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UPDATE

Update on thromboembolic prophylaxis in hip fracture

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KEYWORDS
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Abstract Hip fractures in the elderly is a health problem of first magnitude, with an incidence which is increasing exponentially. The surgery of these fractures, despite progress in recent years in terms of surgical and anesthetic techniques, the widespread use of thromboprophylaxis and better medical cares, remains a high risk procedure in terms of morbidity and mortality.

PALABRAS CLAVE
Profilaxis tromboembólica;
Fractura de cadera

Actualización de la profilaxis tromboembólica en fractura de cadera

Resumen La fractura de cadera en el anciano constituye un problema sanitario de primera magnitud, con una incidencia en crecimiento exponencial. La cirugía de estas fracturas, a pesar de los avances de los últimos años en cuanto a las técnicas quirúrgicas y anestésicas, a la generalización de la profilaxis tromboembólica y a unos mejores cuidados médicos, continúa siendo un procedimiento de alto riesgo en cuanto a morbilidad y mortalidad

Introduction

In a recent, multi-centre study in France,[1] the 1-month mortality was 5.2%, the 3-month mortality 10.6% and the 6-month mortality 14.7% with cardiovascular complications (ischemic cardiomyopathy, cardiac insufficiency, and pulmonary embolism) being the primary cause of death.

Thromboembolic risk factors in hip fracture

From the moment the fracture occurs, thromboplastin is released into the blood stream, and the coagulation system is activated. Moreover, immobilizing the extremity on the fracture side promotes venous stasis, thereby setting up the conditions necessary for venous thromboembolism (VTE) to appear. The published incidence of venography-diagnosed deep vein thrombosis (DVT) within 48 hours of admission and prior to surgical intervention is 62%[2]

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Accordingly, there is broad consensus on the recommendation that thromboembolic prophylaxis be initiated as soon as possible following admission in those patients who will not undergo surgery immediately.[3,4] However, it has not been possible to demonstrate consistently that there is an increased incidence of symptomatic VTE in connection with delaying surgery.[5]

Being more than 75 years of age and being female would be other risk factors,[6] as would be the presence of varices and/or chronic venous insufficiency or a history of thromboembolism.[1]

There have also been reports of a significantly higher incidence of symptomatic VTE in trochanteric fractures (5.2%) compared to subcapital fractures (1.7%),[7] perhaps because in the former group there is more bleeding and less capacity for immediate ambulation.

Thromboembolic prophylaxis

In light of the available scientific evidence, the most recently published consensus guidelines[3,4] award a Grade A Recommendation to pharmacological thromboembolic prophylaxis using the coumarin anticoagulants, low-molecular-weight heparin (LMWH), and fondaparinux. The efficacy of mechanical methods of prophylaxis such as intermittent pneumatic compression, the plantar venous pump, or elastic compression stockings are insufficient when used alone. It is recommended that these be used as an adjunct to pharmacological methods in very high-risk patients and used alone only when pharmacological prophylaxis is contraindicated due to a high risk of bleeding (Grade B Recommendation). Early mobility should be initiated as soon as possible after surgery, obviously, for this constitutes the first measure in thromboembolism prevention.

Despite their comparative efficacy, the coumarins are seldom used in routine clinical practice in our setting because of the need to adjust the dosage based on the INR and because of their numerous pharmacological interactions.

The LMWHs meet the criteria for efficacy, safety, and no required monitoring which, together with their low hospital cost, means that they have been the primary agents used since the 1990s. However, even in the latest clinical trials, they were shown to be less effective than in major orthopaedic surgery: an incidence of 24%-34% for venography-detected DVT and an incidence of 2-3% for symptomatic DVT have been reported.[8,9] Whether LMWH prophylaxis is initiated pre-operatively or post-operatively, the risk of bleeding complications is very low, provided that the standards for administration given in the product's package insert are followed. Because these drugs are eliminated primarily via the kidneys, it is very important that the dosage be adjusted to prevent bleeding in patients whose creatinine clearance is <30 mL/min. As far as the risk of spinal hematoma, in epidural anesthesia this has been found to range from 0.45 to 0.7 cases per 100,000 and is almost always associated with repeated and/or bleeding punctures.[10] In any event, neuraxial anesthesia should be deferred until at least 12 hours after the last dose of LMWH was administered, and the first post-operative dose of LMWH should not be administered until at least 6 hours after the surgical wound is closed—and then only if hemostasis is not compromised (table 1).

Fondaparinux is a pentasaccharide indirect Factor Xa inhibitor that has shown efficacy significantly superior to enoxaparin (8.3% compared to 19.1%) in clinical trials.[9] Administration of this drug should always be initiated post-operatively, at least 6 hours after the procedure is completed, provided that hemostasis is not compromised. Its pharmacokinetic characteristics and renal elimination make it contraindicated in patients whose creatinine clearance is <30 mL/min.; its use is also not advised in the event of a bleeding epidural puncture or when there is a continuous catheter (table 2).[11]

Because coagulation activation persists through the first 6 weeks of the post-operative period[12] and there is evidence that the majority of symptomatic VTE episodes occur after discharge from the hospital,[13,14] both domestic and international consensus guidelines recommend that LMWH or fondaparinux prophylaxis be continued for a total of 28-35 days following surgery.[3,4] The efficacy of this practice has been clearly shown in a double-blind, randomised clinical trial comparing fondaparinux prophylaxis during the hospital stay only with prophylaxis continued for 4 weeks after surgery. Venography performed on both groups at 4 weeks showed a VTE incidence of 35.0% for the first group, while

