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Aspirin for thromboprophylaxis in major orthopedic surgery: old drug, new tricks?

Giuseppe Lippi[1], *Gianfranco Cervellin*[2]

[1] Section of Clinical Biochemistry, University of Verona, Verona, Italy; [2] Emergency Department, University Hospital of Parma, Parma, Italy

Summary. Major orthopedic surgery, mainly entailing hip fracture surgery, hip and knee arthroplasty, is associated with significant morbidity and mortality, which are especially attributable to the high risk of postoperative VTE. Such a considerable risk is mainly due to a procoagulant state sustained by several important mechanisms, including massive release of procoagulants from tissue and bone damage, blood vessel injury, reduced venous emptying, perioperative immobilization and cement polymerization, among others. The risk of VTE during and after major orthopedic surgery approximates 50-80% in patients with no thromboprophylaxis, and persists for up 3 to 6 months after surgery. The anticoagulant or antithrombotic armamentarium entails several anticoagulants such as heparin, coumarins, fondaparinux, and the recently developed DOACs inhibiting either activated factor Xa (i.e., rivaroxaban, apixaban, edoxaban) or thrombin (i.e., dabigatran), as well as aspirin, i.e., the oldest antiplatelet drug to be ever discovered and used in clinical practice. The current guidelines are not in complete agreement regarding the choice of the ideal thromboprophylaxis, since some consider aspirin, and some discourage it. Recent evidence seems to support the use of aspirin in selected situations and in selected protocols. Therefore, we believe that consideration should be made about increasing the use of this old but still effective drug for perioperative prophylaxis of VTE, especially in patients for whom the administration of DOACs may be challenging. (www.actabiomedica.it)

Key words: aspirin, venous thrombosis, deep vein thrombosis, pulmonary embolism, prophylaxis

In a recently published article, Kim et al (1) showed data about the trend of thromboprophylaxis and complications after major lower limb orthopedic surgeries in Korea. Although the findings of this study are somehow interesting from an epidemiological perspective, part of the conclusions seem misleading especially when the authors insinuated that the enhanced risk of both venous thromboembolism (VTE) and bleeding after hip surgery may be due to increased prescriptions of aspirin (and fondaparinux and low molecular weight heparin; LMWH) combined with fewer prescriptions of direct oral anticoagulants (DOACs).

Major orthopedic surgery, mainly entailing hip fracture surgery, hip and knee arthroplasty, is associated with significant morbidity and mortality, which are especially attributable to the high risk of postoperative VTE (2). Such a considerable risk is mainly due to a procoagulant state sustained by several important mechanisms participating to the pathogenesis of venous thrombosis, thus including massive release of procoagulants from tissue and bone damage, blood vessel injury, reduced venous emptying, perioperative immobilization and cement polymerization, among others (2). Interestingly, the risk of VTE during and after major orthopedic surgery approximates 50-80% in patients with no thromboprophylaxis, and persists for 3 to 6 months after surgery (3).

These alarming figures have encouraged many scientific organizations to publish recommendations that

primary thromboprophylaxis should be administered to all patients undergoing major orthopedic surgery. Specific guidance about the possible therapeutic options in this clinical setting has considerably evolved over time (4). Briefly, the anticoagulant or antithrombotic armamentarium entails "conventional" anticoagulants such as heparin (namely LMWH), coumarins (warfarin, acenocoumarol), fondaparinux, but also includes DOACs inhibiting either activated factor Xa (i.e., rivaroxaban, apixaban, edoxaban) or thrombin (i.e., dabigatran), as well as aspirin, i.e., the oldest antiplatelet drug to be ever discovered and used in clinical practice.

According to the current evidence-based guidelines of the American College of Chest Physicians (ACCP) (5), one of the following drugs is recommended for antithrombotic therapy and prevention of thrombosis in patients undergoing major orthopedic surgery: LMWH, fondaparinux, DOACs (dabigatran, rivaroxaban or apixaban), low-dose unfractionated heparin, vitamin K antagonist and aspirin (Grade 1B recommendation). Interestingly, the use of LMWH is preferred over other agents, including aspirin (Grade 2C/2B recommendation) (5). This straightforward recommendation is in apparent disagreement with that of the American Academy of Orthopaedic Surgeons (AAOS). Although the panel of AAOS experts concluded that it is advisable to use pharmacologic agents for preventing VTE in patients undergoing major orthopedic surgery, and that it is still unclear which prophylactic strategy may be optimal, perioperative use of antiplatelet agents such as aspirin or clopidogrel has been discouraged (6). The recommendations of both the ACCP and AAOS have been published more than 5 years ago (i.e., in 2012 and 2011, respectively) and, since then, a number of very recent studies have been published about the potential effectiveness and safety of aspirin in patients undergoing major orthopedic surgery.

