PERIODICUM BIOLOGORUM
VOL. 115, No 2, 125–130, 2013

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Overview

Controversies in regional anaesthesia – patient on anticoagulant therapy

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Received May 15, 2013.

INTRODUCTION

There are many advantages of spinal or epidural analgesia/anesthesia over general anesthesia in patients undergoing orthopedic surgery including reduced postoperative cardiovascular and pulmonary complications, blood loss, 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 anesthesia. A meta analysis of randomized trials revealed that the use of perioperative regional anesthesia 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 % *(1)*.

The rationale for thromboprophylaxis is based on the high prevalence of venous thromboembolism among hospitalised patients. The highest incidence of thromboembolic complications is among orthopaedic 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% *(2)*. 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 *(3)*.

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 Anesthesia) 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 2012, is formally known as the 9th ACCP Conference on Antithrombotic and Thrombolytic Therapy *(4)*.

The combination of regional anesthesia and thromboprophylaxis is standard for many operative procedures. Unfortunately serious complications like perispinal hematoma can occur after spinal or epidural anesthesia performed in patients receiving thromboprophylaxis. Epidural hematoma is defined as a rare, but potentially catastrophic complications of spinal or epidural anesthesia. 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 anesthesia have been reported *(5)*.

In response to these serious complications the American Society of Regional Anesthesia and Pain Medicine (ASRA) held three Consensus Conferences on Regional Anesthesia and Anticoagulation where recommendations how to perform regional anesthesia in patients receiving anticoagulation drugs were achieved. ASRA consensus represents the opinions of experts based on cases reports, clinical series and risks factors for surgical bleeding *(6)*.

In last two decades new antithrombotic drugs are introduced for thromboprophylaxis in orthopedic and others surgical patients and there is question how to perform regional anesthesia procedures with concommitant use of antithrombotic drugs in order to avoid serious bleeding complications. At same time the number of patients receiving antiplatelet drugs is also increased. Many patients with a coronary stent require surgery during antiplatelet thrapy, so the question is how to perform regional anesthesia in these patients or is regional anesthesia contraindicated.

Perioperative management of patients who are receiving VKA therapy

Many patients with prosthetic cardiac valves, atrial fibrillation, hypercoagulable conditions are chronically treated with oral anticoagulants. Patients with DVT or PE are treated with oral anticoagulants for several months. Oral anticoagulants are also used for thromboprophylaxis following many surgical procedures. Oral anticoagulants interferes with the synthesis of the vitamin K-dependent clotting factors, factor II (thrombin), VII, IX and X.

In patients undergoing major surgery or procedures interruption of VKA (Vitamin K antagonists) therapy is required to minimize perioperative bleeding. The neuraxial anesthesia is contraindicated during oral anticoagulant therapy that is not interrupted prior to surgery. Is important to achieve normal or near-normal hemostasis at the time when procedure of regional anesthesia is performed. The residuals pharmacodynamic effect of VKAs and the associated time need for the regeneration of vitamin K-dependent coagulation factors. Elimination half-life of VKA is 8 to 11 h for acenocoumarol and 36 to 42 h for warfarin. Each half-life elapsed corresponds to 50% reduction in anticoagulant affect. Theoretically, since the PT and INR reflect dominantly factor VII activity (factor VII has only a 6-8 h half-life) there might be interval during during wich PT and INR approach normal levels but factors II and X levels are not be adequate for hemostasis. Bleeding may occur if the level of any clotting factor is decreased to 20 – 40% of baseline. Adequate levels of all vitamin K dependent factors are present when INR is in the normal range. INR value of 1.5 is associated with factor VII activity of 40%. Thus, an INR < 1.5 should be associated with normal hemostasis *(7)*.

