THE PERIOPERATIVE MANAGEMENT OF ORAL CHRONIC ANTICOAGULATION THERAPY IN PATIENTS WITH HIP FRACTURES

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SUMMARY

Hip fractures are serious traumatic injuries, especially of the elder patients. The general consequences are long-term functional impairment, nursing home admission and increased mortality. Improving outcomes after hip fractures is translated in improving attention to details, especially cardiovascular disease that necessitates chronic anticoagulant therapy. The management of the anticoagulant therapy in the perioperative period is challenging. It usually needs stopping the oral anticoagulant therapy and changing to subcutaneous injections with heparin products. This period of alternation between the two types of anticoagulants is critical and difficult to supervise because it must not increase bleeding risk and also prevent thromboembolic events. Lately, in the therapeutic arsenal of the cardiovascular pathology, have been introduced the new anticoagulants that have a lower bleeding risk and a easier administration and compliance to treatment. Not all of these management strategies are backed by data come from studies. We suggest here our strategy of managing these complex patients; that is a compilation of guideline strategies, information from expert publications and our own clinical experience.

Key words: oral anticoagulant, hip fracture, thromboembolism, bleeding risk

RéSUMÉ

L’approche périopératoire de la thérapie anticoagulante chronique orale chez les patients aux fractures de la hanche

Les fractures de la hanche sont des blessures traumatiques graves, surtout chez les patients âgés. Les conséquences générales sont la déficience fonctionnelle à long terme, l’admission aux soins infirmiers à domicile et une mortalité accrue. Améliorer les résultats après les fractures de la hanche se traduit dans l’amélioration des techniques chirurgicales et la gestion périopératoire des conditions médicales en accordant une attention particulière aux détails, en particulier les maladies cardiovasculaires qui nécessitent un traitement anticoagulant chronique. La gestion du traitement anticoagulant dans la période périopératoire est difficile. Il est généralement besoin d’arrêter le traitement anticoagulant oral et le remplacer avec des produit d’héparine injectables sous-cutanés. Cette période d’alternance entre les deux types d’anticoagulants est critique et difficile à contrôler, car il ne doit pas augmenter le risque de saignement et doit aussi prévenir les événements thromboemboliques périopératoires. Dernièrement, dans l’arsenal thérapeutique de la pathologie cardio-vasculaire, ont été introduits les nouveaux anticoagulants qui ont un risque de saignement inférieur et une administration plus facile et une meilleure compliance au traitement. Pas toutes ces stratégie de gestion sont soutenus par les études données. Nous suggérons ici notre stratégie de gestion de ces patients complexes; qui est une compilation des stratégies de lignes directrices, des l’informations de publications spécialisées et notre propre expérience clinique.

Mots clés: anticoagulants oraux, fracture de la hanche, tromboembolism, le risque de saignement
INTRODUCTION

The annual number of hip fractures, as our population is ageing, is mathematically proved that will increase. The majority of hip fractures occurs in patients aged 65 or older. Still, despite modern perioperative planning and new therapeutic methods, one out of five hip fracture patients dies within a year since their injury. There are numerous management methods of oral anticoagulants during perioperative period in patients with hip fractures, but their safety and efficacy are not well established. The perioperative management of oral anticoagulant therapy is controversial because of the lack of sufficient evidence from randomized controlled trials. The existing literature and evidence about managing the perioperative anticoagulation makes room to different approaches and good clinical judgement is always best in considering individual and particular cases. This paper intends to share an example of the clinician decision-making, but cannot replace or impart good clinical judgment. [1]

Debate of the problem

The three major conditions which are treated by long term anticoagulant therapy are atrial fibrillation, heart valve surgery and deep vein thrombosis. Others may include stroke, aortic aneurysm and coronary thrombosis. [2] It is well established that continuing oral anticoagulation is associated with an increased risk of bleeding in the peri-procedural period in hip fracture surgery and that the absence of anticoagulant therapy postoperatively confers a marked increased risk for venous thromboembolism (VTE), especially after hip orthopaedic surgery. Emerging data suggest that interruption of warfarin or cumadine in patients with arterial indications, especially after major surgery, confers a higher risk of arterial thromboembolism (ATE) than predicted by mathematical modelling assumptions. The new data from clinical trials regarding postoperative thrombotic events and the difficulty of managing the AVK therapy due to the long half-life has obliged health professionals to change the guidelines regarding perioperative anticoagulation. [2]