Table 1 Method for administering thromboembolic prophylaxis in hip fracture (LMWH). A) When patient undergoes surgery within 48 hours of the fracture, it is correct to initiate prophylaxis post-operatively, from 6 to 12 hours after the procedure is completed; it is recommended that prophylaxis be continued with 1 injection every 24 hours for 6 weeks. B) If it is determined that the patient cannot undergo surgery within the first 48 hours after the fracture, prophylaxis should be initiated on admission, suspended at least 10 hours prior to surgery, and restarted at least 6 hours after the surgical wound is closed.

A) Surgery within the first 48 hr after fracture

Admission	Surgery <48 hr	6 weeks
I.....	I....1st dose 6-12 hr after surgery.....	1 inj q24h.....I

B) Surgery deferred more than 48 hr after fracture

Admission			
I 1st dose.....	Stop 10-12 hr before spinal anaes....I....	Restart 6-12 hr after surgery....I

Table 2 Method for administering thromboembolic prophylaxis in hip fracture (fondaparinux). A) The first dose of fondaparinux should be administered at least 6 hours after the surgical wound has been closed and the therapy continued for 4 weeks. It should not be used in elderly patients of low body weight nor in renal insufficiency. It is not recommended for patients with continuous peridural catheter. B) It is feasible to initiate prophylaxis with LMWH upon admission and switch to fondaparinux (1 injection of 2.5 mg q24h SC) following the surgery.

A) Surgery within the first 48 hr after fracture

Admission	Surgery <48 hr	4 weeks
I.....I	....1st dose >6 hr after surg.....	1 inj q24h.....I

B) Surgery deferred more than 48 hr after fracture

Admission		Surgery >48 hr	4 weeks
I 1st dose.....	Stop >10h before spinal an.....I....	1st dose >6h after surg....1 inj q24h.....I	
LMWH		Fondaparinux	

the incidence was only 1.4% for patients on fondaparinux therapy during those 4 weeks. As far as symptomatic VTE, the incidence was 2.7% for the first group and 0.3% for the second group.[6]

The new oral anticoagulants (dabigatran, rivaroxaban), because they require no laboratory controls and have very few pharmacological interactions, present a very attractive option for continued prophylaxis post-discharge in patients who have difficulty self-administering injections at home. However, in the European Union, so far, use of this drug is authorized only in arthroplasty of the hip and knee, so it is not possible to make a formal recommendation regarding its use in hip fractures.[15,16]

Bleeding complications and thromboembolic complications

Fracture of the hip affects a group of elderly patients who have numerous concomitant disease, and the risk of thromboembolic and vascular complications is quite high. The fragility of this population, who are frequently on platelet antiaggregant and/or anti-inflammatory therapy, also makes them very susceptible to bleeding complications—particularly patients who have low weight and/or reduced renal function. In a multi-centre study in France of hip fractures treated with LMWH for 4 weeks,[1] the incidence of confirmed symptomatic thromboembolic events was 1.34% during the first 3 months following surgery. The incidence of major bleeding during the first 6 months was 1.2%, affecting particularly those patients whose creatinine clearance was less than 30 mL/min. A Japanese study on hip fractures treated with fondaparinux for 2 weeks[17] reported a 10.5% incidence of symptomatic hematoma in the surgical wound and/or a reduction of more than 2 g/dL in patients treated with this drug. Thus, even though thromboembolic prophylaxis is clearly indicated in all patients undergoing surgery for hip fracture, it cannot be prescribed without the risk of bleeding.

Although the majority of patients may benefit from a standard prophylactic regimen, there is a risk of bleeding secondary to accumulation of the drug in patients with reduced renal function and, in contrast, a risk of underdosing in patients with morbid obesity (BMI >40).[18]

Given that renal function deteriorates with age and that the majority of patients who suffer hip fracture are elderly, it is strongly recommended that creatinine clearance be systematically assessed upon admission and that treatment be adjusted if it is <30 mL/min.

Patients who were on platelet antiaggregant therapy prior to the fracture should restart it as soon as the bleeding risk has disappeared.[19] Taking aspirin at low doses (<325 mg/day) concomitantly with LMWH or fondaparinux does not significantly increase the risk of bleeding, nor does LMWH or fondaparinux prophylaxis against VTE afford protection from the risk of arterial thrombosis. In the majority of cases, if the reintroduction of antiaggregant therapy is unduly delayed, the risk of arterial thrombotic complications exceeds the risk of bleeding. In case of elevated risk of bleeding, reducing the dose of LMWH (switching to the dosage for moderate VTE risk) should be considered.

Adjusting the prophylaxis dosage for patients requiring platelet anti-aggregant therapy, patients whose body weight is extreme, and patients with compromised renal function—together with strictly observing safe intervals and schedules for administration of the anticoagulant drugs—will result in an optimal risk-benefit ratio for thromboembolic prophylaxis.

Evidence level

Expert opinion. Evidence Level V.

Conflict of interest

The authors declare that they have no conflict of interest.

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