

# Hemostatic and hemorrhagic problems in neurosurgical patients

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## Abstract

**Background** Abnormalities of the hemostasis can lead to hemorrhage, and on the other hand to thrombosis. Intracranial neoplasms, complex surgical procedures, and head injury have a specific impact on coagulation and fibrinolysis. Moreover, the number of neurosurgical patients on medication (which interferes with platelet function and/or the coagulation systems) has increased over the past years. **Method** The objective of this review is to recall common hemostatic disorders in neurosurgical patients on the basis of the “new concept of hemostasis”. Therefore the pertinent literature was searched to provide a structured and up to date manuscript about hemostasis in Neurosurgery. **Findings** According to recent scientific publications abnormalities of the coagulation system are discussed. Pathophysiological background and the rational for specific (cost)-effective perioperative hemostatic therapy is provided. **Conclusions** Perturbations of hemostasis can be multifactorial and maybe encountered in the daily practice of neurosurgery. Early diagnosis and specific treatment is the prerequisite for successful treatment and good patients outcome.

**Keywords** Hemorrhagic disorders · Postoperative hemorrhage · Coagulopathy · Fibrinolysis · DIC · Thrombosis · Head injury

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## Introduction

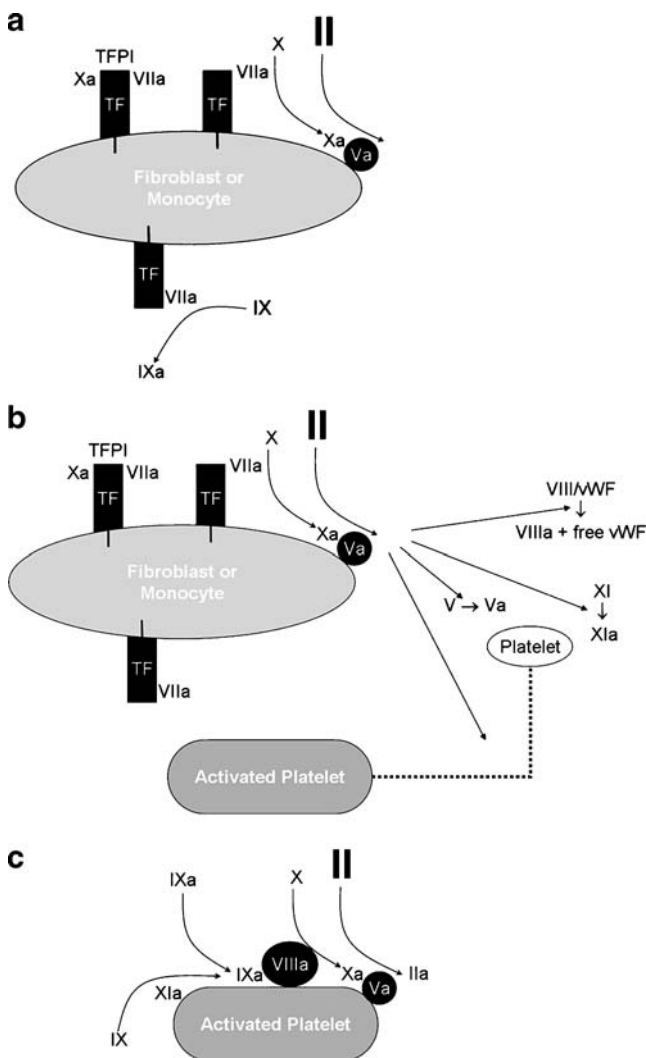
Abnormalities of the hemostatic system can lead to bleeding complications and/or thromboembolic events and can cause severe impairment, or even death, of neurosurgical patients. Aetiology of hemostatic disturbances is multifactorial and can be related to brain neoplasms [163, 257, 258], surgical complexity [108], brain injury [295], as well as the use of anticoagulants and antiplatelet drugs before surgery [228]. Although the classic coagulation model with intrinsic and extrinsic pathways is helpful in understanding perturbations in the routine laboratory tests, it failed to adequately explain in vivo coagulation processes. More recently, a new model has been developed that takes into account the cellular surfaces upon which hemostasis occurs [212]. Therefore, the purpose of this review is to (a) give an overview of hemostasis in general based on the “new” coagulation model, (b) to discuss unique features of the brain parenchyma and the interference with the coagulation system, (c) to suggest an approach to the neurosurgical patient to detect hemostatic problems, (d) to recall various overt and hidden perioperative hemostatic aberrations in neurosurgical patients, (e) to guide the clinician in treating various hemostatic disorders and to recommend treatment strategies based on published studies or if available guidelines, (f) to explain the rational of specific measures to reverse anticoagulation therapy, (g) to point out to aberrations of the coagulation system following head injury and (h) to review the pertinent literature for safety and efficacy of pharmacological prophylaxis of VTE.