Oral anticoagulants – the vitamin K antagonists – warfarin and acenocumarol – have a long half-life and must be discontinued before surgery due to the high bleeding risk during hip surgery procedures. This usually establishes a gap of anticoagulation that makes way for thromboembolic complications. Therefore, it is the general practice to use a bridge of short-life IV unfractioned heparin or subcutaneous fractioned low weight molecular heparin for the period when the oral anticoagulants are withdrawn. Another major drawback of warfarin and coumadine is the need for routine coagulation monitoring and even with monitoring, the international normalised ratio is frequently outside the therapeutic range. [3]

Development of new antithrombotic drugs has been targeted to improve the clinical benefit by reducing bleeding and thromboembolic complications and improving the ease of use. The many limitations of VKAs have provoked the development of new oral anticoagulants. Recently, dabigatran etexilatevaroxaban and apixaban have been introduced as possible substitutes. Furthermore, novel anticoagulant agents are evaluated to treat patients with acute coronary syndromes. Clopidogrel is often used, but this increases the risk of bleeding in patients in whom coronary artery bypass grafting is necessary [4].

Bridging oral anticoagulant therapy with injectable anticoagulant therapy

Our usual protocol for patients who are using oral antivitamin K anticoagulants is formally splited according to weather the bridge is made with IV unfractioned heparin or with subcutaneous low weight molecular heparin. Our protocol is not an unique one, but is the compilation of different protocols widely debated in the medical literature that have showed good medium to long term results. We usually bridge the oral anticoagulant therapy by LMWH but we use the unfractioned heparin for more strict monitoring of thrombotic events and bleeding. For patients whose INR is between 2.0 and 3.0 we discontinue AVK anticoagulant 5 days before surgery (last dose given 6 days before surgery) and allow the INR to spontaneously fall. Warfarin or acenocumarol should be withheld for a longer period of time if the INR is normally maintained above 3.0. The INR should be measured 3 days prior to surgery. If the day before surgery the INR is still unacceptably high, vitamin K must be administered preoperatively or surgery will be delayed until needed.

Bridging with IV unfractioned heparin before surgery

As soon as the patient arrives in the emergency room and the diagnosis of acute hip fracture is established the chronic AVK oral therapy is stopped and usual coagulation tests are done. IV heparin should be discontinued 4 to 6 hours prior to surgery. [5]

Bridging with therapeutic dose subcutaneous low molecular weight heparin (LMWH) before surgery

We generally use as an acceptable alternative to IV unfractionated heparin in outpatient subcutaneous administration of LMWH in therapeutic doses. The advantages are the ease of administration by subcutaneous injection and the twice a day manner of administrating. LMWH should be avoided in patients with renal failure. Weight-adjusted dosing without monitoring anti-factor X levels may be inappropriate for patients who weigh less than 50 kg or greater than 90 kg. Subcutaneous LMWH in a therapeutic dose should be started the second day after the last dose of warfarin. The last pre-operative dose should be administered no less than 24 hours prior to surgery. Some clinicians recommend that half of the total daily dose be given 24 hours prior to surgery.

Restarting AVK drugs after surgery

Post-operatively, warfarin and coumadine should be resumed when the patient is able to take medications by mouth and after the epidural catheter has been removed (if neuraxial analgesia has been used).
**Bridging with IV unfractioned heparin after surgery**

Full dose (therapeutic dose) IV unfractioned heparin should be started no sooner than 24 hours after major surgery when there is adequate post-op hemostasis. If there is evidence of surgical bleeding or if the patient is at high risk of bleeding, it should be delayed further. It should also be delayed while the epidural catheter is in situ (if neuraxial analgesia has been used). In situations where therapeutic dose IV unfractionated heparin is deferred beyond 24 hours, the administration of prophylactic dose LMWH can be considered sooner (as early as the evening of the day of surgery). IV heparin might be started sooner if the thrombotic risk is high and if the surgeon is confident of the intra-operative hemostasis and no excessive postoperative bleeding is evidenced. Heparin should be started without a bolus, at no more than the expected maintenance infusion rate. Heparin should be continued until the INR is therapeutic. [6]

