or hip fractures during the study period, and individuals on VKA therapy represented 1.4% of this population. The VKA group included 24 (37.5%) patients with intertrochanteric fractures, 24 (37.5%) with femoral neck fractures, 2 (3.1%) with shank fractures, and 14 (21.9%) with ankle fractures. Only the patients who received bridging anticoagulation in line with the hospital protocol (n = 64) were included in the analysis. According to the protocol, anticoagulation therapy was discontinued on the day of admission, and enoxaparin (40 mg per day) was given 1 day prior to the orthopedic procedure and 1 day thereafter. All patients were informed about possible risks of discontinuation of OAC and implementation of bridging therapy beforehand, and gave their informed consent to this approach. The control group (n = 69) was comprised of age-, sex- and procedure-matched patients operated on for the same indications, but with neither a history of OAC with VKA nor perioperative bridging anticoagulation. Lower extremity fractures were diagnosed based on a physical examination, as well as pelvic and femoral radiograms.

Patients who received anticoagulation therapy with non-vitamin K or direct oral anticoagulants (NOACs) and/or individuals subjected to conservative treatment of the fracture were excluded from the study. Information about past and present comorbidities was extracted from patients' medical histories. Postoperative bleeding was classified as severe whenever the patient required a transfusion of at least 2 units of packed red blood cells. Severe adverse events were defined as major bleeding or serious cardiovascular events, such as myocardial infarction (MI),

stroke, VTE, or dyspnea after the surgery. The interruption of anticoagulation therapy was 2–7 days. Depending on the type of fracture, the study subjects underwent total hip arthroplasty or interlocking fixation of trochanteric fracture with the intramedullary GAMMA nail. In the case of total hip arthroplasty, the patient was placed on the nonfractured side; a straight incision, approx. 15 cm in length, was made, and either Bipolar or Exeter prosthesis (Stryker Howmedica, Kalamazoo, USA) with acrylic cement was implanted from a posterolateral approach. The mean duration of the procedure, defined as the time between the incision and placement of the last suture, was 70–80 min. Intertrochanteric fractures were treated by intramedullary stabilization with the GAMMA nail. This minimally invasive procedure was associated with only a mild bleeding. The mean time of the surgery was about 60 min.

Laboratory tests

Blood samples for laboratory testing were collected 12 h prior to the surgery and 8 h post-surgery. All laboratory tests were conducted at a local hospital laboratory using standardized assays.

Statistical analysis

Normal distribution of continuous variables was verified with the Kolmogorov-Smirnov test. Statistical characteristics of normally distributed variables are presented as means ± standard deviations (SD). Otherwise, the results are presented as medians (interquartile ranges (IQR)). Prior to statistical analysis, non-normal data was subjected to a logarithmic (log 10) transformation. Depending on the distribution type, the Student's t-test or the Mann-Whitney U test was used for intergroup comparisons of continuous variables. Distributions of categorical variables are presented as numbers and percentages, and were compared using χ^2 test. The results of statistical tests were considered significant whenever a 2-sided p-value was lower than 0.05. All calculations were carried out with STATISTICA v. 9.1 (StatSoft Inc., Tulsa, USA).

Results

Preoperative period

The study included 133 patients with trochanteric or femoral neck fractures (47 men and 86 women) with a mean age of 80 years. Baseline characteristics of the study subjects are summarized in Table 1. None of the controls had indications for VKA therapy. Indications for OAC in the VKA group included AF (n = 56; 87.5%), mechanical valve replacement (n = 7; 10.9%) and a previous VTE (n = 1; 1.6%). A total of 34 patients (53.1%) were treated with warfarin and 30 (46.9%) with acenocumarol. Subjects from the VKA group had higher body weight and body mass index (BMI) than the controls, and more often received aspirin, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and proton pump inhibitors. Moreover, they presented with significantly higher preoperative international normalized ratios (INR), activated partial thromboplastin time (APTT), red cell distribution width (RDW), and creatinine levels, as well as with significantly lower platelet counts and fasting blood glucose concentrations, than the controls. The study groups did not differ significantly in terms of the main diagnoses, comorbidities and medications (Table 1).

