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Contraindications – Hemorrhage and Coagulopathy, and Patient Refusal

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1. Introduction

Widely used in surgical anesthesia, obstetric analgesia, –postoperative pain control and in the treatment of chronic pain, epidural techniques are contraindicated in such conditions as coagulopathy and other bleeding diathesis, patient refusal, hemodynamic instability, increased intracranial pressure and local or systemic infection.

Contraindications for epidural analgesia are patient reluctance, bleeding diathesis, hemodynamic instability, increased intracranial pressure and local or systemic infection. Contraindications are listed in Table 1.

Coagulation defects may be inherited or acquired (Table 2).

2. Contraindications - Hemorrhage and coagulopathy, and patient refusal

2.1 Coagulation and regulation of thrombin generation

Blood coagulation is a physiologic defense mechanism which develops as a response to a vascular damage and protects the integrity of the circulatory system. A hemostatic response to a trauma is a series of complex and interrelated events that necessitate interaction of the vessel wall, plasma proteins and platelets (Colman et al., 2001). This interaction results in one of the three outcomes: Hemorrhage, an appropriate hemostasis or a pathologic thrombosis (Hess & Lawson, 2006).

The cell-based coagulation method is frequently used today in understanding hemostasis. This model is divided into initiation, amplification and propagation phases (Hoffman & Monroe, 2001; Tanaka et al., 2009).

In the initiation phase, the surface of endothelium is activated by molecular or physical (traumatic or surgical) signals and it becomes the focal point of the procoagulant activity. The endogenous heparin molecule is removed from the surface of endothelium and the anticoagulant molecules become subject to thrombomodulin and antithrombin down regulation. A tissue factor is exposed to and the composition of endothelium surface phospholipids changes. To initiate formation of a clot, the tissue factor (TF) recruits

coagulation zymogen factor VII. Activated factor VII (VIIa) converts factor IX and factor X into their active enzyme forms. Activated factor X(Xa) then converts prothrombin (fII) into thrombin (fIIa) and factor V (fV) into factor Va (fVa) (Adams et al., 2007). Thrombin so formed and fibrin which is formed from fibrinogen with the effect of thrombin are in very small amounts.

Coagulopathy and other bleeding diathesis
 Patient refusal
 Hemodynamic instability
 Increased intracranial pressure
 Local or systemic infection
 Pre-existing neurological disorders

Table 1. Epidural blockage contraindications

Inherited

Hemophilia A and Hemophilia B
 von Willebrand disease
 Factor V deficiency
 Inherited disorders of platelet disfunctions
 Inherited hemorrhagic telangiectasia
 Inherited thrombophilia

Acquired

Vitamin K deficiency
 Drug-associated hemorrhage
 Drug-associated hemorrhage
 Disseminated intravascular coagulation
 The Coagulopathy of Massive Trauma
 Idiopathic thrombocytopenic purpura

Table 2. Classification of Coagulation Defects

In the amplification phase of thrombus, activated platelets bind to endothelium, activate factors V, XI and VIII and increase formation of thrombin through a positive feedback cycle (Adams et al., 2007; Hoffman & Monroe, 2001; Tanaka, 2009). Thrombocytes play a major role in localized clotting reactions in the trauma area. Thrombocytes bind and adhere to von Willebrand factor (vWF), thrombin, platelet receptors and subendothelial collagen in the trauma area and they form an aggregation. In this way, the surface for generation of required thrombin is formed for an effective hemostasis (Falati et al., 2002). As a result of the activation of platelets, cofactors Va and VIIIa quickly get localized on the surface of thrombocytes (Monroe et al., 1994). Factor Va accelerates and intensifies the activation of factor Xa. Factor VIIIa accelerates the binding of factor XIa to IXa (Adams et al., 2006) and enables continuation of procoagulant responses (Gailani & Broze, 1991).

In the propagation phase, fibrin polymerization and fibrin clotting occur. Thrombin first cleaves fibrinopeptide A and fibrinopeptide B particles from fibrinogen molecule and generates fibrin monomers and then fibrin polymers when these monomers aggregate. Thrombin also activates factor XIII to enable formation of cross-links among fibrin polymers

and a firm fibrin clot (Hornyak & Shafer, 1992). A large amount of thrombin generated on the surface of thrombocyte is responsible for stabilization of the clot rather than supporting the polymerized fibrin (Hoffman & Monroe, 2007).

The coagulation cascade should be controlled and strictly monitored to confine it only in the area required. Many coagulation factors are serine protease and the coagulation process is regulated by serine protease inhibitors protein C and S, tissue factor pathway inhibitor (TFPI) and antithrombin. These agents inhibit clotting and formation of localized clot in the injured area. The fibrinolytic system in turn is activated and plays a role in dissolving the clot, healing the injury and reforming the tissue (Levy et al., 2010).

As a result, the competition of the procoagulant, anticoagulant, fibrinolytic and antifibrinolytic ways are regulated and remain in balance in human physiology. However, if a surgical stress, trauma or disease pushes any of these ways of competition out of balance, then it results in a pathologic condition that leads to either a hemorrhage or thrombosis (Hess & Lawson, 2006).