Many patients perioperatively should receive bridging anticoagulation during interruption of VKA therapy. Bridging anticoagulation means the administration of a short acting anticoagulant during interruption of VKA therapy when INR is not within a therapeutic range aiming to minimize the risk for thromboembolism, such as stroke and systemic embolism in patients with a mechanical heart valve or atrial fibrillation and to minimize the risk for recurrent thrombosis in patients with prior VTE. In high risk patients the therapeutic dose (the dose that is similar to that used for acute VTE or acute coronary syndrome) of low molecular weight heparins (LMWH) or unfractioned heparin (UFH) is proposed. In patients with moderate risk the prophylactic dose is recommended (the dose that is used typically to prevent postoperative VTE) *(8)*.

Regional anesthesia management of the patient receiving VKA antagonists

1. Discontinue VKA antagonists 5 days preoperatively and verify PT normalization before neuraxial block.
2. In patients with a mechanical heart valve, atrial fibrillation or VTE at high risk for thromboembolism the bridging therapy with LMWH is suggested during interruption of VKA therapy.
3. Mmonitor the PT and INR daily.
4. Neuraxial anestheis or removing indwelling neuraxial catheters are possible when the INR is < 1.5

Low molecular weight heparins (LMWH)

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 anesthesia 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 given intraoperatively or early postoperatively to patients undergoing continuous epidural anesthesia 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 anesthesia relative to the dose of LMWH, traumatic needle placement, and catheter removal during therapeutic levels of anticoagulation. In many patients the impact of renal function is underestimated. In patients with severe renal insufficiency the anticoagulant effect is exaggerated ant the elimination half live prolonged from 4–5 to as long as 16 hours *(9)*.

Regional anesthesia management of the patient receiving LMWH

Preoperative LMWH

1. Perform neuraxial techniques at least 10–12 h after a thromboprophylaxis dose and 24 h after a high therapeutic dose of LMWH.

Postoperative LMWH – twice dosing regimen

1. With twice daily dosing administer first dose no earlier than 24 h after operation.
2. Remove indwelling catheters before initiation of LMWH thromboprophylaxis.
3. The first dose of LMWH administered 2 h after catheter removal and 24 h after needle/catheter placement.

Postoperative LMWH – once dosing regimen

1. Once daily dosing requires 6–8 h between needle/catheter placement ant the first dose of LMWH.

New anticoagulants

Because of great importance of thromboprophylaxis anticoagulated drugs are under permanent investigations. 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 continuously 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 anesthesia must be carefully considered. Importantly, until large series become available, we can apply lessons learned from LMWH experience to develop initial management recommendations.

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 anesthesisin 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 preventing 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.

Anesthetic 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.

1. The first dose is administered no less than 6 hours after completion of central nerve blockade (CNB).
2. 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 should 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. (*11, 12*)

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 shuld be used with caution in patients with moderate hepatic impairment.

Anesthetic management of the patient receiving Rivaroxaban

1. Folowing a CNB, there should be a delay of on less than 6 hours before rivaroxaban treatment is initiated (24 hours if the procedure has been traumatic or bloody).
2. 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).
3. Spinal anesthesia: when spinal anesthesia 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.
4. Epidural anesthesia: it is possible to perform epidural anesthesia 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 anesthesia 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 anesthesia and the prolonged half life warrants a cautious approach *(11,12)*.

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 the modification of clotting tests.

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.

Anesthetic management of the patient receiving Dabigatran

1. The first dose of dabigatran should be given no less than 6 hours after a CNB or catheter removal.
2. The first dose should wait a minimum of 2 hours after removal of an epidural catheter (manufacturers recommendation).
3. Spinal anesthesia: after performing spinal atraumatic anesthesia 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.
4. Epidural aneshesia: dabigatran cannot be administered if epidural anesthesia 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 anesthetic 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 (11,12).

Is important to notice that first dose of new anticoagulants is given postoperatively, so neuraxial blockade performed preoperatively is safe procedure. The question is safety of neuraxial blockade in patients receiving new anticoagulants for thromboprophylaxis who needed reoperation. The number of these patients is small, and there is no reported study of these problem. There is also no case report of possible complication in these patients so further investigation is needed.

