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Education/new procedure

New anticoagulants and regional anaesthesia in patients undergoing orthopedic surgery

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Abstract

Background and Purpose: *there are many advantages of regional anaesthesia for orthopedic procedures. In perioperative period orthopedic patients received thromboprophylaxis with low mollecular weight heparins (LMWH) or new anticoagulated drugs. The most popular new drugs for thromboprophylaxis in patients with joint replacement are fondaparinux, rivaroxaban and dabigatran. After introduction of LMWH for thromboprophylaxis serious complications including spinal hematoma have been reported. It is very important perform regional anaesthesia in patients receiving anticoagulated drugs according to recommendations. These article reviews the actual recommendations and the current status and management of these new drugs.*

Recent findings*: recent studies are outlined that the risk of spinal hematoma after neuraxial anaesthesia may be higher than estimated. The use of new anticoagulant drugs should take into account the pharmacological profile of each drug to safely perform regional anaesthesia, mainly the time to reach peak plasma level and half-life.*

Conclusion*: When new anticoagulant drugs are used for thromboprophylaxis in orthopedic surgery, the performance of neuraxial anaesthesia is safe method if is based on the pharmacology of drugs. All methods of regional anaesthesia should be perfomed according to accepted recommendations regarding the time of block and the time of drug administration.*

INTRODUCTION

Regional anaesthesia and analgesia are widely used in perioperative treatment of orthopedic patients. There are many advantages of spinal or epidural analgesia/anaesthesia over general anaesthesia in patients undergoing orthopedic surgery including reduced postoperative cardiovascular and pulmonary complications, blood loss and need for transfusion and decreased incidence of thromboembolic complications. Many studies confirmed reduction in perioperative mortality and morbidity including reduction in incidence of thromboembolic complications if operative procedures are performed under regional anaesthesia. A meta analysis of randomized trials revealed that the use of perioperative regional anaesthesia can decrease mortality by approximately 30 %, deep venous thrombosis by 44 %, pulmonary embolism by 55 %, respiratory depression by 59 % and the need for transfusion by 55 %.

The rationale for thromboprophylaxis is based on the high prevalence of venous thromboembolism among hospitalised patients. The highest incidence of thromboembolic complications is among ortho-

paedic patients scheduled for total joint replacement surgery. Without thromboprophylaxis the prevalence of deep venous thrombosis is over 50 % after total knee or hip replacement surgery. The incidence of calf deep venous thrombosis (DVT) is 40% to 80%, proximal DVT 10% to 20%, clinical pulmonary embolism (PE) 4% to 10%, fatal PE 0.2% to 5%. However, the high incidence of thromboembolic complications is confirmed after general surgery procedures, after urologic, gynecologic and trauma surgery. In many patients, multiple risk factors are present, and the risks are cumulative. Formal risk assesment models for DVT or PE have been proposed for surgical patients. According to risk assesment models the prophylaxis recommendations are used in perioperative treatment. In a random survey of fellows of the American College of Surgeons, 86 % claimed they used prophylaxis in 1993, this proportion rising to 96 % by 1997.

Improvement in patient outcomes when regional anaesthesia techniques are used is due to the attenuation of the hypercoagulable response and the associated reduction in the frequency of thromboembolism. However this effect is insufficient as the sole method of thromboprophylaxis. In orthopedic patients thromboprophylaxis should be administered perioperatively. There are many recommendations how to perform thromboprophylaxis. The most popular are ACCP (American College of Chest Phycians) recommendations, but there are also ESA (Europena Society of Anaesthesia) recommendations and national recommendations. For example, the initial recommendations were presented in 1986 by ACCP stated that patients undergoing hip or knee arrhoplasty receive dextran, adjusted dose standard heparin (approximately 3500 U every 8 hours), warfarin (started 48 hours preoperatively to achieve a prothrombin time (PT) 1.25–1.5 times baseline), or dextran plus intermittent pneumatic compression. The duration of thromboprophylaxis is continued after hospital discharge for a total of 10 to 35 days.