(a) Overview of hemostasis based on the “new” coagulation system

The complex process of hemostasis is determined by the interaction of endothelial and subendothelial cells, platelets, leukocytes, coagulation factors, and coagulation inhibitors.

The three major steps of the coagulation process are the initiation, amplification, and propagation phases (Fig. 1). Vascular injury leads to intravascular exposure of tissue factor (TF). TF binds circulating factor VII to form TF-FVIIa complexes. This initial step results in activation of factor X and IX (Josso loop) on TF-bearing cells (initiation phase). It has to be considered that intravascular TF exposure can also be a result of invasive tumor growth or expression of TF on the surface of stimulated leukocytes in connection with acute or chronic inflammatory reactions.

Platelets are localized to the site of injury by adhesion to the subendothelial matrix mediated by interaction between



**Fig. 1** Three major steps in the cell-based model of coagulation activation. **a** *Initiation* of coagulation occurs on TF-bearing cells as activated FX binds its cofactor FVa, to activate a small amount of thrombin. **b** *Amplification* of the procoagulant signal by thrombin (FIIa) by activating cofactors, FXI and platelets. **c** The thrombin burst required for effective hemostasis is generated on the platelet surface during the *propagation* phase. Modified according to Hoffmann and Monroe “Coagulation 2006: A Modern View of Hemostasis” [129]

collagen, von Willebrand factor (vWF) and GPIb receptors on the surface of platelets. During the initiation phase, activated factor X (FXa) generates a small amount of thrombin, which is not high enough to produce a hemostatic sufficient fibrin clot, but leads to an activation of platelets and further enzymatic coagulation factors (factor XI, VIII and V) (amplification phase). Activated platelets release thromboxane and their granule contents (ADP, serotonin, vWF, PF4, calcium and coagulation factors), which results in activation and aggregation of further platelets. Furthermore, they alter their surface by expressing negative charged phospholipids (flip-flop-mechanism) to facilitate calcium-mediated coagulation factor binding. The further activation of coagulation factors and the subsequent thrombin generation takes place on the surface of activated platelets (propagation phase). Thrombin itself potentiates its generation by activation of factor XI, VIII and V, which results in a thrombin burst, sufficient to cleave fibrinogen and activate factor XIII (FXIII) as well as thrombin activatable fibrinolysis inhibitor (TAFI). Soluble fibrin monomers polymerize and are cross-linked by FXIII. Thereby fibrin and platelets form a stable clot that is anchored at the extracellular matrix due to the cross-linking of fibrin with adhesive proteins.

(b) Features of brain parenchyma and the interference with the coagulation system

There is a growing body of evidence suggesting that normal brain parenchyma and different brain tumors have a (local) influence on coagulation and fibrinolysis. Tissue factor (TF), the main initiator of the coagulation process, is abundantly expressed in normal brain tissue [7, 28] and astrocytic tumors, depending on their grade of malignancy [115]. On the other hand, patients with severe head injury have significantly higher TF concentrations compared to patients with moderate head injury [231]. Reports on the expression of tissue plasminogen activator (tPA)—an initiator of fibrinolysis—are contradictory for benign and malignant brain tumors [6, 99, 246]. Goh et al. [99] described about 50% of tPA expression in meningiomas compared to glioblastomas, while Sawaya et al. [246] showed that benign tumors contain three times more tPA compared to malignant tumors. However, in the latter study, no correlation of tissue tPA to plasma tPA was found. The total fibrinolytic activity was decreased by about 15% in patients with malignant tumors, with a decrease in tPA and an increase in protein C [263]. Tissue extracts of different brain tumors lead to a variable inhibition of plasmin [262]. Patients with glioblastomas and intracerebral metastasis had significantly higher plasma tissue factor pathway inhibitor (TFPI) concentrations [95], which might reflect a compensatory mechanism to a general procoagulatory activation