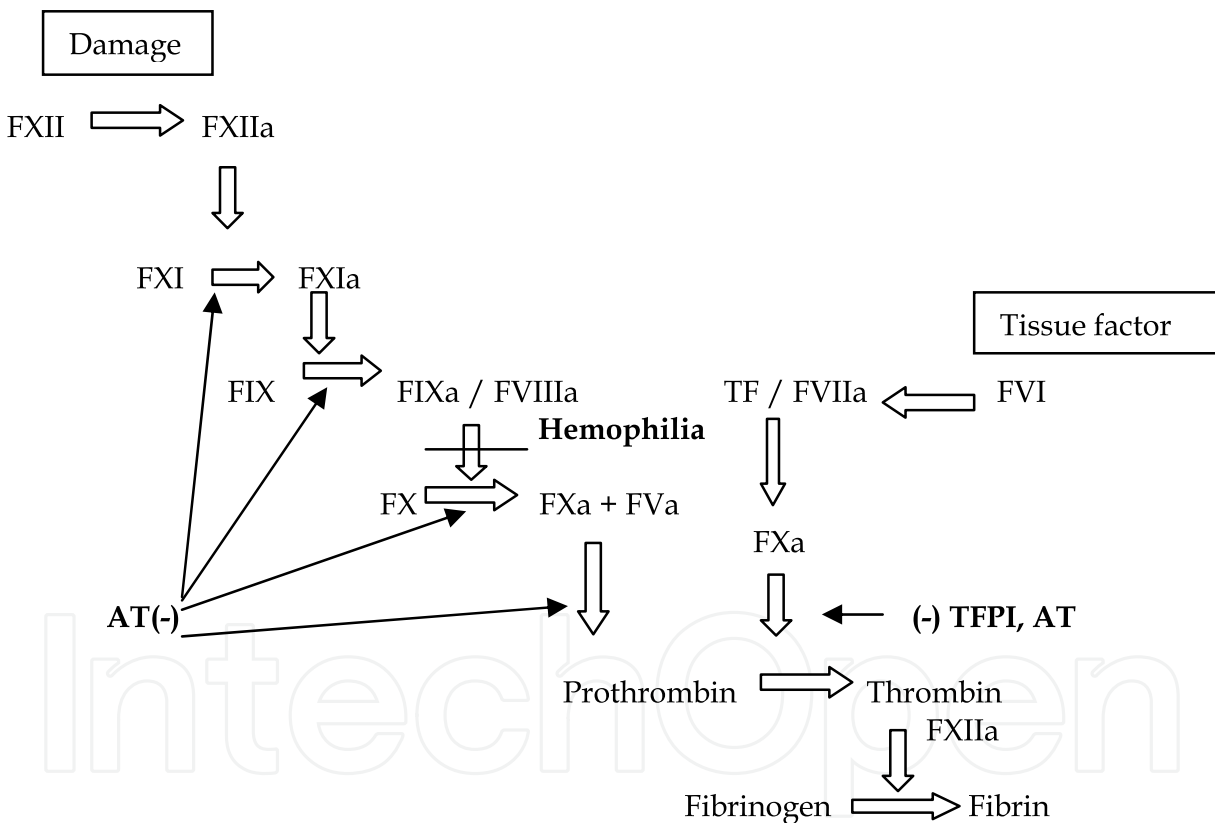


Fig. 1. Model of coagulation and regulation of thrombin generation.

2.2 Preoperative coagulation evaluation

The screening tests to determine bleeding risk in patients is ideally carried out in the preoperative period. Identification of hemostatic defects in this way helps in the preoperative period in the management of unpreventable bleeding. A history or a family history of bleeding in anamnesis increases the risk. The history of drug usage and the effect of used medicament to the coagulation cascade should be questioned.

Petechia, purpura, bleeding of nose or gums, hematuria, melena and other signs of bleeding should be noted as risk-increasing factors (Adams et al., 2007). Especially petechia (capillary) and purpura, which are physical characteristics of bleeding, as well as hematoma and ecchymose resulting from a large blood vessel bleeding should be well-explained. In detecting an inherited coagulopathy, presence of bleeding without any history of a disease or anticoagulant drug usage in the patient directly attracts the attention to an inherited defect.

Laboratory tests should be conducted in relation to the patient's clinical condition and history of bleeding and the type of planned surgery (Table 3).

Although preoperative scanning tests are not required in healthy individuals, neuraxial blockade, coagulation examinations and platelet counts should be conducted in cases in which clinical history indicates a probability of hemorrhage (Morgan et al., 2008).

Laboratory tests	Normal values
Prothrombin time	10-14 sec
Partial thromboplastin time	22-35 sec
International normalized ratio (INR)	0.80-1.30
Platelet Count	150.000-450.000/ μ L
Bleeding time	3-8 min
Thrombin time	9-25 sec
Fibrinogen assay	
Healthy individuals	200-400 mg/dL
With severe illness	400-800 mg/dL
Specific factors and inhibition levels	

Table 3. Laboratory tests and normal values

No testing is required in patients who have no history of bleeding and will undergo a minor surgery. In patients who have no history of bleeding but will undergo a major surgery, counts of partial thromboplastin time (PTT) and trombocyte is recommended. In patients with hemostatic disorders, the number of trombocytes, bleeding time, PTT and thromboplastin time should be measured (Adams et al., 2007).

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the most widely used tests in screening coagulation disorders. PT is affected by reductions of Factors VII, X, V, and prothrombin such as occur with vitamin K antagonist therapy (Levy et al., 2008) or severe liver disease (Tripodi et al., 2007). aPTT is sensitive to gross reductions of Factors V, VIII, IX, XI, XII, and to a lesser extent, prothrombin (Tanaka et al., 2009). These screening coagulation tests are abnormal when there is a deficiency of one or more of the soluble coagulation factors (Hoffman & Monroe, 2007).

A consensus could not be reached about the minimum hemostatic condition required by regional techniques. One of the most common views is that if there is a thrombocyte function as a minimum threshold, then the hemostatic capacity is sufficient. Although a number of tests are carried out to assess the thrombocyte function today, it is not possible to arrive at definite information about the adequacy of coagulation. In these circumstances, the administration of a regional anesthesia and the minimum hemostatic condition that is required to apply the anesthesia can be realized if;

- the number of functional platelets $>80-100\ 000\ \mu\text{L}^{-1}$,
 - international normalized ratio (INR) < 1.5 ,
 - activated prothrombin time (aPTT) $<45\ \text{sec}$.
- (Llau et al., 2005; Tyagi & Bhattacharya, 2002; Mentegazziet al., 2005).

2.3 Coagulation defects

2.3.1 Inherited coagulation defects

Inherited coagulation defects generally appear because of the absence or insufficiency of a single coagulation factor.

2.3.1.1 Hemophilia A and hemophilia B

Hemophilia A and B are X-linked recessively inherited disorders. The incidence of hemophilia is 1 in 5000 male births and that of hemophilia B is 1 in 30000 (Tuddenham & Cooper, 1994).

Characterized by excessive bleeding in various parts of the body, hemophilia develops due to a mutation of factor VIII (Hemophilia A) and factor IX (Hemophilia B) coagulation genes. The chance of inheriting a gene defect from a hemophilia carrier is 50%. A patient's son is affected with a chance of 50% at every pregnancy and her daughter, who is also a carrier of the disease, is also affected with a chance of 50% (Cahill & Colvin, 1997). However, hemophilia may also develop in 30% of the cases as a result of a spontaneous mutation without any history of hemophilia in the family (Mannucci & Tuddenham, 2001).

Hemophilia is classified according to the level of the clotting factor. A hundred percent of the said factor which is contained in 1 mL of normal plasma is referred to as 1 unit. Normal plasma activity is between $5\ \text{U}\cdot\text{dl}^{-1}$ and $15\ \text{U}\cdot\text{dl}^{-1}$ (50-150%) (DiMichele & Neufeld, 1998). The level of normal factor in seriously affected patients is $<1\%$, in moderately affected 1-4% and in mildly affected 5-50% (Cahill & Colvin, 1997). While those with serious hemophilia are susceptible to spontaneous bleeding episodes, the ones with mild hemophilia have bleeding after a trauma or surgery (Mannucci & Tuddenham, 2001).