The ACCP guidelines are widely recognized as a practice standard for VTE prevention and treatment, and have been regularly updated throughout recent decades. The most recent version, issued in 2009, is formally known as the 8th ACCP Conference on Antithrombotic and Thrombolytic Therapy.

The combination of regional anaesthesia and thromboprophylaxis is standard for many operative procedures. Unfortunately serious complications like perispinal hematoma can occur after spinal or epidural anaesthesia performed in patients receiving thromboprophylaxis. Although rare, the seriousness of this complication mandates very cautious use of antithrombotic medications in patients having neuraxial blockade. In a review of the literature between 1906 and 1994 year 61 cases of spinal hematoma associated with epidural or spinal anaesthesia have been reported. Great importance of spinal hematoma was recognised after approval of LMWH for clinical use. LMWH heparins are in use in Europe from 1989 and in USA from 1993. In 1997, only 4 years after the release of LMWH for general use in USA in May 1993, a series of 43 patients who had developed perispinal hematoma after receiving the LMWH enoxaparin concurrently with spinal or epidural anaesthesia have been reported. Many of these patients suffered neurologic impairment, including permanent paralysis, despite decompressive laminectomy. The median age was 78 years (28–90), and 78 % of patients were women. Concomitant antiplatelet therapy was present in several cases. Nearly 90% of these complications occured in patients receiving enoxaparin as prophylaxis after primarily total knee or hip replacement. Many of these events occurred when LMWH was administered intraoperatively or early postoperatively to patients undergoing continuous epidural anaesthesia and analgesia. At same time 10 cases of spinal hematoma have been reported in Europe. The possible explanation for this apparent difference in incidence in Europe may be a result of a difference in dose and dose schedule. For example, in Europe the recommended dose of enoxaparin is 40 mg once daily initiated 12 hours preoperatively while in USA is 30 mg twice daily. The predisposing factors also include the presence of an underlying hemostatic disorder, traumatic needle or catheter insertion, repeated insertion attempts or blood return, time of catheter insertion or removal, use of continuous epidural catheters, administration of medications known to increase bleeding. Manufacturers of LMWHs subsequently added a boxed warning to the prescribing information, alerting clinicians to this potential effect. However, it became clear that at least some of these outcomes resulted from lack of attention to timing of the neuraxial anaesthesia relative to the dose of LMWH, traumatic needle placement, and catheter removal during therapeutic levels of anticoagulation.

In response to these serious complications the American Society of Regional Anaesthesia and Pain Medicine (ASRA) held three Consensus Conferences on Regional Anaesthesia and Anticoagulation where recommendations how to perform regional anaesthesia in patients receiving anticoagulation drugs were achieved. These recommendations were published in the Journal of Regional Anaesthesia and Pain Medicine.

In last two decades new antithrombotic drugs are introduced for thromboprophylaxis in orthopedic patients and there is question how to perform regional anaesthesia procedures with concommitant use of antithrombotic drugs in order to avoid serious bleeding complications.

New anticoagulants

Because of great importance of thromboprophylaxis anticoagulated drugs are under permanent investigation. All new drugs have focused their developement on trying to posses the characteristics of the ideal anticoagulant. These characteristics include: possibility of oral (one tablet, once daily) and parenteral (once daily) adminstration, high effectivity in reducing thromboembolic events, low rate of complications (focus on bleeding), possibility of reversal, predictable pharmacokinetics, predictable dose response, rapid onset of action, no need for routine monitoring, wide therapeutic window, no dose adjustment

required, no interaction with other drugs and inhibition of both free and clot-bound activated coagulation factors. Of course no licensed medication has all these properties.

New antithrombotic drugs that target various steps in the hemostatic system with many of these properties are continuallly under development. The most extensivelly studied are direct Factor X and thrombin inhibitors. Many of these agents have prolonged half-lives and are difficult to reverse without administration of blood components. In last decade three new anticoagulation drugs are licensed for thromboprophylaxis in orthopedic surgery. There are two Factor X selective inhibitors (parenterally administered Fondaparinux and perorally administered Rivaroxaban) and Dabigatran, new direct thrombin inhibitor given perorally. After serious complications reported with introduction of LMWH in clinical use special caution is given to regional aneshesia and these drugs. The administration of these drugs in combination with regional anaesthesia must be carefully considered. Importantly, until large series become available, we can apply lessons learned from LMWH experience to develop initial management recommendations.