Nielen et al carried out a retrospective study including 3261 patients undergoing total knee replacement and 4016 patients undergoing total hip replacement, aimed to compare efficacy and safety of DOACs, LMWH and aspirin (7). Compared with patients undergoing aspirin therapy, LMWH and DOACs were associated with a 2.0 (95% confidence interval [95% CI], 0.2-17.2) and 9.4 (95% CI, 1.1-82.0) enhanced risk of gastrointestinal bleeding after total hip replacement, respectively. The administration of LMWH was also found to be associated with a 20.9-fold (95% CI, 1.9-232.3) higher risk of gastrointestinal bleeding after total knee replacement compared with aspirin. As regards clinical efficacy, the risk of post-operative VTE after total hip replacement was found to be non-significantly higher with DOACs than with aspirin (hazard ratio [HR], 4.7; 95% CI, 0.6-37.9), but was clearly higher using LMWH than aspirin (HR, 39.5; 95% CI, 18.0-87.0). Similarly, the risk of post-operative VTE after total knee replacement was much higher with LMWH than with aspirin (HR, 17.2; 95% CI, 6.9-43.0).

Bala et al carried out a large analysis of Humana and Medicare database for identifying all primary total knee arthroplasty performed between the years 2007-2016 (8), for recognizing potential differences in incidence of VTE and bleeding in patients undergoing total knee arthroplasty and taking different antithrombotic drugs (i.e., warfarin, LMWH, DOACs and aspirin). The administration of DOACs was associated with the lowest overall incidence of deep vein thrombosis (i.e., 2.9%), closely followed by aspirin (3.0%), then by LMWH (3.5%) and warfarin (4.8%). Similarly, DOACs were also the most effective drugs for preventing pulmonary embolism (0.9%), closely followed by LMWH (1.1%), aspirin (1.2%) and then by warfarin (1.6%). Notably, aspirin administration was associated with the lowest incidence of postoperative anemia (19%), followed by warfarin (22%), LMWH (23%) and DOACs (23%).

Chu et al carried out another retrospective study including 342401 patients undergoing major orthopedic surgery (231,780 total knee arthroplasty and 110,621 total hip arthroplasty), who received chemoprophylaxis with aspirin or anticoagulant drugs (warfarin, LMWH, DOACs, fondaparinux) for 7 days after surgery (9). The administration of aspirin was found to be associated with lower risk of post-operative VTE after total knee arthroplasty (adjusted odds ratio [OR], 0.34; 95% CI, 0.24-0.48]) and a similar risk of post-operative VTE after total hip arthroplasty (adjusted OR 0.82; 95% CI, 0.45-1.51) compared with conventional anticoagulant treatments.

Schab et al retrospectively compared data of 198 patients undergoing major orthopedic surgery without interrupting their aspirin therapy for cardiovascular prevention (44 unicompartmental knee arthroplasty and 154 total knee arthroplasty), with a control group consisting of 403 patients who were not taking antiplatelet agents (102 unicompartmental knee arthroplasty and 301 total knee arthroplasty) (10). No differences could be found between the two groups in early or late blood loss, as well as in transfusion rates. Notably, no difference was also observed in surgical time and length of hospital stay.

More recently, Anderson et al carried out a multicenter, double-blind, randomized, controlled study including 3424 patients undergoing total hip or knee arthroplasty, and who were then randomized to receive for 30 days once-daily oral rivaroxaban (10 mg) or the same dose of rivaroxaban during the first five days, then switched to aspirin (81 mg daily) after the fifth postoperative day. Interestingly, the results of extended prophylaxis with aspirin after five days of rivaroxaban were not significantly different from those obtained with extended rivaroxaban in the prevention of symptomatic venous thromboembolism (11).

Unlike the conclusions of Kim et al (1), recent evidence clearly attests that aspirin is more effective and safe than LMWH and warfarin for preventing VTE in patients undergoing major orthopedic surgery, and its efficacy and safety profile are globally comparable to those of DOACs in this clinical setting (7-11). Along with the well-known biological effects on both arterial and venous thrombi (12), aspirin has also some advantages compared to DOACs, including a much lower cost (i.e., an especially important aspect in low income countries) and no need for laboratory monitoring, an aspect that is now posing important challenges for clinical laboratories due to the constantly increasing number of DOACs licensed for use in many countries worldwide. Therefore, we believe that consideration should be made about increasing the use of this old but still effective drug for perioperative prophylaxis of VTE, especially in patients for whom the administration of DOACs may be challenging (i.e., in the elderly, or in patients with low compliance, impaired renal or liver function).

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Correspondence:
Prof. Giuseppe Lippi
Section of Clinical Biochemistry, University Hospital of Verona
Piazzale LA Scuro - 37100 Verona (Italy)
E-mail: giuseppe.lippi@univr.it; ulippi@tin.it