There are case reports in the literature notifying the occurrence of an epidural hematoma following a lumbar puncture in patients who were not known to have hemophilia (Bernhardt et al., 2008; Faillace et al., 1989). The use of a regional block in patients with bleeding disorders is controversial because of the risk of developing hematoma which leads to epidural or spinal bleeding and a permanent neurological damage. However, the use of a regional block is not contraindicated when the coagulation tests (platelet quantity, PT, aPTT, INR and fibrinogen) are normal and the relevant factor level is $>50\ \text{IU}\cdot\text{dl}^{-1}$ or is raised to $>50\ \text{IU}\cdot\text{dl}^{-1}$ through a prophylactic treatment (Lee et al., 2006; Silverman et al., 1993; Dhar et al., 2003).

An epidural intervention should be applied with a midline approach by an experienced anesthetist (Abramovitz & Beilin, 2003). A mixture of low-dose local anesthetics and narcotics should be used to attain analgesia by protecting the motor function (Dhar et al., 2003). Motor block measurements should be carried out frequently until the catheter is removed. If the degree of the motor block is higher than expected and the length of anesthesia is prolonged, a magnetic resonance imaging should be made to control development of an epidural hematoma.

It is important to check the factor levels before the epidural catheter is removed.

2.3.1.2 von Willebrand disease (vWD)

Von Willebrand disease (vWD) is an inherited hematologic disorder which involves vWF deficiency and is the most prevailing bleeding disorder affecting nearly 1% of the general population (Rodeghiero et al., 1987). vWD is divided into three types according to the qualitative and quantitative deficiency of the vWF level. The vWF level is decreased in vWD Type 1; it is normal in Type 2, but there is a function disorder. The vWF deficiency is serious in vWD Type 3. The most common one is Type 1 which constitutes approximately 70% of the cases. While vWD Types 1 and 2 are inherited autosomal dominantly, Type 3 is inherited autosomal recessively (Lee et al., 2006).

vWF is necessary for adhesion of platelets to form a platelet clump in an injured endothelium. It is also the carrier protein of Factor VIII. When vWF is deficient, the time of bleeding is prolonged and patients generally have abnormal bleedings such as epistaxis, menorrhagia and postpartum bleeding (Varughese & Cohen, 2007). Tendency to bleeding is moderate in vWD Type 1 and 2, but serious in Type 3. Pregnant women with vWD have a progressively increasing FVIII coagulation activity (FVIII:C), and vWF antigen (vWF:Ag) and vWF activity (vWF:AC) during pregnancy, which all return to the baseline after delivery (Greer et al., 1991; Punnonen et al., 1981; Kadir et al., 1998). The increase in the variables showing such platelet activity is apparent in pregnant women with vWD Type 1, moderate in Type 2 and very little or nil in Type 3. Because of the differences in hemostatic responses, the factor levels with plasma vWF:Ag, vWF:AC and FVIII:C should regularly be monitored in pregnant women with vWD.

When the vWF activity becomes $<50 \text{ IU}\cdot\text{dl}^{-1}$ during an invasive intervention or a delivery, a prophylactic treatment should be initiated using a coagulation factor concentrate with vWF. A prophylactic treatment is not necessary at delivery in women with vWD Type 1. Treatment becomes necessary in vWD Type 2 if a cesarean section is being carried out or a perineal trauma occurred. Women with vWD Type 3 require treatment in all types of delivery (Lee et al., 2006).

The risk of developing a spinal hematoma after an epidural anesthesia is very rare in obstetric patients (1:200000). However, this risk increases in patients with serious coagulopathy (Moen et al., 2004). Neuraxial interventions are contraindicated in patients with vWD whose bleeding disorders are not healed. Although vWD is quite common among bleeding disorders, there are very few case reports describing an anesthetic method for vWD patients (Hara et al., 2009; Caliezi et al., 1998; Jones et al., 1999; Milaskiewicz et al., 1990; Cohen et al., 1989). Paucity of large case series showing that epidural interventions are safe makes anesthetists hesitate when conducting anesthesia on women with vWD.

When the vWF activity becomes $>50 \text{ IU}\cdot\text{dl}^{-1}$ in women with vWD Type 1 or this value is reached through replacement, an epidural anesthesia can safely be administered. However, the decision of using an epidural anesthesia should be made jointly by an experienced anesthetist, a hematologist and a gynecologist (Lee et al., 2006). Epidural anesthesia is not recommended for patients with vWD Type 2 and 3 (Pasi et al., 2004). An epidural anesthesia should be administered by an experienced anesthetist.

2.3.1.3 Factor V deficiency

Factor V deficiency is a congenital bleeding disorder which prevails very rarely (1 in 1000000) in the population (Asselta et al., 2006). Factor V itinerates as an inactive cofactor in the plasma and is activated by thrombin. Activated factor V works as a cofactor with factor VIIIa and factor Xa to convert prothrombin into thrombin (Fogerty & Connors, 2009).

Factor V deficiency is classified as quantitative (type 1) and qualitative (type II) (Asselta et al., 2006). When the plasma FV antigen level becomes <15%, it is classified as a serious Type I deficiency and when it becomes <60-65%, as a moderate Type I deficiency. A moderate to serious level of bleeding occurs in serious Type I deficiency (Asselta et al., 2006; Vellinga et al., 2006).

There is no evident information on the use of neuraxial techniques in these patients. However, it was reported that the neuraxial techniques were safe in labor epidural analgesia when the FV level becomes > 60% (Le Gouez et al., 2011). In pregnancy, prothrombin time (PT) can be normal although the FV level is low (Cerneca et al., 1997). For this reason, PT alone is not sufficient in determining the FV level. The FV level should be reassessed to be able to remove the epidural catheter safely (Kadir et al., 2009).

2.3.1.4 Inherited hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as the Osler-Weber-Rendu Syndrome, is a congenital autosomal dominant multiple vascular dysplasia which is seen in 1 person out of 5000-8000 (Begbie et al., 2003). This disease is characterized by multiple arteriovenous malformations (AVMs) associated with the lack of capillaries joining arteries with veins in the solid organs of a body and telangiectasis of cutaneous and mucous membranes (Hereditary Hemorrhagic Telangiectasia Foundation International Inc., 2007). Vascular dysplasia is mostly seen in pulmonary, cerebral, gastrointestinal and spinal vascular structures. The course of the disease may progress silently or in a life-threatening manner from a high-output heart failure secondary to arteriovenous shunting, a systemic emboli, rupture of AVMs up to a fatal hemorrhage (Lomax & Edgcombe, 2009).