Postoperative period

During the postoperative period, severe bleeding occurred in 19 (29.7%) patients from the VKA group and in 13 (18.8%) controls (Table 2). Severe adverse events were more common in the VKA group than in controls (n = 8; 12.5% vs n = 1; 1.5%; p = 0.01). No significant intergroup differences were found in the incidence of cardiovascular complications, such as MI, stroke and VTE, as well as in terms of other complications (Table 2). Patients on VKA received more fresh frozen plasma units and required longer preoperative hospitalization. Within the VKA group, intertrochanteric fractures and femoral neck fractures occurred more often in patients with bleeding than with lower extremity fractures (intertrochanteric fractures: n = 10; 52.6% vs n = 14; 31.1%; femoral neck fractures: n = 9; 47.4% vs n = 15; 33.3%; other fractures: n = 0 vs n = 16; 34.6% in patients with hemorrhage and in patients without hemorrhage, respectively; p = 0.03) (Table 3). Patients from the VKA group who experienced perioperative hemorrhage did not differ from other subjects from this group in terms of their basic characteristics, medications and laboratory parameters (Table 3).

Discussion

The findings presented here demonstrate that patients operated on due to trochanteric or femoral neck fractures, both with prophylactic LMWH bridging and without it, were not at increased risk for bleeding and TEs.

Risk of bleeding is a major concern related to bridging anticoagulation. Recent evidence suggests that periprocedural bleeding-to-thrombosis ratio in bridged and non-bridged patients approximates 13:1 and 5:1, respectively, which implies that the former group is at a considerable risk of bleeding.[19] Indeed, according to literature, anticoagulation-related hemorrhage is associated with increased morbidity and mortality, which surpasses the benefits of perioperative bridging.[20,21] Thromboembolic events occur rarely during periprocedural period; in contrast, bleeding complications after implementation of bridging therapy