[100] in patients with these tumors. Taken together, these findings indicate that brain tumors [100, 277] and the injured brain itself [151, 223] have a direct influence on coagulation and fibrinolysis. This could be (at least partially) an explanation for the common occurrence of intratumoral thrombosed vessels in glioblastomas and the high incidence of systemic thromboembolic complications such as deep vein thrombosis (DVT) [2, 139, 220, 254] or pulmonary emboli (PE) [116] due to an associated procoagulatoric state in neurosurgical patients. This is of particular interest because patients with high-grade glioma and VTE do not differ with regard to their genetic predisposition (e.g., thrombophilic conditions such as prothrombin or Factor V Leiden mutation) compared to patients without VTE [267].

(c) Suggested approach to the neurosurgical patient to detect pre-existing hemostatic problems

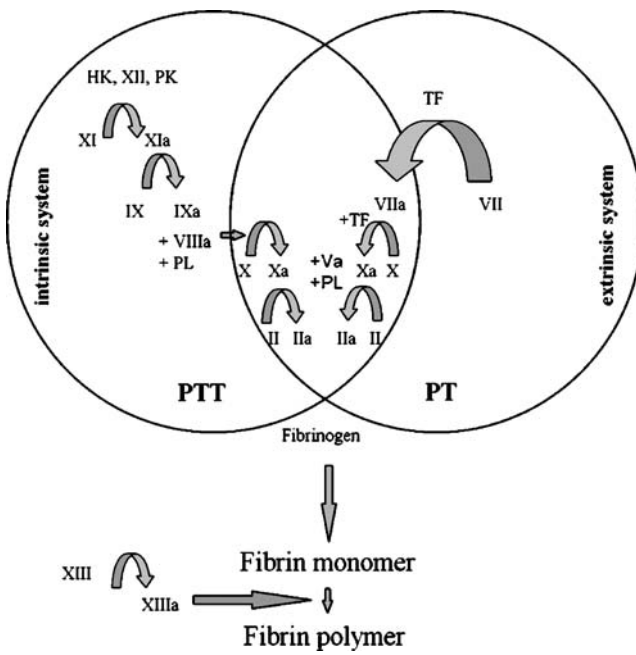
As in other surgical disciplines in neurosurgery, the increased number of elderly patients is accompanied by an increased patient's co-morbidity. Moreover, these patients commonly take medications that interfere with the coagulation system or platelet function. A small number of specific questions asked at admission can be helpful in assessing patients' bleeding history and the usage of a medication that interferes with the coagulation system or platelet function. The meaning of a standardized questionnaire to evaluate a bleeding tendency was demonstrated in a prospective study conducted by Koscielny including more than 5,600 patients [169]. From those patients with a positive bleeding history in the questionnaire, 40% had impairment of primary hemostasis (platelet-vessel wall-interaction) mostly detected with the Platelet Function Analyzer 100 (PFA-100). Table 1 gives an example of some of these questions, which can be easily integrated in the evaluation of the patient's history.