A successful anesthesia can be administered to patients with HHT only if the existing specific AVMs are known, cardiovascular instability is avoided and a prophylaxis is applied for systemic emboli that may develop as a result of AVM shunting. Spinal AVMs constitute a relative contraindication for regional techniques (Lomax & Edgcombe, 2009).

2.3.1.5 Inherited disorders of platelet dysfunctions

2.3.1.5.1 Glanzmann's thrombasthenia

Glanzmann's Thrombasthenia a congenital, hereditary and hemorrhagic disorder caused by qualitative and quantitative impairment of platelet glycoprotein (GP) IIb/IIIa. Bleeding such as purpura, epistaxis, gingival hemorrhage and menorrhagia are seen in these patients due to defective platelets in the formation of hemostatic clump. The disorder can clinically be diagnosed through the signs of normal number of platelets, abnormal platelet aggregation and prolonged bleeding time (George et al., 1990).

2.3.1.5.2 Bernard-Soulier syndrome

Bernard-Soulier syndrome is a rarely seen bleeding disorder inherited in an autosomal recessive way. This disease develops in connection with the abnormality or lack of platelet membrane glycoprotein GPIb-V-IX and it is characterized by giant platelets, thrombocytopenia in various grades and prolonged bleeding time (Kostopanagiotou et al., 2004). Clinically it progresses with excessive bleeding not proportionate to the degree of thrombocytopenia and the bleedings are fatal (Bernard, 1983).

2.3.1.6 Inherited thrombophilia

2.3.1.6.1 Protein C deficiency

Protein C deficiency is a thrombotic disease inherited in an autosomal dominant way with a prevalence of 0.2-0.5% in the population (Aiach et al., 1997; Reitsma, 1997; Walker, 1997). Protein C is the central protein of the major antithrombotic system of hemostasis. Protein C itinerates in the plasma as an inactive zymogen linked to vitamin K. It is activated in endothelium by the thrombomodulin-thrombin complex. Activated Protein C inactivates coagulation factor Va and VIIIa. It also has a fibrinolysis function by neutralizing inhibitor of tissue-type plasminogen activator (TPAI) (Esmon, 1989).

Protein C deficiency is at increased risk for deep vein thrombosis and pulmonary embolism, especially during pregnancy and the post partum period. For this reason patients are administered thromboemboli prophylaxis and thrombosis therapy during preoperative and postoperative periods. Continuation of anticoagulation therapy, on the other hand, may increase the risk of re-bleeding with life-threatening mass effect (Ranasinghe et al., 2008; Sternberg et al., 1991). It is important to discuss a benefit-loss balance for these patients before a neuraxial procedure.

2.3.1.6.2 Antithrombin III deficiency

Antithrombin III deficiency is a hereditary disorder received in an autosomal dominant way and is seen in the population at a rate between 1/2000 and 1/5000 (Rosenberg, 1975). It is a glycoprotein which inhibits factor IIa (thrombin) and antithrombin factor Xa. Antithrombin deficiency is of the highest clinical significance among the congenital thrombophilia as it causes life-threatening thromboses (Maclean & Tait, 2007). A long-lasting anticoagulant therapy becomes inevitable in these patients due to a recurring venous thromboemboli (VTE) risk. A prophylactic anticoagulation should be administered to asymptomatic individuals especially in high-risk episodes (e.g. surgery, immobility and pregnancy) (Birnbach & Grunebaum, 1991).

LMWH is particularly recommended as an anticoagulant treatment of antithrombin deficiency. The use of LMWH is restricted in regional anesthesia due to the risk of bleeding. The American Society of Regional Anesthesia (ASRA) guidelines today recommends to discontinue the treatment at least 24 h before any neuraxial procedure is initiated (if the treatment is used in the right intensity) (Horlocker et al., 2003). This period of discontinued anticoagulant treatment in patients with high risk of VTE constitute a critical interval. In the last ten years, the use of antithrombin concentrations is recommended in high-risk situations (e.g. cesarean section, elective surgery and delivery) (Tiede et al., 2008). There are a limited number of case reports stating successful administration of epidural anesthesia and

analgesia under an antithrombin treatment in hereditary antithrombin deficiency (Pamnani et al., 2010).

2.3.2 Acquired coagulation defects

2.3.2.1 Vitamin K deficiency

Patients with vitamin K deficiency should be given oral or parenteral treatment depending on the reason of the deficiency. In a vitamin K deficiency, only the prothrombin time (PTT) is prolonged. Vitamin K deficiency is extremely common among hospitalized patients for multiple reasons. Poor diet (lack of leafy vegetables) often results in hospitalization.

Warfarin is a competitive inhibitor of vitamin K. The amount of vitamin K required to reverse its effect depends on the amount of warfarin in blood.

2.3.2.2 Drug-associated hemorrhage

Drug-associated hemorrhage may stem from heparin, vitamin K antagonists, platelet aggregation inhibitors, glycoprotein IIb/IIIa inhibitors or direct thrombin inhibitors.

Regional anesthesia in the presence of anticoagulation

- a. Anesthetists should be aware of the potential risk of bleeding when conducting regional anesthesia techniques in patients who receive antithrombotic treatment and are planned to undergo a surgery. When a potent antithrombotic drug was involved, this often has resulted in avoidance of regional anesthesia techniques due to the concern about the patient's safety. Therefore, some national anesthesia societies have published guidelines describing how to safely conduct regional anesthesia when using antiplatelet, anticoagulant and thrombolytic medication. The first national recommendations on neuraxial anesthesia and antithrombotic drugs were published by the German Society for Anesthesiology and Intensive Care in 1997 (Gogarten et al., 1997), followed by the American Society of Regional Anesthesia (ASRA) in 1998 (Horlocker & Wedel, 1998), and Belgian anesthesiologists in 2000 (Belgian Guidelines 2000). In this context, there are a large number of recommendations approved by scientific anesthesia societies (Horlocker et al., 2003; Llau et al., 2005; Vandermeulen et al., 2005; Samama et al., 2002). This enabled comparison of similarities and differences in some important situations (Llau et al., 2007).