Central nerve blocks and new anticoagulants

Current recommendations on the use of anticoagulants with neuraxial anaesthesia are based on drug-specific pharmacodynamics. All guidelines focus on safety according to the delay between the last dose of anticoagulant and catheter withdrawal, but may underestimate the risk of bleeding associated with the next dose if they allow only a very short delay between catheter removal and the next dose of anticoagulant. However, there is a risk of vessel injury when the catheter is removed, and hence the risk of bleeding remains after the next dose of anticoagulant if the delay is too short. An alternative suggestion for managing epidural catheters or spinal needles in the setting of anticoagulation has been put forward, taking into account both of the safety delays between catheter withdrawal and the last dose of anticoagulant, and between catheter removal and the next dose. This suggestion has the advantage that it is based on the drug-specific pharmacology of the anticoagulant being used, particularly the elimination half-life, and time to reach maximum anticoagulant activity. This has been used rather than Tmax (time to reach maximum plasma concentration) as it is the drug's pharmacodynamic profile, rather than its phormacokinetics, which directly affects anticoagulant activity. Furthermore, this allows the suggestion to be applied to all anticoagulants, including those in which the pharmacodynamics and pharmacokinetics are not temporally correlated. This suggestion could provide a universally applicable method of estimating when to remove the neuraxial needle or catheter and when to restart anticoagulation. With performing central nerve blocks there is always possible vessel injury. After vessel injury clot formation is important to stop bleeding. It is estimated that time needed for stable clot formation is 8 hours, and this time should be reached before maximum anticoagulant activity of administered anticoagulant drug.

The rules based on the pharmacokinetics can be summarized as follows:

1. The first dose of the anticoagulant after a central nerve block must be administered so to ensure an interval of at least 8 hours between the end of surgery and the peak plasma level of the drug.
2. The removal of a epidural catheter must be delayed by an interval of at least two half-lives have elapsed for the anticoagulant being used. This is because only 25 % of the anticoagulant activity will remain after two half-lives and waiting longer than two half-lives has a diminishing effect on any further decrease. The residual drug activity provides a reasonable balance between the risk of haemorrhagic complications and the risk of thrombosis.
3. The safety interval between the removal of catheter and the next anticoagulant administration must be delayed by a time calculated from the hemostasis time minus the peak plasma level of the drug (the longer peak level, the shorter the time delay).

Fondaparinux

Fondaparinux is licensed for the prevention of venous thromboembolism (VTE) in high risk patients. It is an injectable synthetic pentasaccharide that acts indirectly on factor Xa via antithrombin III. Fondaparinux was approved in December 2001 and FDA released fondaparinux (Arixtra) with a block box warning similar to that of the LMWHs and heparinoids.

It is highly selective, without any effect on factor IIa (thrombin) or platelets. Its half life is 17–20 hours in normal individuals allowing for single-daily dose, but may be significantly prolonged in patients with renal impairment. In the perioperative setting fondaparinux treatment should start 6 hours postoperatively, provided surgical haemostasis is secured. Kidney function sholud be monitored. Investigators reported a spinal hematoma among the initial dose-ranging study. No additional spinal hematoma was reported in the combined series of 3600 patients who underwent spinal or epidural anaesthesisin in combination with fondaparinux thromboprophylaxis.

Nevertheless, its use in orthopedic patients has remained somewhat limited. This may be because of concerns over possible increased bleeding risk relative to some other anticoagulants. Because of bleeding risk, fondaparinux is contraindicated in patients who weigh less than 50 kg, and its package insert recommends caution when it is used in the elderly due to an increased risk of bleeding in patients aged 65 or older. Additionally, the Pentasaccharide in Major Knee Surgery (PENTAMAKS) study found fondaparinux to be associated with a significantly higher incidence of major bleeding compared with enoxaparin (2.1% vs 0.2%; p=0.006) in major knee surgery, although it was superior to enoxaparin in prevent-

ing VTE. Other possible reasons for slow adoption of fondaparinux include its long half-life, which results in a sustained antithrombotic effect, its lack of easy reversibility, and a contraindication in patients with renal insufficiency.