Table 1. Characteristics of the study subjects

Variable	Overall (n = 133)	VKA group (n = 64)	Controls (n = 69)	p-value
Age [years]	80 (72–86.5)	79.5 (72.25–86)	80 (68.5–87)	0.78
Male gender, n [%]	47 (35.3)	28 (43.8)	19 (27.5)	0.07
Body weight [kg]	70.0 (63.0–80.0)	72.0 (65.0–85.7)	69.0 (61.5–76.0)	0.03
Body height [cm]	165.7 (±8.0)	165.7 (±7.5)	165.8 (±8.5)	0.92
BMI [kg/m^2]	25.7 (23.2–28.4)	26.0 (23.5–30.0)	25.1 (23.0–27.5)	0.04
Current smoker, n [%]	2 (2.90)	0 (0.0)	2 (2.90)	1.00
Diagnosis				
Intertrochanteric fracture, n [%]	49 (36.84)	24 (37.50)	25 (36.23)	0.76
Femoral neck fracture, n [%]	48 (36.09)	24 (37.50)	24 (34.78)	–
Lower leg fracture, n [%]	7 (5.26)	2 (3.13)	5 (7.25)	–
Other fracture, n [%]	29 (21.80)	14 (21.88)	15 (21.74)	–
Indication for anticoagulation				
VTE, n [%]	1 (0.75)	1 (1.56)	0 (0.00)	0.48
AF, n [%]	56 (42.11)	56 (87.50)	0 (0.00)	<0.0001
Artificial heart valve, n [%]	7 (5.26)	7 (10.94)	0 (0.00)	0.005
Comorbidities				
CHD, n [%]	71 (53.38)	40 (62.50)	31 (44.93)	0.06
MI, n [%]	16 (12.03)	11 (17.19)	5 (7.25)	0.11
Previous stroke, n [%]	11 (8.27)	6 (9.38)	5 (7.25)	0.76
Arterial hypertension, n [%]	96 (72.18)	51 (79.69)	45 (65.22)	0.08
DM, n [%]	19 (14.29)	9 (14.06)	10 (14.49)	1.00
Hyperthyroidism, n [%]	8 (6.02)	6 (9.38)	2 (2.90)	0.15
Hypothyroidism, n [%]	7 (5.26)	3 (4.69)	4 (5.80)	1.00
CKD, n [%]	8 (6.02)	4 (6.25)	4 (5.80)	1.00
COPD, n [%]	6 (4.51)	2 (3.13)	4 (5.80)	0.68
Asthma, n [%]	4 (3.01)	1 (1.56)	3 (4.35)	0.62
Superficial thrombosis, n [%]	4 (3.01)	3 (4.69)	1 (1.45)	0.35
Previous gastric ulcer, n [%]	5 (3.76)	3 (4.69)	2 (2.90)	0.67
HF, n [%]	5 (7.81)	5 (7.81)	0 (0.0)	1.00
Medications				
VKA type				
Acenocumarol, n [%]	–	30 (46.88)	0 (0.0)	–
Warfarin, n [%]	–	34 (53.13)	0 (0.0)	–
LMWH				
Enoxaparin, n [%]	131 (98.50)	64 (100.00)	67 (97.10)	0.5
Nadroparin, n [%]	2 (2.90)	0 (0.00)	2 (1.50)	–
ASA, n [%]	106 (79.70)	61 (95.31)	45 (65.22)	<0.0001
β-blocker, n [%]	92 (69.70)	53 (84.13)	39 (56.52)	0.0006
ACEI, n [%]	104 (78.20)	56 (87.50)	48 (69.57)	0.02
ARB, n [%]	4 (3.01)	2 (3.13)	2 (2.90)	1.00
Aldosterone antagonist, n [%]	3 (2.26)	2 (3.13)	1 (1.45)	0.61
Calcium channel blocker, n [%]	18 (13.53)	13 (20.31)	5 (7.25)	0.04
Statin, n [%]	82 (61.65)	44 (68.75)	38 (55.07)	0.11
Fenofibrate, n [%]	20 (15.04)	12 (18.75)	8 (11.59)	0.33
Amiodarone, n [%]	2 (1.50)	2 (3.13)	0 (0.00)	0.23
Furosemide, n [%]	36 (27.07)	21 (32.81)	36 (27.07)	0.17
Metformin, n [%]	9 (6.77)	3 (4.69)	6 (8.70)	0.50
PPIs, n [%]	48 (36.09)	30 (46.88)	18 (26.09)	0.02

Table 1. Characteristics of the study subjects (cont.)

Variable	Overall (n = 133)	VKA group (n = 64)	Controls (n = 69)	p-value
NSAIDs, n [%]	6 (4.51)	5 (7.81)	1 (1.45)	0.11
Laboratory tests				
INR	1.43 (1.10–2.50)	2.59 (1.79–3.33)	1.10 (1.05–1.18)	<0.0001
APTT [s]	31.00 (27.65–37.85)	36.60 (31.35–44.36)	28.30 (25.60–30.80)	<0.0001
FBG [g/L]	3.20 (2.90–3.57)	2.96 (2.72–3.62)	3.23 (2.99–3.56)	0.02
WBC [10^3/μL]	10.20 (8.00–12.85)	10.30 (8.05–13.25)	10.20 (8.00–12.50)	0.67
RBC [10^6/μL]	4.05 (3.40–4.38)	4.04 (3.32–4.43)	4.06 (3.55–4.37)	0.60
HGB [g/dL]	12.10 (10.35–13.35)	11.90 (9.83–13.48)	12.30 (10.80–13.30)	0.35
HCT [%]	36.90 (31.60–39.90)	36.75 (30.43–40.33)	37.10 (32.35–39.90)	0.55
RDW [%]	14.30 (13.60–15.25)	14.50 (13.83–15.80)	13.90 (13.40–14.80)	0.02
PLT [10^3/μL]	198.00 (155.00–255.00)	176.50 (136.50–241.50)	212.00 (172.50–260.00)	0.01
Glucose [mmol/L]	123.00 (108.75–145.00)	122.00 (110.00–138.50)	127.00 (108.00–148.00)	0.52
Creatinine [μmol/L]	74.00 (58.25–94.75)	82.00 (63.00–108.00)	71.00 (54.50–91.00)	0.01
eGFR [mL/min]	80.00 (57.50–98.00)	78.00 (55.00–94.00)	80.00 (62.00–102.25)	0.28