The European Society of Anesthesiology (ESA) has recently published recommendations about the time intervals between the neuraxial blockage and removal of the catheter and the administration of an anticoagulant when anticoagulant agents are being used (Gogarten et al., 2010). Such guidelines are continuously being updated because new anticoagulants are regularly being developed and they are based on large case series, case reports and pharmacologic data of anticoagulant drugs rather than controlled studies.

Administrators of neuraxial block on patients receiving antithrombotic treatment should be weary of possible hematoma formation resulting into neurologic deficit. Epidural hematoma related to neuraxial anesthesia is a rare but potentially devastating complication (Guffey et al., 2010; Li et al., 2010; Han et al., 2010). The risk of hemorrhage is lowest in spinal anesthesia, which employs fine needles, and highest in epidural catheter anesthesia, which requires the largest needle gauges available. Nearly half of all cases of bleeding occur during the removal of an epidural catheter, and this procedure must be regarded as critical as catheter insertion

(Vandermeulen et al., 1994). Catheter manipulation and removal carry similar risks to insertion, and the same criteria should apply. Appropriate neurological monitoring is essential during the postoperative recovery period and following catheter removal.

b. Antithrombotic drugs and Regional Anesthesia

This is used if it is believed to be more beneficial than the alternative methods. Anticoagulants, antiplatelet drugs and thrombolytics are used for the prevention and treatment of stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism in many patients undergoing surgery (Table 4). (Donegan et al., 2007). The risk of developing epidural hematoma is reduced if care is taken for the characteristics of these drugs and the safe time intervals needed for administering the regional technique (Llau et al., 2001). Neuraxial anesthesia can be accepted in these patients only if coagulation is optimized and monitoring is done during the application.

Drugs groups

Heparins
Anti- Xa agents
Direct thrombin inhibitors
Vit K Antagonists
Antiplatelet drugs

Table 4. Antithrombotic drugs

Regional anesthesia in patients on treatment with unfractionated heparins

Factor IIa produces an anticoagulant effect by inhibiting the antithrombin III enzyme activity on IXa and Xa (Weitz, 1997; Hirsh & Raschke, 2004). Unfractional heparin (UH) is administered subcutaneously (sc) or intravenously (iv). Its half-life varies according to the dose (Llau et al., 2007).

Coagulation tests need not be done for patients who receive sc UH in prophylactic doses (<15000IU/day) However, a thrombocyte count should be carried out in patients who have received treatment for more than 5 days and for whom there is a need to distinguish heparin-induced thrombocytopenia. The treatment should be suspended 2 to 4h before removing the catheter. The next heparin dose should be postponed until 1h after the procedure (Gogarten et al., 2010).

Although the UH dose used in venous thromboprophylaxis is safe, the risk of bleeding increases in therapeutic doses. For this reason, insertion and removal of catheters is contraindicating in patients receiving therapeutic treatment. If a safe removal of neuraxial blockage or catheter is planned, administration of intravenous (iv) heparin should be suspended for at least 4h and it should be ascertained before the procedure that aPTT, activated clotting time (ACT), anti-Xa activity and thrombocyte quantity are all normal. It should be avoided for 2h in low doses if an intraoperative heparinization is planned and for 6-12 hours if a full heparinization is planned (Gogarten et al., 2010).

Regional anesthesia in patients on treatment with low molecular weight heparins

This is widely used to prevent and treat deep vein thrombosis (DVT) by inhibiting factor Xa formation. It became superior to the other anticoagulants as it has high level of bioavailability,

the risk of bleeding is low and it can easily be used without any need for monitoring blood clotting (Vandermeulen, 2010). LMWH reaches the peak plasma level approximately 4h after a subcutaneous procedure and its activity continues for 24h (Hirsh et al., 2001).

In order to avoid any bleeding complication, there must be at least 12h (in prophylactic dose of LMWH) or 24h (in therapeutic dose of LMWH) between the last dose of LMWH and the removal of the neuraxial blockage or epidural catheter (Vandermeulen et al., 1994; Bergqvist et al., 1993). The next LMWH dose should be applied 4h after the epidural/spinal puncture or catheter removal (Gogarten et al., 2010). The probability of developing a heparin-induced thrombocytopenia (HIT) after LMWH is ten times less as compared to UH (Warkentin et al., 1995).

However, a thrombocyte count is recommended after using LMWH for more than 5 days (Vandermeulen, 2010).

Danaparoid

Danaparoid is a glycosaminoglycan containing 84% heparan sulphate, 12% dermatan sulphate and 4% chondroitin sulphate. Its anti-thrombotic effect occurs through antithrombin-induced inhibition of factor Xa (Ibbotson & Perry, 2002). Coagulation is monitored by using only the anti-X activity. It is used as an alternative to UH and LMWH in prevention and treatment of pulmonary emboli and VTE in patients with a history of danaparoid HIT (Wilde & Markham, 1997). Since it has a 22-hour elimination half-life, a preoperative danaparoid administration should be avoided in patients who are planned to undergo a neuraxial blockage (Gogarten et al., 2010).

Regional anesthesia in patients on treatment with factor Xa inhibitors

Fondaparinux

Fondaparinux is a selective reversible inhibitor of coagulation factor Xa. It has a high affinity with antithrombin III without affecting active thrombin and platelet aggregation (Weitz et al., 2004).

A single dose of it is used daily because the half-life of this compound is 18-21h (Boneu et al., 1995). The safe interval between a fondaparinux application and a single-shot neuraxial anesthesia is 6h. The catheter can be removed 36h after the last dose. A Fondaparinux dose should be given at least 12 hours after removing the catheter (Llau Pitarch et al., 2005).

Rivaroxaban

Rivaroxaban is a selective factor Xa inhibitor. It is currently administered orally as a single dose of 10 mg to prevent a deep vein thrombosis following a total hip and knee prosthesis surgery. It reaches a maximum plasma level in 2-4h. APTT is prolonged depending on the dose. It prolongs PT with a close correlation with the plasma concentration (Kubitza et al., 2005). A time interval of 22-26h is required between the last dose of rivaroxaban and removal of the neuraxial catheter (Gogarten et al., 2010). The next dose of rivaroxaban should be applied 4-6 h after the catheter is removed (Gogarten et al., 2010).

Apixaban

Apixaban is an oral, reversible, rivaroxaban-linked direct inhibitor of factor Xa. Its half-life is between 10-15 h (Weitz et al., 2008). There must be a time interval of 26-30h between the last

dose of apixaban (2.5mg) and catheter removal. Its next dose should be given 4-6 hours after catheter removal (Gogarten et al., 2010).

