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CHARACTERISTICS OF THROMBOPROPHYLAXIS IN ELDERLY PATIENTS BEFORE AND AFTER ORTHOPEDIC HIP AND KNEE SURGERY

Abstract: Elderly patients with a hip fracture are at significantly higher risk for developing venous thromboembolism (VTE). The incidence of fatal pulmonary embolism (PE) occurs in 2-3% of patients after elective hip and knee surgery and about 6-7% after hip fracture surgery, with a higher risk in men (10,2%) than in women (4,7%). The use of pharmacological prophylaxis significantly reduces the incidence of symptomatic VTE. Pharmacological prophylaxis includes the use of antiplatelet drugs (aspirin), unfractionated heparin (UFH), low molecular weight heparins (LMWH), vitamin K antagonists (VKA), Fondaparinux and direct oral anticoagulants (DOAC). The use of low molecular weight heparins (LMWH) - enoxaparin, represents the gold standard of thromboprophylaxis in orthopedic surgery, and for now, they are the only drugs that are recommended for thromboprophylaxis in hip fracture surgery. Rivaroxaban is used in the prophylaxis of VTE in elective hip and knee surgeries at a fixed dose of 10 mg once daily, and apixaban at a dose of 2,5 mg twice daily in knee arthroplasty for at least 14 days, and after hip arthroplasty for at least 35 days. Early hip fracture surgery as soon as possible, preferably within 24 hours, and no later than 48 hours after admission to the hospital, significantly reduces the morbidity and mortality of elderly patients.

Key words: thromboprophylaxis, venous thromboembolism, low molecular weight heparin, aspirin, rivaroxaban, apixaban, hip fracture

Venous thromboembolism (VTE), which includes pulmonary thromboembolism (PT) and deep vein thrombosis (DVT), is a significant cause of mortality and morbidity in hospitalized patients. Elderly patients with a hip fracture are at significantly higher risk for developing venous thromboembolism (VTE). Without pharmacological prophylaxis, DVTs are registered by contrast venography in 54% of patients after elective hip arthroplasty (THA) and in 64% of patients after total knee arthroplasty

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(TKA), most of whom DVT was asymptomatic (1). The incidence of fatal PE occurs in 2-3% of patients after elective hip and knee surgery and about 6-7% after hip fracture surgery, with a higher risk in men (10.2%) than in women (4.7%). Chronic renal failure, heart failure and atrial fibrillation are independent risk factors for increased mortality after orthopedic surgery (2, 3).

The use of pharmacological prophylaxis significantly reduces the incidence of symptomatic VTE: DVT occurs in 0.7% and PE in 0,3% of patients after elective hip surgery, and in elective knee surgery DVT occurs in 0,9% of patients and PE in 0.3% of patients. The use of adequate thromboprophylaxis reduces the incidence of VTE after hip fracture surgery to 1.4-3.5% (4, 5).

Risk factors for the development of thromboembolism are: obesity, arterial hypertension, smoking, age, varicose veins, positive family history, thrombophilia, oral contraceptives, hormonal therapy, malignancies, pregnancy, immobility, anesthesia and central venous catheters (6). The key risk factors for the development of VTE after orthopedic surgery are: previous VTE, cardiovascular diseases, increased BMI (obesity is associated with a 2-4 times greater risk of developing VTE), older age (over 85 years), thrombophilia, varicose veins and male gender (7).

Pharmacological prophylaxis of venous thromboembolism (VTE) after orthopedic hip and knee surgery includes the use of antiplatelet drugs (aspirin), unfractionated heparin (UFH), low molecular weight heparins (LMWH), vitamin K antagonists (VKA), Fondaparinux and direct oral anticoagulants (DOAC) (8).

Acetyl-salicylic acid (aspirin) irreversibly inhibits the cyclooxygenase enzyme and stop the production of thromboxane, which leads to platelet aggregation and thrombus formation. Aspirin has been shown to be more effective in preventing VTE than placebo, but significantly inferior to low molecular weight heparins (LMWH). Most recommendations do not advise the use of aspirin as the only therapeutic agent in the prevention of VTE in orthopedic surgery, and one meta-analysis from 2016. showed that aspirin can be used in the prophylaxis of VTE in elective hip and knee surgeries. In recent recommendations, it is recommended to use Rivaroxaban for the first 5 days after surgery, and then continue with aspirin at a dose of 81 mg once a day (9).