Antiplatelet medications

There are two types of antiplatelet agents: agents with irreversibly and agents with reversibly inhibition of platelet function. Antiplatelet agents that irreversibly inhibit platelet function include ASA, clopidogrel, ticlopidin and prasurgel. For each day after interruption of any ot these agents 10% to 14% of normal platelet function is restored, so it takes 7 to 10 days for an entire platelet pool to be replenished.

Antiplatelet drugs that reversibly inhibit platelet function include dipyridamole and nonsteroidal antiinflammatory drugs. Dipyridamole has a half-life of 10 h, nonsteroidal antiinflammatory drugs have half-lives that vary from 2 to 6 h (ibuprofen, ketoprofen, indometacin), to 7 to 15 h (celecoxib, naproxen) to > 20 h (piroxicam).

In order to restore platelet function and to avoid bleeding the recommendation is preoperative stopping of antiplatelet medication. But according recent CHEST recommendations in patients at moderate to high risk for cardiovascular events who are receiving ASA therapy and require noncardiac surgery continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery is recommended. In patients at low risk stopping of ASA is suggested.

Special caution is given to patients with coronary stents having surgery. The number of these patients is growing, so one retrospective study of 17.797 stented patients found that 11% of patients require surgery during a 2 year period after stent placement and that 4% required surgery within 1 year of stent placement *(13)*.

Patient management is problematic because of concerns about the incidence of stent related coronary thrombosis if antiplatelet therapy is interrupted. In several retrospective studies with > 2.200 patients who had surgery within 2 years of stent placement the incidence of postoperative stent thrombosis was 2% and 5% *(14)*.

The possible role of the bridging therapy in patients with coronary stents who require surgery is uncertain. There are only a few case reports assesed the use of short acting antiplatelet drugs such as UFH, LMWHs or glycoprotein IIb/IIIa antagonists in the perioperative setting. Studies are needed to asses the role of bridging therapy *(7)*.

Recent recommendations suggest that in patients with a coronary stent who receiving dual antiplatelet therapy the surgery should be postponed for at least 6 weeks after placement of a bare-metal stent and for a least 6 months after placement a drug-eluciting stent. In patients who require surgery in this period continuing dual therapy around the time of surgery is recommended instead of stopping antiplatelet therapy 7 to 10 days before surgery. The question is how to perform regional anesthesia in patients with stents. Is neuraxial blockade contraindicated in this period? Several large studies demonstrated safety of central blockade in patients receiving ASA or NSAID preoperatively. There is no large studies with patients receiving ticlopidin or clopidogrel, but there are case

reports of 3 spinal hematomas attributed to neuraxial technique and ticlopidine or clopidogrel *(7, 15)*.

Anesthetic management of the patient receiving antiplatelet medication1.

1. Nonsteroidal anti-inflammatory drugs seem to represent no added significant risk for spinal hematoma in patients having spinal/epidural anesthesia.
2. The actual risk of spinal hematoma with ticlopidin and clopidogrel is unknown. The normalization of platelet function is needed before spinal/epidural anesthesia, so discontinuation of therapy is recommended. The suggested time interval between discontinuation and neuraxial anesthesia is 14 days for ticlopidine and 7 days for clopidogrel.
3. In patients with coronary stent who needed continuing therapy around the time of surgery the neuraxial anesthesia is not recommended.

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 were 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 anesthesia. Special caution is also given to patients receiving antiplatelet medications. 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 anesthesia and catheter placement. With this cautious approach the danger of spinal bleeding is minimum. Unfortunatelly there are no prospective randomised studies analysing regional anesthesia and new anticoagulated drugs or antiplatelet medications in patients with coronary stent, and further investigations are necessary before definitive recommendations of performing spinal/epidural anesthesia and catheter manipulation will be proposed.

Reported studies confirmed safe use of regional anesthesia procedures in patients taken anticoagulated drugs. It should be remmembred that decision to perform regional anesthesia in the patients receiving antithrombotic drugs should be made on an individual basis weighing risk of neuraxial bleeding with the benefits of regional anesthesia. The procedures of regional anesthesia must be performed according the guidelines of blockade in anticoagulated patients.

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