Regional anesthesia in patients treated with direct thrombin inhibitors

This group of drugs uses direct selective thrombin inhibition to produce both perioperative thromboprophylaxis and therapeutic anticoagulation. They also inactivate thrombin-linked fibrin and prevent thrombus from further growing (Gogarten et al., 2010). Their anticoagulant effects can be monitored using aPTT and ecarin clotting time (ECT) (Greinacher, 2004).

Hirudins: bivalirudin, desirudin and lepirudin

All hirudins are potent anticoagulants and bind thrombin irreversibly. They can be used in HIT patients because they do not interact with thrombocyte factors (Lubenow & Greinacher, 2002). Lepirudin and desirudin have a half-life of 1.3-2 h and bivalirudin 25-30 min (Robson et al., 2002; Dasgupta et al., 2000). In patients with normal renal function, there must be at least 8-10 h of time between the last dose of a hirudin and insertion of a neuraxial blockage / catheter or removal of the catheter. The next dose may be given 2-4 h after catheter removal.

Argatroban

Argatroban is a reversible direct thrombin inhibitor (Kaplan, 2003; Kathiresan et al., 2002). Its half-life is 35-45 min (Yeh & Jang, 2006). It is applied intravenously 0.5-2 µkg/min in patients with normal organ functions and it prolongs aPTT about 1.5 to 3 times that of the normal. There must be at least 4 h of time between the last dose of argatroban and insertion or removal of a neuraxial blockage / catheter. The next dose may be given 2 h after catheter removal.

Dabigatran

Dabigatran oral is a reversible thrombin inhibitor which is used for VTE prophylaxis (Weitz et al., 2008). It is used every other day because it has a long half-life (12-17 h). The first dose of dabigatran is applied 4 h postoperatively. There must be 4 h between its last dose and catheter removal. The next dabigatran dose can be given 2 h after catheter removal (Boehringer-Ingelheim, 2009).

Regional anesthesia in patients treated with Vit K Antagonists

Neuraxial block is definitely contraindicated in patients treated with Vit K antagonists such as acenocoumarol, phenprocoumon and warfarin. All of these drugs cause coagulation factor II, VII, IX and X deficiencies and protein C and S inhibitions (Ansell et al., 2004). A few days after discontinuation of these drugs, coagulation returns to normal; the progress can be controlled by using the international normalized ratio (INR). Vit K antagonists are discontinued 3-5 days prior to the administration of regional technique in the preoperative period and one of the other anticoagulants, particularly LMWH, is temporarily administered to the patient (Dunn & Turpie 2003). INR should be <1.4 before the regional technique. If the epidural catheter needs to be removed under a warfarin therapy, it should be removed before the anticoagulant effect begins (INR<1.4) (Llau Pitarch et al., 2005).

Regional anesthesia in patients on treatment with antiplatelet drugs

Antiplatelet agents are compounds used for preventing arterial thrombosis in various clinical processes (Samama et al., 2002; Tufano et al., 2002). They inhibit platelet functions and are classified according to their mechanisms of action:

Acetylsalicylic acid (ASA)

ASA shows its effect by irreversibly inhibiting the cyclooxygenase enzyme. Its time of action is as long as a platelet life (7-10 days) (Vandermeulen, 2010). The bleeding effect of ASA depends on its dose (Serebruany et al., 2005). It inhibits generation of thromboxane A₂ in low doses and prostacyclin in high doses. It was shown that the risk of spontaneous bleeding was quite low in patients having normal quantity of platelets who use low doses of ASA during an anti platelet treatment (McQuaid & Laine, 2006). When ASA or non-steroidal anti-inflammatory drugs (NSAIDs) are used alone, the risk of a spinal/epidural hematoma does not increase and they do not constitute a contraindication in using regional techniques. A limited number of studies in the literature demonstrate that spinal hematoma does not pose an extra risk in this group of patients CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) (Collaborative Group., 1994; Horlocker et al., 1995; Horlocker et al., 2002).

It was shown that a postoperative thromboprophylaxis was more beneficial than a preoperative one (Hull et al., 2000).

For this reason, it is recommended to administer a VTE prophylaxis involving ASA in the postoperative period following the regional technique (Llau et al., 2005).

The suggestion that the use of ASA should be discontinued 7 days before the operation in patients getting ready for an operation is outstanding among other recommendations (Kövesi & Royston, 2002). Having a break for 7 days will increase the risk of developing cardiovascular and neurologic complication (Burger et al., 2005). It is recommended that antiaggregants, ASA in particular, should be restarted between postoperative 6 and 24 h (Llau et al., 2007).

Thienopyridines

Thienopyridines which consist of ticlopidine and clopidogrel show their effect by antagonizing adenosine diphosphate (ADP) in the purine receptors of thrombocytes. These drugs reach their peak activity 3-5 days after having been received and their antiaggregant effect extends up to 7-10 days (Patrono et al., 2004). The half-life of ticlopidine is 30-50 h and that of clopidogrel is 120 h (Vandermeulen, 2010). Thienopyridines have a very large antiaggregant capacity. There is no data indicating that they are being safely used in regional techniques. However, there are reports notifying development of a spinal epidural hematoma following the neuraxial block in a clopidogrel therapy (Litz et al., 2004). Today, it is not recommended to administer a regional technique to patients who are under the influence of ticlopidine or clopidogrel. Nevertheless, a regional technique can safely be administered after suspending the clopidogrel therapy for 7 days and the ticlopidine therapy for 10 days (Llau et al., 2007).

GP IIb/IIIa receptor antagonists

GPIIb/IIIa receptor antagonists which consist of abciximab, tirofiban and eptifibatid are among the most effective drugs today for inhibition of platelet aggregation. They show their

effect by reversibly inhibiting glycoprotein IIb/IIIa receptors of platelets. They are mostly used in treating acute coronary syndrome. After being applied, eptifibatide/tirofiban is effective for 8-10 h and abciximab for 24-48. A thrombocytopenia may develop within 1 to 24 hours after they are administered (Dasgupta et al., 2000; Huang & Hong, 2004). Use of a regional technique or removal of catheter can be done 8 h after the last dose of eptifibatide/tirofiban or 24-48 h after the last dose of abciximab (Gogarten, 2006). A thrombocyte count should however be done to confirm that there is no thrombocytopenia (Llau et al., 2007). Safe time interval before and after a neuraxial block in patients receiving antithrombotic drugs were defined in table 5.