Anaesthetic management of the patient receiving Fondaparinux

The actual risk of spinal hematoma with fondaprinux is unknown. Consensus statement are based on the sustained and irreversible antithrombotic effect, early postoperative dosing and the spinal hematoma reported during initial clinical trials.

- The first dose is administered no less than 6 hours after completion of central nerve blockade (CNB).
- In patients with ongoing treatment, fondaparinux should be witheld at least 36 hours before the initiation of a CNB.

Until further clinical experience is available, performance od neuraxial technique sholud occur under conditions used in clinical trials (single-needle pass, atraumatic needle placement, avoidance of indwelling neuraxial catheters). If this is not feasible, an alternate method of prophylaxis should be considered.

Rivaroxaban

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor, with an oral biovaliability of 80 %. It is approved for use in Europe and Canada for tromboprophylaxis after total hip or knee replacement. There are many clinical trials comparing rivaroxaban with LMWH (enoxaparin) in patients with joint replacement. According these studies rivaroxaban have superiority with less incidence or thromboembolic events and simplicity of oral administration. Current studies are assessing the role of rivaroxaban in treating thrombosis and prophylaxis of VTE in medical patients and in preventing arterial thromboembolism in both high-risk atrial fibrillation and acute coronary syndrome patients.

Rivaroxaban has predictable pharmacokinetics with high oral biovaliability and a rapid onset of action. The absorbtion after oral intake is nearly 100%. The peak level is reached at 2–4 hours, and its half life is 5–9 hours. Inhibition is maintained for 12 hours. After administration approximately 66 % undergoes metabolic degradation, with half being eliminated renally and the other half through fecal route. The final 33 % undergoes direct renal excretion mainly through active renal secretion. Elimination half life is 9 hours in healthy subjects and is prolonged to 13 hours in elderly with decline in renal function (dose adjustment is needed in patients with renal insufficiency). For patients in whom rivaroxaban is indicated, no coagulation monitoring is required.

In patients with hip or knee arthroplasty the recommended dose is an oral once-daily 10 mg tablet. The first dose should be given 6–8 hours after wound closure. It is not necessary to adjust dose in the presence of mild or severe renal impairment (creatine clearance 15–80 mL/min) and it is contraindicated in hepatic desease with coagulopathy and clinical bleeding risk, and should be used with caution in patients with moderate hepatic impairment.

Anaesthetic management of the patient receiving Rivaroxaban

- Folowing a CNB, there should be a delay of on less than 6 hours before revaroxaban treatment is initiated (24 hours if the procedure has been traumatic or bloody)
- In patients with ongoing treatment, there should be a delay of no less than 18 hours between the last dose and the initiation of a CNB (manufacturers recommendation).
- Spinal anaesthesia: when spinal anaesthesia has been performed, rivaroxaban can be given at 6–8 hours after wound closure as thromboprophylaxis. If a traumatic puncture occurs the first dose should be delayed for 24 hours.
- Epidural anaesthesia: it is possible to perform epidural anaesthesia with a permanent catheter for postoperative analgesia. The first dose with catheter in place will be given 6–10 hours after the end of surgery. Between the administration of drug and the removal of catheter it is necessary at least 18 hours. In elderly patients, due to prolonged half-life this time shold be longer and it could be established in 22–26 hours. The minimal interval between catheter removal and next dose of rivaroxaban should be 4 hours.

Regional anaesthesia was performed in more than half of patients included in clinical trials but no information regarding needle placement or catheter introduction was included. Although there have been no reported spinal hematomas, the lack of information regarding specifics or regional anaesthesia and the prolonged half life warrants a cautious approach.