ACEI – angiotensin converting enzyme inhibitors; AF – atrial fibrillation; APTT – activated partial thromboplastin time; ASA – acetylsalicylic acid; ARB – angiotensin receptor blockers; BMI – body mass index; CHD – chronic heart disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; FBG – fibrinogen; HCT – hematocrit; HF – heart failure; HGB – hemoglobin; INR – international normalized ratio; PPIs – proton-pump inhibitors; LMWH – low molecular weight heparin; MI – myocardial infarction; NSAIDs – non-steroidal anti-inflammatory drugs; PLT – platelets; RBC – red blood cell count; RDW – red blood cell distribution width; ST – stroke; VKA – vitamin K antagonist; VTE – venous thromboembolism; WBC – white blood cell count.

are far more common and this preventive measure does not seem to provide an evident antithrombotic benefit.[20] Nevertheless, various forms of bridging anticoagulation are still commonly used in patients qualified for invasive procedures.[20] In our study, average blood loss in bridged patients (3.11 g/dL of hemoglobin) tended to be greater than in nonbridged subjects, but the difference was insignificant. Blood loss in patients operated on due to intertrochanteric fracture or hip neck fracture was greater than in individuals with other types of lower extremity fractures. Probably, this was associated with the older age of patients with intertrochanteric and hip neck fractures, and with a larger extent of surgical procedures performed in this group. Altogether, our findings imply that prophylactic administration of enoxaparin to older patients qualified for orthopedic surgeries is not associated with increased risk of major bleeding. Nevertheless, irrespective of bridging anticoagulation or lack thereof, the risk of bleeding in this group is still high, as shown by a large proportion of our patients who required postoperative blood transfusions.

Beneficial effects of bridging in patients at increased risk of TE are unclear, and we still lack sufficient evidence in this matter from well-designed clinical trials. However, the results of observational studies suggest that implementation of bridging therapy is associated with a substantial decrease in the incidence of VTE events, even in high-risk populations.[20,22] Therefore, until adequate evidence from clinical trials becomes available, individualized bridging anticoagulation therapy still should be considered in patients with established risk factors for VTE, such as mechanical mitral valve, or acute or recent VTE. Evidence from retrospective studies suggests that bleeding-to-thrombosis profile of bridged patients with implanted mechanical valves, i.e., with an established risk factor for TEs, may be relatively favorable.[23,24] Whenever bridging therapy is deemed necessary, more conservative strategies should be considered, namely, low-dose heparin, administration of heparin solely in the postoperative period, delayed initiation of postprocedural heparin bridging, delayed onset of postprocedural heparin bridging, and early cessation of warfarin when a international normalized ratio (INR) value reaches 2.0 or more.[25–27] Early discontinuation of VKA and administration of enoxaparin, 40 mg once a day, are a preferred bridging strategy at our department. Such an approach may raise some controversies, especially in patients with mitral valve prostheses. Unfortunately, the subset of our patients who received VKA due to the implantation of mechanical valves was too small to conduct a subgroup analysis (n = 11). Although none of these subjects developed a TE episode during the follow-up period, it is still unclear whether bridging with higher doses of LMWH or nonfractioned heparin should be recommended for patients from this group prior to a major surgical procedure.