Normal laboratory data of standard coagulation tests neither exclude a perioperative bleeding complication nor guaranty sufficient hemostasis [67, 214]. However, up to now, they are part of the routine preoperative work up in neurosurgical patients. Figure 2 shows the classical plas-matic coagulation model, which is helpful for routine screening of coagulation perturbations. The routine coagulation testing usually includes partial thromboplastin time (PTT), prothrombin time (PT), fibrinogen, and platelet count. Figure 3 suggests an algorithm to determine a bleeding diathesis [adapted from [185, 192]]. A prolonged PT (respectively a lowered Quick value or an elevated INR) may indicate a coagulation factor deficiency (FII, FV, FVII, FX, fibrinogen), impaired hepatic synthesis, vitamin K deficiency, anticoagulant therapy (vitamin K antagonist, thrombin inhibitors), or dilutional respectively consumption

**Table 1** Detailed questions according to Luxemburg et al. [192] included in the preoperative patients assessment to evaluate increased bleeding tendency. The bleeding history is assessed as positive if the answer to one of the questions is "yes" (in question 11, only for drugs that inhibit coagulation)

1.	Have you noticed more nosebleeds in yourself, even without an obvious cause?
2.	Do you often develop hematomas, even without bumping into anything, or small, dot-shaped bleeds? If you responded "yes" to this question, please report whether these symptoms also occur on the trunk or other unusual locations.
3.	Have you noticed that your gums are bleeding without any obvious cause?
4.	Do you develop bleeds or hematomas more than once or twice a week?
5.	Do you feel that after cuts or abrasions (while shaving, for example), you bleed for longer than usual?
6.	Have you ever had prolonged and severe bleeds after or during operations (for example, tonsillectomy, appendectomy, giving birth)?
7.	Have you ever had prolonged and severe bleeds during or after tooth extraction?
8.	Have you ever received blood or blood products during an operation? Please report the type of operation.
9.	Has there ever been a tendency to bleed in your family?
10.	Are you taking painkillers of antirheumatic drugs? If so, please enter the name of the drug(s).
11.	Are you taking other medication? If so, please enter the name of the drug(s).
The following question applies to women/girls only:	
12.	Do you feel that you have prolonged menstruation (>7 days) and/or a high frequency of tampon change?

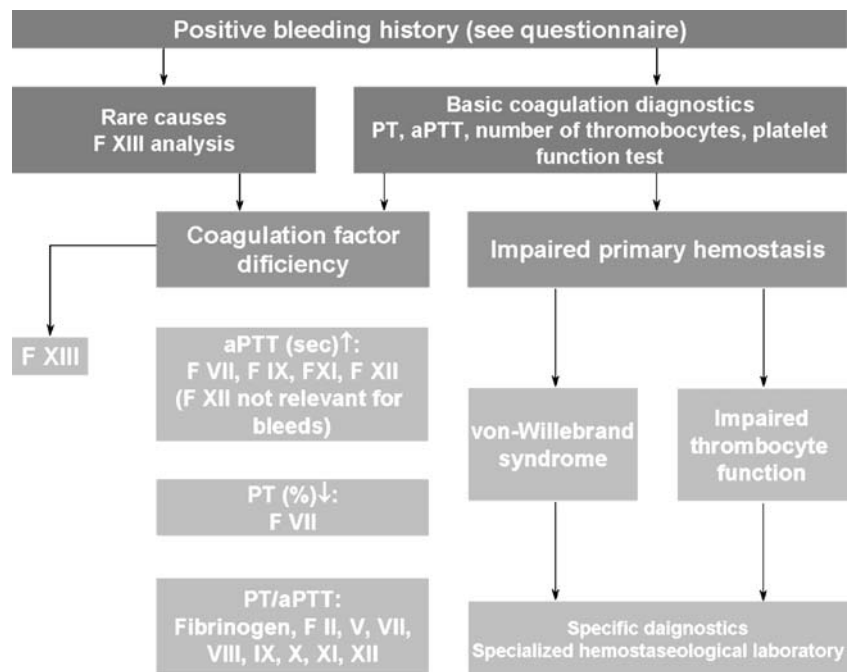
coagulopathy. A prolonged PTT can be due to coagulation factor deficiency (FII, FV, FVIII [hemophilia A, von-Willebrand syndrome], FIX [hemophilia B], FX, FXI, FXII, fibrinogen, prekallikrein, high molecular weight kininogen [HK]), treatment with unfractionated heparin or direct thrombin inhibitors (hirudin, argatroban), impaired hepatic synthesis, vitamin K deficiency, dilutional respectively consumption coagulopathy or antiphospholipid antibodies (Lupus anticoagulants). Unfortunately standard