Vitamin K antagonists (VKA) inhibit the synthesis of vitamin K-dependent procoagulant factors: F II, F VII, F IX, F X and proteins C and S and are used in the prevention of VTE after orthopedic surgery. Anticoagulant activity is monitored through the prothrombin time (PT), which is estimated using the INR (International Normalized Ratio) with therapeutic values between 2 and 3 and a target INR of 2.5. Acenocoumarol has a half-life of 8-11 hours, and Warfarin 2,5 days, which is important in therapeutic monitoring during the use of the drug: initial INR monitoring should begin after the second or third dose of the drug, and then INR measurement for several days or once a week, and then after reaching therapeutic doses of the drug at least once a month. When it is necessary to start prophylaxis immediately, the effect is achieved

by simultaneous administration of low molecular weight heparin (LMWH) and VKA, until the therapeutic INR is reached, when LMWH is switched off. Overlapping is also done when you want to turn off VKA and apply LMWH (8).

Unfractionated heparin (UFH) blocks antithrombin (AT) and the heparin/AT complex inactivates thrombin (F II) and factors: Xa, IXa, XIa and XIIa. Parenteral administration of heparin (intravenous or subcutaneous) is necessary, and its therapeutic effect is monitored through the activated partial thromboplastin time (aPTT). According to the recommendations, unfractionated heparin can be used in the prevention of VTE after elective hip and knee surgeries, as well as after hip fracture surgeries. The most common side effects of UFH administration are heparin-induced thrombocytopenia (HIT) and osteoporosis (10, 11).

The use of low molecular weight heparins (LMWH) – enoxaparin, represents the gold standard of thromboprophylaxis in orthopedic surgery. LMWH are more potent inhibitors of F Xa than heparin, they are administered subcutaneously once or twice a day with a significantly more favorable pharmacodynamic and pharmacokinetic profile than UFH and other anticoagulants. According to studies, LMWHs are significantly superior to UFH and VKA in the prevention of VTE after orthopedic surgery with a significantly lower percentage of bleeding risk and a significantly lower risk of developing HIT (0.2%) compared to UFH (2.6%). Enoxaparin is used for thromboprophylaxis in a dose of 30 mg subcutaneously twice a day or in a single dose of 40 mg for at least 35 days after hip arthroplasty, and for at least 14 days after knee arthroplasty. The same doses of enoxaparin are administered after hip fracture surgery for at least 35 days. LMWH are currently the only drugs recommended for thromboprophylaxis in hip fracture surgery. It is recommended to start the application of LMWH after 12 hours after the surgery (10, 12).

Fondaparinux is a synthetic pentasaccharide with a specific inhibition of factor Xa of coagulation that is significantly higher than LMWH and a longer half-life in plasma (about 17h) compared to LMWH (about 4h) with a lower incidence of VTE compared to LMWH (enoxaparin and dalteparin) and UFH. Fondaparinux dose of 2.5 mg administered subcutaneously once a day is used in VTE prophylaxis and acute coronary syndrome (ACS) therapy. Treatment of PE and DVT is 7,5 mg/day of Fondaparinux for patients weighting 50-100 kg, 5 mg/day for patients weighting less than 50 kg and 10 mg/day subcutaneously for patients weighting more than 100 kg (13).

Direct oral anticoagulants (DOAC): apixaban, rivaroxaban and dabigatran compared to VKA have an advantage due to the application of fixed doses, without the need for monitoring (14).

Rivaroxaban is a direct inhibitor of activated factor X (F Xa). It is used for the prophylaxis of VTE in elective hip and knee surgeries in a fixed dose of 10 mg once a day. The initial dose should be started 6 to 10 hours after elective surgery and administered for at least 14 days after knee replacement, and for at least 35 days after hip

replacement. Currently, it is not recommended as routine prophylaxis after hip fracture surgery, although recent studies support the use of rivaroxaban after hip fracture surgery with a low risk of bleeding, but greater than LMWH (15, 16).