In line with current recommendations, surgical treatment of hip fractures in older patients should be implemented early, optimally within 24–48 h post-admission.[28] However, adherence to these guidelines can be quite challenging in the case of patients on VKA anticoagulation therapy; reversal of OAC to prevent excessive bleeding may cause a significant delay in a major orthopedic procedure, such as hip surgery.[29,30] Such a delay is associated with increased morbidity and mortality.[31] Vitamin K antagonists therapy can be reversed passively, by interruption of warfarin and waiting until INR returns to the reference range (<1.2),

Table 2. Postoperative characteristics of the study subjects

Variable	Overall (n = 133)	VKA group (n = 64)	Controls (n = 69)	p-value
Complications				
Hemorrhage, n [%]	32 (24.1)	19 (29.7)	13 (18.8)	0.16
PE/VTE, n [%]	4 (3.01)	4 (6.25)	0 (0.00)	0.05
MI, n [%]	1 (0.75)	1 (1.56)	0 (0.00)	0.48
ST, n [%]	1 (0.75)	1 (1.56)	0 (0.00)	0.48
SAEs, n [%]	9 (6.77)	8 (12.50)	1 (1.45)	0.01
Other complications, n [%]	1 (1.45)	4 (6.25)	5 (3.76)	0.20
Perioperative care				
PRBCs, n [%]	33 (24.81)	19 (29.69)	14 (20.29)	0.23
PRBCs [units]	2.00 (2.00–4.00)	2.00 (2.00–4.00)	2.00 (2.00–2.50)	0.44
FFP, n [%]	19 (14.29)	11 (17.19)	11 (17.19)	0.46
FFP [units]	2.00 (2.00–2.00)	2.00 (2.00–2.00)	1.50 (1.00–2.00)	0.009
Preoperative [days]	4.00 (2.00–5.00)	4.00 (3.00–6.00)	3.00 (2.00–4.00)	0.0009
Postoperative [days]	5.00 (4.00–7.00)	6.00 (5.00–8.00)	6.00 (4.00–7.00)	0.06
Postoperative laboratory tests				
INR	1.17 (1.06–1.39)	1.17 (1.06–1.39)	1.19 (1.13–1.25)	0.72
APTT [a]	29.30 (27.23–31.78)	30.40 (26.80–34.10)	29.55 (27.13–32.75)	0.36
FBG [g/L]	3.01 (2.60–3.30)	2.52 (2.37–2.98)	3.18 (2.98–3.46)	<0.0001
WBC [10^3/µL]	9.40 (7.33–12.20)	9.60 (7.10–12.40)	8.90 (7.45–11.55)	0.48
RBC [10^6/µL]	3.64 (3.26–4.03)	3.64 (3.24–4.13)	3.65 (3.27–4.02)	0.86
HGB [g/dL]	10.65 (9.63–11.90)	10.70 (9.70–11.90)	10.60 (9.60–12.00)	0.86
HCT [%]	32.95 (29.43–36.30)	33.00 (29.20–36.90)	32.90 (29.55–36.05)	0.53
RDW [%]	14.60 (13.50–15.90)	15.10 (13.80–16.20)	14.30 (13.30–15.30)	0.01
PLT [10^3/µL]	205.00 (162.00–278.75)	198.00 (147.00–284.00)	207.00 (172.50–270.00)	0.33

APTT – activated partial thromboplastin time; FBG – fibrinogen; FFP – fresh frozen plasma; HCT – hematocrit; HGB – hemoglobin; INR – international normalized ratio; MI – myocardial infarction; PLT – platelets; PRBCs – packed red blood cells; PE – pulmonary embolism; RBC – red blood cell count; SAEs – serious adverse events; ST – stroke; VTE – venous thromboembolism; WBC – white blood cell count.