	Route of administered	before NB/CW	after NB/CW
Unfractionated heparin	sc, iv	4h	1h
Low-molecular-weight heparins			
prophylactic	sc	12h	4h
therapeutic	sc	24h	4h
Danaparoid	sc	CI	CI
Factor Xa inhibitors			
Fondaparinux	sc	36-42h	6-12h
Rivaroxaban	oral	22-26h	4-6h
Apixaban	oral	26-30h	4-6h
Direct thrombin inhibitors			
Hirudins	sc, iv	8-10h	2-4h
Argatroban	iv	4h	2h
Dabigatran	oral	4h	2h
Vit K Antagonists			
warfarin	oral	INR<1.4	Restart after CW
Antiplatelet drugs			
<i>Acetylsalicylic acid (ASA) *</i>	oral	No CI	Postoperative 6-24h
<i>Thienopyridines</i>			
Ticlopidine	oral	10 days	-
Clopidogrel	oral	7 days	-
<i>GP IIb/IIIa receptor antagonists</i>			
Abciximab	iv	24-48 h	-
Eptifibatide or tirofiban	iv	8 h	-

NB:Neuraxial block;CW:Catheter withdrawalCI:Contraindication INR:International normalized ratio

* When ASA is given as a single drug, neuraxial block could be performed freely

Table 5. Safe time interval before and after a neuraxial block in patients receiving antithrombotic drugs

2.3.2.3 Disseminated intravascular coagulation (DIC)

The magnitude of a trauma may be accompanied by a coagulation change. Specific injuries such as impairment of the central nervous system, bone fractures and amniotic fluid emboli

are often accompanied by disseminated intravascular coagulation (DIC) (Levi & Ten, 1993). The embolized material gains strength with thromboplastin and causes intravascular coagulation as the direct clotting factors are consumed (Hess & Lawson, 2006).

In patients with DIC following an acute trauma, the level of fibrinogen usually goes down first. This drop in fibrinogen is followed by consumption of other coagulation factors. The prothrombin time (PTT) and the active partial thromboplastin time (aPTT) are prolonged and the number of platelets and the level of fibrinogen drop (Gando et al., 1992; Ordog et al., 1985).

In patients with post-traumatic DIC, a distinct drop in the levels of protein C and antithrombin indicates an anticoagulant activity deficiency (Gando, 2001; Gando et al., 1988; Gando et al., 1992; Chesebroet et al., 2009).

DIC divides into two phenomena, fibrinolytic (hemorrhagic) and antifibrinolytic (thrombotic). DIC has the character of a fibrinolytic phenomenon in the early stage of the trauma, that is, after approximately 24-48 h and is accompanied by massive hemorrhages (Sawamura et al., 2009). DIC becomes a thrombotic phenomenon in the later stage of the trauma, that is, after approximately 3-5 days. It is then characterized by a development of multiorgan dysfunction (MODS) (Gando, 2001).

2.3.2.4 The coagulopathy of massive trauma

In patients with serious trauma, coagulopathy is associated with the loss, consumption and dysfunction of coagulation factors. Coagulopathy is aggravated by hemodilution, acidosis and hypothermia (Armand & Hess, 2003).

Hemodilution occurs due to a massive blood loss. A massive bleeding causes a decrease in the number of platelets, shortening of coagulation time, an increase in fibrinogen turnover and consumption of coagulation factors (Turpini & Stefanini, 1959). Moreover, the liquid and blood products and massive transfusion of hypovolemia result in a dilution which intensifies the coagulopathy (Armand & Hess, 2003).

Acidosis occurs as a result of tissue hypoperfusion and hypoxia associated with a shock. When pH becomes <7.1, the propagation stage of thrombosis comes to be blocked (Martini, 2009).

A serious hypothermia decreases coagulation enzyme activity and impairs platelet functions (Martini, 2009; Wolberg et al., 2004).

2.3.2.5 Idiopathic thrombocytopenic purpura (ITP)

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune thrombocytopenic coagulopathy, which is seen in 1 person out of 100000. It is characterized by a persistent thrombocytopenia which develops as a result of destruction of platelets by the reticuloendothelial system due to antibodies that adhere to thrombocytes (Kessler et al., 1982). Platelets have an important role in continuation of coagulation cascade in the hemostatic system and in formation of hemostatic clumps (Beilin et al., 1997). A low number of platelets impairs surgical hemostasis by increasing the risk of hemorrhage and may cause anesthetic complications such as hematoma (Chow et al., 2011). Patients with ITP should be distinguished from the other causes of thrombocytopenia including sepsis, pregnancy-

induced hypertension, disseminated intravascular coagulation, drug-induced thrombocytopenia, thrombocytopenia associated with autoimmune diseases (systemic lupus erythematosus, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and hereditary forms of thrombocytopenia) (Webert et al., 2003).

The number of platelets helps distinguish the other diseases involving coagulopathy in clinical settings.

In patients with ITP, platelet functions are normal, and the number of platelets is low and stable (Abramovitz & Beilin, 2003).

In assessing platelet functions of ITP patients, the bedside tests of bleeding time and thromboelastography as well as platelet function analysis tests (aggregometry or flow cytometry) can be used (Beilin et al., 1997).

Traditionally, regional anesthesia is believed to be contraindicating in thrombocytopenia. What lies behind this belief is that the absolute cut-off point of platelets was accepted to be $100.000/\text{mm}^3$ because the bleeding time was prolonged when the number of platelets went below $100.000/\text{mm}^3$. Following the belief that a neuraxial anesthesia is not safe below the absolute platelet number, many clinicians avoid carrying out any epidural procedures (Harker & Slichter, 1972; Bromage, 1993). Many textbooks and articles of our time suggest that epidural applications can be done safely at $<100.000/\text{mm}^3$ (Beilin et al., 1997; Rasmus et al., 1989; Rolbin et al., 1988; British Committee for Standards in Haematology General Haematology Task Force, 2003). Most of the anesthetists believe that epidural anesthesia is not contraindicating in clinical practice within the interval of $80\text{-}100 \times 10^3 \text{mm}^3$ (Stamer et al., 2007; Beilin et al., 1997; Van Veen et al., 2010).

Safe administration of epidural techniques to thrombocytopenic patients depends not only on the absolute platelet number but also on the reason underlying the thrombocytopenia, the rate at which the number of platelets decrease and the presence of a coagulopathy (Douglas & Ballem, 2008; Kam et al., 2004). Presence of coagulopathy contraindicates the use of regional anesthesia. However, a neuraxial block can be used in thrombocytopenic patients when their platelet quantity is adequate and stable, platelet functions are normal and there is no clinical evidence of a coagulopathy (Van Veen et al., 2010). The anesthetist should decide on a regional anesthesia on such patients after assessing the risks and benefits involved.