Apixaban is a direct inhibitor of activated factor X (F Xa) which is approved for the prophylaxis of VTE after elective hip and knee surgeries, as well as the treatment of acute VTE and PE. According to the current recommendations, prophylactic doses of apixaban are 2.5 mg twice a day, which start 12-24 hours after surgery and continue for at least 35 days after elective hip surgery and at least 14 days after elective knee surgery. Apixaban is still not recommended for thromboprophylaxis after hip fracture surgery (16).

Dabigatran is a selective, reversible, direct thrombin inhibitor. For thromboprophylaxis in elective orthopedic surgeries, it is used in a dose of 220 mg or 150 mg per day, and it is not recommended in thromboprophylaxis after hip fracture surgery (16).

Hip fractures are frequent injuries of the elderly population and lead to a greater number of sequelae - such as immobility, worsening of the general condition and increased mortality. There are clear recommendations and evidence that early hip fracture surgery as soon as possible, preferably within 24 hours, and no later than 48 hours after admission to the hospital, is the gold standard, which significantly reduces morbidity and mortality. Numerous comorbidities that are present in the elderly population (coronary artery disease, diabetes, dementia, renal insufficiency) are associated with increased mortality in patients with hip fracture and may be a cause of delay in surgery. Postponing hip fracture surgery for more than 48 hours significantly increases one-year mortality and leads to complications that arise as a result of prolonged immobilization and lead to an increased risk of developing pneumonia, urinary infections, sepsis and decubitus. Numerous observational studies have shown that surgery within 12 hours of hip fracture is associated with a low incidence of mortality, and retrospective cohort studies have shown that delaying surgery 24 hours after hip fracture increases the incidence of 30-day mortality by 1.8% per hour (17).

COVID-19-positive elderly patients undergoing hip fracture surgery are at increased risk for developing postoperative complications including respiratory tract infections, ARDS, deep vein thrombosis and pulmonary embolism, longer hospitalization and intensive care unit stays, and increased mortality (18).

Anticoagulation and antiaggregation therapy is an integral part of the therapy of patients after the age of 65 in the treatment of coronary disease, atrial fibrillation, venous thromboembolism, cerebrovascular diseases, valvular heart diseases and artificial valves. About 30-40% of patients with a hip fracture are prescribed anticoagulation or antiplatelet therapy, which carries an increased risk of bleeding, hematoma development, an increased need for transfusions, and an increased risk of developing infections and longer hospitalization (19).

The incidence of DVT preoperatively occurs in 6-9% of patients within 48 hours of hip fracture surgery, and 54-62% if the intervention is delayed for more than 48 hours. Duplex scan of blood vessels of the lower extremities is not recommended as a routine method if the intervention is within 48h, and studies recommend imaging DVT of the lower extremities if surgery is delayed after 48h and evaluation of D-dimer in clinically suspected VTE. In the case of confirmed DVT, the use of therapeutic doses of low molecular weight heparin (LMWH) – enoxaparin 1mg/kg every 12 hours is recommended. Several prospective randomized control studies have shown that the administration of Rivaroxaban 10 mg once a day before surgery effectively reduces the risk of developing preoperative DVT in patients with a femoral neck fracture without an increased risk of developing bleeding, as an alternative of the administration of LMWH (enoxaparin 30 mg/12h s.c. or 40 mg s.c. once daily) which is the first line therapy in current recommendations (20, 21, 22).

The most common indication for anticoagulant therapy in the elderly population is atrial fibrillation with an incidence of 7-10% in patients with a hip fracture. Current recommendations are to stop vitamin K antagonists-VKA (warfarin or acenocoumarol) before hip surgery, in patients receiving VKA for VTE or transient ischemic attack (TIA) that they had in the last 3 months, genetically proven thrombotic disease, have atrial fibrillation with CHADS2 score >5, patients with a mechanical valve, previous cerebrovascular insult and some of the risk factors: unregulated hypertension (>140/90 mmHg), over 75 years or diabetes mellitus, with “bridge” with prophylactic doses of LMWH up to 12 hours before surgery and achieving an INR of less than 1,5 when it is safe time for hip fracture surgery and reducing the risk of bleeding and the need for transfusions (23).