or actively, by the administration of vitamin K, fresh frozen plasma, clotting factor concentrates, or a combination thereof. In line with current guidelines, prior to a major surgery, INR should be lower than 1.5.[32] Our findings confirm that this recommendation is followed strictly in clinical practice. Bleeding and neurological complications may be also associated with the insertion or removal of a spinal or epidural catheter in an anticoagulated patient and, therefore, warfarin therapy is an absolute contraindication to regional anesthesia.[33] In St. Lucas Hospital in Tarnów (Poland), regional anesthesia is given solely to patients whose INR is lower than 1.2. To the best of our knowledge, no specific guidelines regarding anticoagulation reversal in patients with hip fracture have been published thus far. In the case of patients scheduled for elective orthopedic surgeries of the hip, most orthopedic surgeons follow a "wait and watch" policy, with discontinuation of warfarin approx. 5 days prior to the procedure in order to decrease INR to a subtherapeutic level.[34] Similarly, no guidelines exist regarding bridging therapy in patients on long-term warfarin therapy who have been qualified for a major elective orthopedic procedure. However, administration of LMWH is recommended in high-risk patients as long as their INR remains at a subtherapeutic level. Decision on an anticoagulation strategy used in such group of patients should be made jointly by a hematologist, cardiologist, anesthesiologist, and orthopedic surgeon. In line with current guidelines, in patients subjected to major orthopedic surgeries, extended pharmacological prevention of TE with LMWH or another anticoagulant administered for up to 35 days post-procedure should be preferred over a short-term prophylaxis; thromboprophylaxis should be started no later than within the first 12 h post-surgery.[35,36] In our study, past history of VTE, if any, could be adequately documented on the basis of medical documentation.

This study is not free from potential limitations. Firstly, owing to the retrospective character of the analysis, a postoperative follow-up of patients after hip and trochanteric surgeries was quite short (up to 35 days) and we had no access to information on the incidence of TE or stroke after discharge. Therefore, it cannot be excluded that some patients with unstable anticoagulation might have experienced TE shortly after cessation of the bridging. Secondly, pharmacological thromboprophylaxis followed the same protocol in all patients and, therefore, we were unable to analyze the potential effects of its type, duration and