Dabigatran

Direct thrombin inhibitors are new class of anticoagulants used primarily in the treatment of heparin-induced thrombocytopenia and percutaneous coronary interventions. Dabigtran etexilate is prodrug that inhibits both free and clot-bound thrombin. The drug is absorbed from the gastrointestinal tract with bioavaliabity of 5 %. After absorbtion is converted to active metabolite, dabigatran. Plasma level peak at 2 hours. The half life is 8 hours after single dose and up to 17 hours after multiple doses. Because 80 % of the drug is excreted unchanged by the kidneys, it is contraindicated in patients with renal failure. Its elimination is dependent on kidney function, and is contraindicated in patients with severe renal impairment (creatine clearence < 30 mL/min). In patients with creatine clereance 30–50 mL/min and in patients over 75 years the daily dose should be reduced to 150 mg. It is not recommended in patients with elevated liver enzymes more than two times the upper limit of normal.

There is no specific antidote, but reversal of anticoagulant effect is theoretically possible with administration

of recombinant factor VIIa, although this has not been atempted clinically. In the case of bleeding the best option could be to administer prothrombin concentrates or fresh frozen plasma depending on te modification of clotting test.

Dabigatran has been licensed for thromboprophylaxis in patients undegoing hip or knee arthroplasty and is under evaluation in ongoing trials for prevention of stroke in patients with atrial fibrillation, acute VTE treatment and secondary prevention of cardiac events in patients with acute coronary syndrome.

There are many clinical trials comparing thromboembolic events in patients with joint replacement receiving dabigatran or LMWH (enoxaparin). According these studies the incidence of thromboembolic events is less with administration of dabigatran. Dose recommendations are 110 mg 1 to 4 hours after surgery, and thereafter 220 mg/day for up to 35 days. The dosing is once daily given perorally.

Anaesthetic management of the patient receiving Dabigatran

- The first dose of dabigatran should be given no less than 6 hours after a CNB or catheter removal.
- The first dose should wait a minimum of 2 hours after removal of an epidural catheter (manufacturers recommendation).
- Spinal anaesthesia: after performing spinal atraumatic anaesthesia the first dose can be given at 1–4 hours after the end of surgery. If a traumatic/hemorrhagic puncture occurs the first dose of dabigatran should be delayed for 24 hours.
- Epidural aneshesia: dabigatran cannot be administered if epidural anaesthesia with insertion of permanent catheter has been performed. Once a dose of the anticoagulant has been given, the safety time between the removal of catheter and the next administration of drug would be 36 hours, but this practice has not been valid anywhere.

Among published studies there was no randomisation regarding anaesthetic technique or criteria based on the performance of neuraxial block, including the presence of an indwelling catheter or traumatic needle/catheter placement. There have been no reported spinal hematomas, but the lack of information regarding the specifcs of block performance and the prolonged half-life warrants cautious approach.

CONCLUSION

The alarmingly high incidence od spinal hematomas reported during 1990s after introduction of LMWH for thromboprophylaxis led to numerous national and international guidelines intented to reduce the risk of spinal bleeding where CNBs are performed in patients given anticoagulated drugs. The new anticoagulated drugs introduced in last 10 years (fondaparinux, rivaroxaban and dabigatran) are administered with great caution in patients receiving spinal/epidural anaesthesia. Pharmacologic properties are very important for safe management of these drugs and CNBs. Elimination half time, peak effect, time needed for cloth formation must be calculated before performing spinal/epidural anaesthesia and catheter placement. With this cautious approach the danger of spinal bleeding is minimum.There are many studies performed in patients with joint replacement and no case of spinal hematoma is reported. Unfortunatelly there are no prospective randomised studies analysing regional anaesthesia and new anticoagulated drugs, and further investigations are necessary before definitive recommendations of performing spinal/epidural anaesthesia and catheter manipulation will be proposed.

Reported studies confirmed safe use of regional anaesthesia procedures in patients taken anticoagulated drugs. It should be remmembred that decision to perform regional anaesthesia in the patients receiving new antithrombotic drugs should be made on an individual basis weighing risk of neuraxial bleeding with the benefits of regional anaesthesia. The procedures of regional anaesthesia must be performed according to the guidelines of blockade in anticoagulated patients. With these guidelines the benefits of regional anaesthesia in orthopedic procedures will improve clinical results and patients satisfactions with minimal risks regarding possible complications of concomitant use of anticoagulated drugs and neuraxial anaesthesia.

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