Warfarin has a half-life of 36 hours, and the drug should be disrupted 5 days before elective hip and knee surgery to normalize hemostasis, and in elderly patients, this period is even longer and they have an unpredictable trend of INR reduction, especially in cases of hip fractures. In patients who are on VKA therapy and have a low risk of developing VTE, multiple studies have shown a significant benefit from an active reverse strategy that significantly reduces the time to surgery, without an increased risk of bleeding and thromboembolic events. Oral or intravenous vitamin K, fresh frozen plasma (FFP) and prothrombin complex concentrate are used as reversible agents. Through studies, the use of vitamin K has been shown to be a safe approach without increasing thrombotic complications. Vitamin K in a dose of 1 to 10 mg in a slow intravenous infusion has been shown to be safe (usually smaller doses: 2-5 mg i.v.) with rare complications (anaphylaxis). Oral administration of the same doses of vitamin K achieves a slower effect than intravenous infusion. Fresh frozen plasma (FFP) achieves rapid reversal of anticoagulation without causing further resistance to warfarin or heparin, and the effects last 8-12 hours after application and it is optimal to apply up to 4 hours before the procedure with smaller doses of vitamin

K to increase the anticoagulation effect, which accelerates time to surgery, without increasing the risk of complications. Prothrombin complex concentrate contains high concentrations of coagulation factors, including F II, F VII, F IX and F X and inactivate warfarin 5 times faster than fresh frozen plasma, but have an increased risk of developing subsequent thrombogenic events: cerebrovascular insult, myocardial infarction, PE, DVT, thats why they are given in the third line to achieve reversible anticoagulation in selected patients with hip fractures. Warfarin can be continued 24 hours after surgery in uncomplicated patients with established haemostasis (20, 22).

Direct oral anticoagulants (DOACs): dabigatran – direct thrombin inhibitor and direct factor Xa inhibitors (apixaban, rivaroxaban and edoxaban) have been used more often in recent years in patients with a high risk of thromboembolic events. DOACs are established as the first line of therapy for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation and the treatment of venous thromboembolism, without the need for routine monitoring and a safer pharmacokinetic profile than VKA. There are a smaller number of studies related to the perioperative use of DOAC in hip fractures, and a larger number of studies followed the use in elective hip and knee surgeries. It is recommended to stop therapy with Xa inhibitors (apixaban, rivaroxaban and edoxaban) 48 hours before elective hip and knee interventions, and in patients with kidney damage 72 hours before elective procedures. Dabigatran should be disrupted 48 hours before elective procedures, and in patients with creatinine clearance (Cl Cr) less than 50 ml/min, it is recommended to delay therapy 96 hours before the procedure. In some studies, the recommended interval of therapy delay is shortened to 24 hours before the procedure for rivaroxaban and edoxaban, and for dabigatran at least 12 hours before the elective procedure if there is a lower risk of hemorrhagic events or in emergency operations. If the patients have a high risk for thrombotic events, the period until the elective intervention can be bridged with prophylactic doses of low molecular weight heparin (LMWH), and the last dose should be given 12 hours before the intervention. DOACs are recommended to be continued as soon as possible after surgery, and 48 hours after surgery is a safe enough time with established haemostasis (24)

Recent studies indicate that patients taking antiplatelet therapy – aspirin or clopidogrel should not have delayed surgery, but spinal or regional anesthesia should be avoided in patients on clopidogrel because of the risk of spinal hematoma development. Dual antiplatelet therapy (DAPT) is indicated in high-risk cardiovascular patients, patients who have recently undergone coronary intervention. The most common combinations of DAPT therapy are aspirin with clopidogrel, prasugrelor, ticragrelor or glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban). DAPT is associated with a significantly higher risk of bleeding during surgical interventions (14.7%) compared to aspirin (4.1%). Premature termination of DAPT, especially in conditions after a hip fracture when prothrombotic activity and platelet activation are increased, can lead to stent thrombosis, especially within 30 days of BMS implantation, or within 6 months of

DES implantation. In these high-risk patients, regardless of the high risk of bleeding, it is not recommended to stop DAPT, but to replace P2Y12 inhibitors with glycoproterein IIb/IIIa inhibitors that have a short elimination half-life (T ½) and can be stopped immediately before the intervention and continued as soon as posible after the intervention. In patients receiving antiplatelet therapy, intravenous administration of tranexamic acid is safe in emergency surgeries with a high risk of bleeding and has a better safety profile than administration of platelet infusion. With significantly increased risks of bleeding during surgery, an infusion of 2 doses of platelets can be given 2 hours after the last dose of aspirin and 12-24 hours after the last dose of clopidogrel. Tigacrelor and prasugrel, as much more potent antiplatelet agents than clopidogrel, carry an increased risk of bleeding during hip and knee surgery, and platelet infusion does not reduce the risk of hemorrhagic complications during the intervention (17).