Table 3. Characteristics of bridged patients with and without hemorrhage

Variable	Bridged patients (n = 64)	Bridged patients with hemorrhage (n = 19)	Bridged patients without hemorrhage (n = 45)	p-value
Age [years]	79.50 (75.25–86.00)	84.00 (76.00–87.00)	78.00 (72.50–84.50)	0.13
Male gender, n [%]	28 (43.75)	7 (36.84)	21 (46.67)	0.59
Weight [kg]	72.00 (65.00–85.75)	72.50 (63.75–82.25)	72.00 (65.00–90.00)	0.76
Height [cm]	165.65 (±7.51)	164.78 (±6.42)	165.65 (±7.51)	0.56
BMI [kg/m^2]	26.09 (23.52–30.02)	26.85 (22.86–31.81)	25.93 (23.98–29.58)	0.82
Diagnosis				
Intertrochanteric fracture, n [%]	24 (37.50)	10 (52.63)	14 (31.11)	0.03
Femoral neck fracture, n [%]	24 (37.50)	9 (47.37)	15 (33.33)	–
Lower leg fracture, n [%]	2 (3.13)	0 (0.00)	2 (4.44)	–
Other fracture, n [%]	14 (21.88)	0 (0.00)	14 (31.11)	–
Comorbidities				
VTE, n [%]	1 (1.56)	0 (0.00)	1 (2.22)	1.00
AF, n [%]	56 (87.50)	19 (100.00)	37 (82.22)	0.09
Artificial heart valve, n [%]	7 (10.94)	0 (0.00)	7 (15.56)	0.09
CHD, n [%]	40 (62.50)	13 (68.42)	27 (60.00)	0.58
MI, n [%]	11 (17.19)	2 (10.53)	9 (20.00)	0.48
Stroke, n [%]	6 (9.38)	1 (5.26)	5 (11.11)	0.66
Hypertension, n [%]	51 (79.69)	14 (73.68)	37 (82.22)	0.50
DM, n [%]	9 (14.06)	3 (15.79)	6 (13.33)	1.00
Insulin, n [%]	7 (10.94)	3 (15.79)	4 (8.89)	0.42
Hyperthyroidism, n [%]	6 (9.38)	0 (0.00)	6 (13.33)	0.17
Hypothyroidism, n [%]	3 (4.69)	0 (0.00)	3 (6.67)	0.55
CKD, n [%]	4 (6.25)	2 (10.53)	2 (4.44)	0.58
COPD, n [%]	2 (3.13)	1 (5.26)	1 (2.22)	0.51
Asthma, n [%]	1 (1.56)	0 (0.00)	1 (2.22)	1.00
Superficial thrombosis, n [%]	3 (4.69)	1 (5.26)	2 (4.44)	1.00
Gastric ulcer, n [%]	3 (4.69)	2 (10.53)	1 (2.22)	0.21
Complications				
PE/VTE postoperative, n [%]	4 (6.25)	0 (0.00)	4 (8.89)	0.31
MI postoperative, n [%]	1 (1.56)	0 (0.00)	1 (2.22)	1.00
ST postoperative, n [%]	1 (1.56)	1 (5.26)	0 (0.00)	0.30
SAEs postoperative, n [%]	8 (12.50)	1 (5.26)	7 (15.56)	0.42
Other complications, n [%]	4 (6.25)	0 (0.00)	4 (8.89)	0.31
Perioperative care				
PRBCs, n [%]	19 (29.69)	19 (100.00)	0 (0.00)	<0.001
FFP, n [%]	11 (17.19)	5 (26.32)	6 (13.33)	0.28
FFP [units]	2.00 (2.00–3.00)	2.00 (2.00–3.00)	2.00 (2.00–2.50)	0.90
Preoperative hospital stay [days]	4.00 (3.00–6.00)	4.00 (3.00–5.00)	4.00 (2.50–6.00)	0.98
Postoperative hospital stay [days]	6.00 (5.00–8.00)	7.00 (5.00–9.00)	6.00 (4.00–7.50)	0.05
Medications				
VKA type	–	–	–	–
Acenocumarol, n [%]	30 (46.88)	10 (52.63)	20 (44.44)	0.60
Warfarin, n [%]	34 (53.13)	9 (47.37)	25 (55.56)	–
LMWH, n [%]	–	–	–	–
Enoxaparin, n [%]	64 (100.00)	19 (100.00)	45 (100.00)	–
Nadroparin, n [%]	–	–	–	–
LMWH preoperative [h]	10.5 (±4.0)	10.74 (±3.78)	10.4 (4.13)	0.76

Table 3. Characteristics of bridged patients with and without hemorrhage (cont.)