**Bridging with therapeutic dose subcutaneous LMWH after surgery**

Therapeutic dose subcutaneous LMWH should be started no sooner than 24 hours after hip surgery. If there is evidence of surgical bleeding or if the patient is at high risk of bleeding, it should be delayed further. It should also be delayed while the epidural catheter is in situ (if neuraxial analgesia has been used). [7]

**Management of novel anticoagulant oral therapy in perioperative period:**

The emergence and anticipated routine clinical use of novel oral anticoagulants (NOACs), such as the direct factor IIa (thrombin) inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban and apixaban, have the potential to greatly simplify perioperative anticoagulant management because of their relatively short elimination half-lives, rapid onset of action, predictable pharmacokinetic properties, and few drug-drug interactions.

Rivaroxaban (Xarelto) and Apixaban (Eliquis) targets factor Xa (FXa) have a peak plasma concentration after administration in two to four hours. The preoperative drug interruption will be predicted on the drug elimination half-lives (8-9 hours for rivaroxaban, 7-8 hours for apixaban) and the drug dependence on renal clearance (33% for rivaroxaban, 25% for apixaban). We suggest that rivaroxaban is stopped 2 days before surgery (ie, skip 1 dose) as this would correspond to approximately 4 half-lives expired and a minimal (~ 6%) residual anticoagulant effect at surgery. A longer duration of interruption is probably required in patients with impaired renal function. For post-operative resuming of therapy we suggest using a low-dose regimen for the first 2 to 3 days in patients undergoing major surgery followed by a treatment-dose regimen thereafter. This would imply resuming rivaroxaban 10 mg once daily for 2 days, starting on the morning after surgery, and increasing to 20 mg once daily thereafter.

Dabigatran (Pradaxa) is taken orally as a prodrug called dabigatran etexilate and is a factor IIa (fIIa) inhibitor. In plasma, the peak level of the drug occurs after two hours. Eight per cent is excreted by the kidneys and the drug has a half-life of 14–17 hours. After initially being evaluated in hip and knee surgery, it was introduced as an anticoagulant in the field of cardiovascular diseases to prevent stroke in high-risk patients with AF. In patients who are receiving dabigatran and require elective surgery, the timing of pre-operative dabigatran interruption to ensure a minimal or no residual anticoagulant effect at surgery is predicted on 3 factors: (1) elimination half-life of dabigatran, (2) patient renal function and its effect on dabigatran elimination, and (3) planned surgery and anesthesia. [8] In patients with renal function that is normal (CrCl > 80 mL/min) or mildly impaired (CrCl, 50-80 mL/min) dabigatran has an elimination half-life of 14–17 hours, which implies that in such patients the last dabigatran dose should be given 3 days before surgery (ie, skip 4 doses). This period of interruption corresponds to a minimal (~ 3%-6%) anticoagulant effect at surgery. Usually, because hip surgery has a relatively high bleeding risk, dabigatran is resumed 48-72 hours after surgery by 150 mg twice daily.

For all the new oral anticoagulant therapy it is used the bridging approach with either IV unfractioned heparin or with low molecular weight heparin administered subcutaneously as described for AVK oral anticoagulants. [9,10,11,12,13,14,15,16]

**DISCUSSIONS**

The periprocedural management of patients on chronic oral anticoagulant therapy is a common but complex clinical problem, with little high quality data for sufficient clinical practice guided therapy. A careful assessment of patient- and procedural-related risks of thrombosis and bleeding must be done to develop a thoughtful periprocedural antithrombotic strategy. The hip fracture surgery is a procedure that implies on one hand risk of bleeding intra and post-operatively with significant use of blood products transfusion and on the other hand has an increased risk of thromboembolic events. The own patient’s thromboembolic risk should drive whether there is a need for an aggressive periprocedural antithrombotic strategy (such as the use of heparin bridging therapy in the case of warfarin or discontinuing NOACs closer to the time of surgery), whereas it is the procedural bleed risk that determines how that strategy is used in the postprocedural setting (such delayed reinitiation of heparin bridging therapy or the NOACs).

**CONCLUSION**

There is a need for further clinical research to allow more evidence-based recommendations for periprocedural antithrombotic therapy. With some large multicenter registries for oral anticoagulation therapy and the ongoing phase 3 studies that are providing periprocedural related outcomes the future for these complex managing patients looks brighter.
Acknowledgement

This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531"