Neuroaxial anesthesia in patients who have elective hip and knee surgery, and receive antiplatelet therapy, there is an increased risk of spinal hematoma development. Aspirin does not have to be stopped before the intervention, and prasugrel and clopidogrel should be delay 7 days before the intervention, ticagrelor 5 days before the intervention, tirofiban and epifibatide 8 hours before, and abciximab 48 hours before neuraxial anesthesia during the performance of elective surgeries (25).

Preoperative echocardiography is recommended before hip fracture surgery for risk stratification in patients with heart failure, valvular disease, or atrial fibrillation, as well as in patients with dyspnea of unknown cause. Elderly patients have an increased risk of developing myocardial infarction after hip fracture surgery and an increased troponin level after the intervention carries an increased risk of postoperative mortality (26).

Anemia is often present in the elderly population and carries an increased risk of postoperative complications. Pre-orthopedic surgery blood transfusion is recommended in patients with symptoms of anemia or in asymptomatic patients with a hemoglobin level below 80g/l. Preoperative administration of intravenous iron has limited benefit, and carries an increased risk of developing myalgia and arthralgia (27).

Diabetes mellitus type 2 (DMT2) is the second most common comorbidity after hypertension in elderly patients with hip fracture. Hyperglycemia carries an increased risk for the development of postoperative complications, periprosthetic infections, and increased postoperative mortality and length of hospitalization. The use of insulin is the most reliable method of glycemic regulation in the perioperative period and according to the ADA recommendations, the target glycemic values for hip fracture surgery are below 7.8 mmol/l (less than 140 mg/dl), and for elective surgeries below 10 mmol/l (180 mg/ dl). The recommendation is daily control of glycemia fasting and after meals with corrections of insulin doses and achieving optimal glycoregulation in the early postoperative period in order to reduce complications and mortality (28).

Patients with end-stage renal disease requiring hemodialysis have a 4,4 times higher risk of developing hip fractures due to decreased bone density and a significantly

higher risk of mortality (45% higher mortality during 2 years after surgery) and surgical complications (29). Perioperative preparation of patients includes an assessment of the risk of cardiovascular complications, hemodialysis the day before hip fracture surgery, and elective surgery can be performed at least 6 hours after hemodialysis with heparin, which minimizes the risk of perioperative bleeding, postdialysis blood pressure to be less than 130/80 mm Hg and hemoglobin minimum 90-100 g/l with hematocrit greater than 30% and glycosylated hemoglobin (HbA1c) 6-8% (30).

Osteoporosis as a cause of fractures is constantly increasing and often occurs even with minor trauma, especially in elderly people who are characterized by fragility and an increased tendency to hip fractures. Bone density measurement is not necessary before the orthopedic procedure, but is recommended after the operation for further treatment. The prophylactic administration of vitamin D (800 IU/day) along with calcium (1200 mg/day) is recommended in the early postoperative treatment regardless of the level of vitamin D in the blood, and later dosing depending on the level of vitamin D in the blood, as well as the use of osteoporosis therapy: oral or parenteral bisphosphonates (31).

Multiple studies have shown that chronic obstructive pulmonary disease (COPD) increases the risk of hip fracture by 1,5 times. In severe forms of COPD, postoperative mortality is 1.66 times higher than in those with milder forms of COPD due to the increased risk of developing pneumonia, wound infections and developing sepsis (32).

Conclusions

Older age and the presence of comorbidities increase postoperative mortality after elective hip and knee surgery, and significantly increase after hip fracture surgery. According to the current recommendations, the goal of thromboprophylaxis is to start as early as possible after surgery after establishing haemostasis in order to reduce the risk of developing VTE, reduce in-hospital and one-year mortality and enable hip fracture surgery as early as possible in relation to the risk factor stratification in elderly patients and associated comorbidities.

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