Variable	Bridged patients (n = 64)	Bridged patients with hemorrhage (n = 19)	Bridged patients without hemorrhage (n = 45)	p-value
LMWH postoperative [h]	21 (±8)	21.47 (±7.57)	20.80 (±8.25)	0.76
LMWH postoperative [days]	32.73 (±12.53)	36.47 (±14.36)	31.16 (±11.48)	0.24
Laboratory and laboratory-based characteristics				
Preoperative				
INR	2.59 (1.79–3.33)	2.22 (1.64–3.31)	2.75 (1.80–3.33)	0.54
APTT [s]	36.60 (31.35–44.36)	38.20 (31.30–47.80)	36.60 (31.35–44.36)	0.76
FBG [g/L]	2.96 (2.72–3.62)	2.90 (2.46–3.40)	2.99 (2.75–3.73)	0.29
WBC [10^3/µL]	10.30 (8.05–13.25)	10.10 (7.20–13.80)	10.30 (8.20–13.20)	0.71
RBC [10^6/µL]	4.04 (3.32–4.43)	3.40 (2.76–4.03)	4.20 (3.76–4.50)	0.0004
HGB [g/dL]	11.90 (9.83–13.48)	10.40 (8.30–12.20)	12.40 (10.50–13.70)	0.0044
HCT [%]	36.75 (30.43–40.33)	30.70 (25.50–36.70)	38.00 (31.95–41.90)	0.0026
RDW [%]	14.50 (13.83–15.80)	14.40 (14.00–15.10)	14.60 (13.75–15.85)	0.85
PLT [10^3/µL]	176.50 (136.50–241.50)	148.00 (127.00–243.00)	186.00 (151.00–240.00)	0.24
Glucose [mmol/L]	122.00 (110.00–138.50)	121.00 (109.25–143.00)	122.00 (110.00–137.00)	0.85
Creatinine [µmol/L]	82.00 (63.00–108.00)	73.00 (61.00–120.00)	85.00 (69.25–104.00)	0.37
eGFR [mL/min]	78.00 (55.00–94.00)	82.50 (56.75–116.00)	72.00 (54.00–92.00)	0.29
Postoperative				
INR	1.17 (1.06–1.39)	1.22 (1.04–1.36)	1.17 (1.06–1.41)	0.81
APTT [s]	30.40 (26.80–34.10)	30.40 (26.60–34.10)	30.35 (26.85–34.08)	0.99
FBG [g/L]	2.52 (2.37–2.98)	2.44 (2.22–2.99)	2.56 (2.38–2.99)	0.45
WBC [10^3/µL]	9.60 (7.10–12.40)	9.00 (6.30–12.40)	9.80 (7.45–13.03)	0.27
RBC [10^6/µL]	3.64 (3.24–4.13)	3.33 (2.79–3.55)	3.88 (3.44–4.23)	0.0013
HGB [g/dL]	10.70 (9.70–11.90)	10.00 (9.10–10.70)	11.10 (10.03–12.08)	0.0007
HCT [%]	33.00 (29.20–36.90)	30.60 (28.80–33.90)	34.75 (30.16–39.18)	0.0047
RDW [%]	15.10 (13.80–16.20)	15.50 (14.30–16.40)	15.05 (13.73–16.18)	0.36
PLT [10^3/µL]	198.00 (147.00–284.00)	175.00 (142.00–210.00)	222.00 (149.25–293.50)	0.08

ACEI – angiotensin-converting-enzyme inhibitors; AF – atrial fibrillation; APTT – activated partial thromboplastin time; ASA – acetylsalicylic acid; ARB – angiotensin receptor blockers; BMI – body mass index; CHD – coronary heart disease; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; FBG – fibrinogen; FFP – fresh frozen plasma; HF – heart failure; INR – international normalized ratio; PPIs – proton-pump inhibitors; LMWH – low molecular weight heparin; MI – myocardial infarction; NSAIDs – non-steroidal anti-inflammatory drugs; PLT – platelets; RBC – red blood cell count; SAEs – serious adverse events; ST – stroke; VKA – vitamin K antagonist; VTE – venous thromboembolism; WBC – white blood cell count.

anticoagulant dose on the outcome. Thirdly, due to the relatively small sample size, we did not conduct subgroup analyses, e.g., according to specific indications for VKA or comorbidities. Finally, none of our subjects received NOACs and, consequently, application of these agents in perioperative bridging of surgical orthopedic patients is yet to be established.

Conclusions

Periprocedural anticoagulation management in patients requiring urgent orthopedic procedures is a common issue and available evidence regarding the best practices in this matter is limited.

Perioperative bridging anticoagulation in orthopedic patients on anticoagulation therapy with VKA does not seem to be associated with an increase in thromboembolic risk nor with higher risk of bleeding.

Bridging therapy with LMWH in patients undergoing orthopedic procedures should be individualized to minimize thromboembolic and bleeding risks in the perioperative period.

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