Since there is the risk of developing epidural hematoma in thrombocytopenic patients when either inserting or removing an epidural catheter, it is necessary to check the number of platelets before the procedure. The epidural catheter should be removed at the earliest opportunity when clinical data verifies that there is no coagulopathy involved (Douglas, 2001).

2.4 Patient refusal

A face-to-face interview should be held with the patient and the benefit-loss balance of the intended method should be explained. The procedure should not be attempted before obtaining the patient's consent.

In regional anesthesia patient cooperation is required to a certain extent. Achieving this may be difficult or even impossible in patients with dementia, psychosis or emotional dysregulation (Morgan et al., 2008).

2.5 Hemodynamic instability

The observable cardiovascular effect of an epidural anesthesia is complex and variable, and it is associated with a number of factors. The magnitude of sympathetic denervation, balance of sympathetic and parasympathetic activities, pharmacological effect of systemically absorbed local anesthetics, adrenalin content of anesthetic solutions, blood distribution associated with cardiac filling and cardiovascular functions of patients all play a role in the circulatory effect of an epidural anesthesia (Veering & Cousins, 2000).

The cardiovascular response of an epidural anesthesia depends not only on the somatic, sensory and blocked motor fibres but also on the decrease in preganglionic sympathetic tone. Local anesthetics administered to the epidural area pass into the systemic circulation by being absorbed through a local perfusion and cause a blockage of the sympathetic system (Hickey et al., 1986; Shimoji et al., 1987).

The individual cardiovascular response to the sympathetic blockage differs according to the pre-blockage degree of sympathetic tones (Veering & Cousins, 2000). Clinical use of epidural anesthesia is limited due to its risk of aggravating a preexisting systemic hypotension.

2.6 Increased intracranial pressure

Intracranial pressure (ICP) changes are characterized by the change of complains in the intracranial compartment. There is a close relationship between intracranial volume changes and ICP. When complains decrease, intracranial content increases. When ICP increases, blood flow to the brain decreases and the cerebral perfusion pressure declines (Adams & Rapper, 1997).

The effect of lumbar epidural anethesia on intracranial pressure (ICP) has been studied both in animals (Bengis & Guyton, 1977) and humans (Usubiaga et al., 1967). It is known that epidural injections, at least transiently, increase ICP. With the increase in ICP, the elastance and resistance of the epidural area also increase (Grocott & Mutch, 1996). Intracranial hypertension has long been considered a contraindication to epidural anesthesia.

2.7 Local or systemic infection

The latest structural and functional studies showed that there is a firm interaction between inflammation, coagulation and fibrinolytic system (Esmon, 2003). Inflammation initiates clotting, impairs fibrinolytic system and decreases the activity of natural anticoagulant mechanisms. When inflammation starts as a local infection, coagulation activation begins as a host response to prevent propagation of microorganisms in the systemic circulation. Only in patients with very severe infection, the systemic coagulation system is activated when inflammatory cytokines disseminate in the circulation (Chrousos, 1995; Harris BH & Gelfand, 1995).

It is still controversial to use neuraxial anesthesia in patients with sepsis and systemic inflammatory response syndrome (SIRS) due to the concern that it might worsen hemodynamic instability and trigger potential problems. Active protein C therapy can be used in treating patients with serious sepsis. Insertion of an epidural catheter is contraindicated in patients with serious sepsis who are undergoing an active protein C

therapy (Horlocker et al., 2003). Use of an epidural catheter in these patients will not only expose them to a higher risk but will also prevent the use of APC which would improve the patient's treatment (Gibson & Terblanche, 2011).

2.8 Pre-existing neurological diseases

It has been controversial in the past and also in our time to use neuraxial blocks in patients with a neuromuscular disease (Schmitt et al., 2004; Al-Nasser, 2002). Neuraxial blocks are hesitantly used because there is not a unique guideline for these diseases, the published data contradict each other and local anesthetics involve a potential risk of neurotoxicity (Martucci et al., 2011; Dolmass et al., 2003).

The symptoms may worsen after the block in patients who previously had a neurologic deficit or a demyelinating disease. It is impossible to differentiate whether such condition resulted from the complications developed after the block or the exacerbation of the existing disease. Some clinicians oppose, for this reason, to use neuraxial blocks in such patients (Morgan et al., 2008).

The basic problem is the lack of controlled studies to assess the potential risk that may increase in various neurologic diseases after a neuraxial application. There is also a theoretic risk of some complications (local anesthetic toxicity, nerve damage, hemorrhage and infection) which develop secondary to a regional anesthesia in this specific group of patients. However, there are a limited number of case reports showing that regional anesthesia is not accompanied by the underlying aggravation (Pogson et al., 2000; Stoelting & Dierdorf, 2002).

A neuraxial blockage may be preferred after a detailed discussion of the individual disease is made without overlooking the risk of worsening the neurologic function.

3. Conclusion

Anesthesia societies, in patient with coagulation defect and anticoagulant agents uses, developed guidelines to help anesthesiologists to predict the optimal time for neuraxial techniques. These guidelines based on clinical experiences and case series. The most basic common features of these guidelines are the nontraumatic implementation of the neuraxial analgesia by experienced anesthesiologists. Of course the management of individual risks and benefits must perform carefully.

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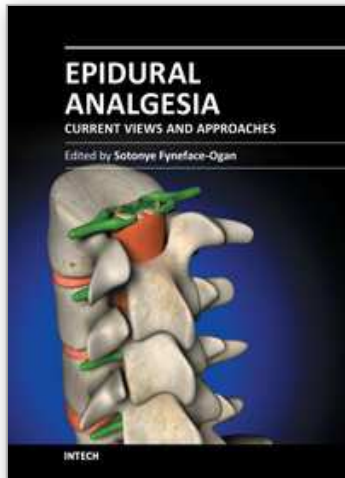
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Epidural analgesia is a form of pain relief administered through the space surrounding the dural sheath either by direct injection or via catheter. The agent, when administered, can cause both a loss of sensation (anesthesia) and a loss of pain (analgesia), by reversibly interrupting the transmission of signals through nerves in or near the spinal cord. This form of pain relief has been found useful in many clinical situations. This book intends to provide an in-depth review of the current knowledge on epidural analgesia. The use of this form of analgesia is explored by contributors from different perspectives, including labor and delivery, postoperative analgesia in both pediatric and geriatric patients, and its role during anesthesia and surgery. In order to provide a balanced medical view this book was edited by an obstetric anesthesiologist.

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