**Fig. 2** The classic model of coagulation activation as a simplified flowchart showing the order of factor activation (indicated by the arrows). These two pathways are conceived as each leading to formation of the factor Xa/Va complex, which generates thrombin. The pathways are assessed clinically using the prothrombin time (PT) for the extrinsic pathway and the partial thromboplastin time (PTT) for the intrinsic pathway. Modified according to [129]. *HK*High molecular weight kinogen; *PK*Prekallikrein; *PL*Phospholipids

coagulation tests leave a diagnostic gap (PTT and PT can be normal!), especially for von Willebrand syndrome as the most common hemostatic disorder, coagulation factor XIII (FXIII) deficiency or hereditary, respectively, acquired

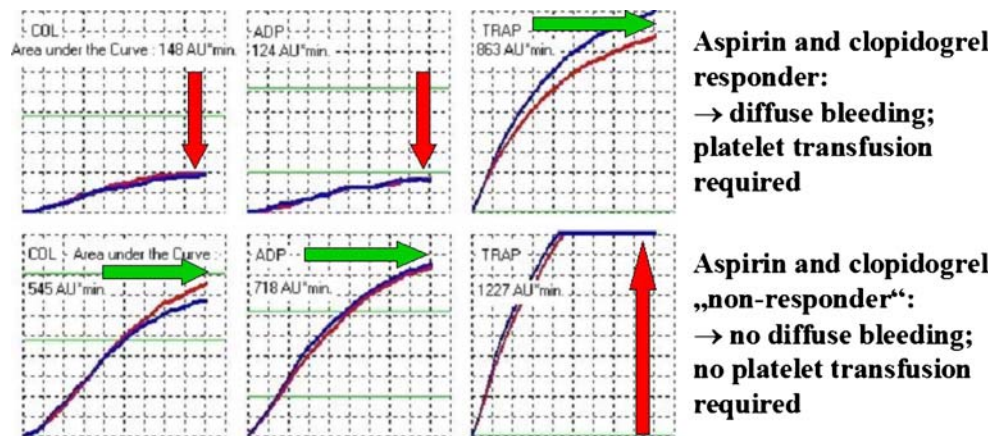
**Fig. 3** Algorithm to determine a bleeding diathesis, adapted from [185, 192]



platelet dysfunction. Particularly, platelet dysfunction mediated by antiplatelet drugs (like aspirin or clopidogrel) cannot be detected by platelet count, but rather by a standardized questionnaire. In case of a positive history, further tests with respect to disorders of primary hemostasis should be done [233]. In this context, it has to be considered that PFA-100 is appropriate for detecting von Willebrand syndrome and aspirin effects, but fails to verify clopidogrel-mediated platelet dysfunction. This limitation is of great importance in context to the increasing number of patients with dual antiplatelet therapy after coronary stent implantation. Contrary to PFA-100, whole-blood impedance aggregometry (Multiplate) facilitates, besides detection of aspirin effects, as well the monitoring of clopidogrel and GPIIb/IIIa receptor blocker effects [329]. Therefore, point-of-care (POC) platelet function analysis, in favour carried out by whole-blood impedance aggregometry (Multiplate), should be performed in case of emergency neurosurgery to verify or exclude antiplatelet drug effects (Fig. 4). This is particularly important in cases of intracranial bleeding and unknown patients' history and medication.

There are no generally accepted absolute limits for routine coagulation tests defined by scientific evidence, which definitively permit or decline a neurosurgical procedure, neither from a medical nor from a legal aspect. However, elective procedures should be scheduled only with normal test results. If abnormalities are detected, an intensive laboratory work up is recommended, and patients should be referred for consultation by a hemostaseologist even if this results in the postponing of the operation.

**Fig. 4** Multiplate analysis in two patients with dual antiplatelet therapy (aspirin plus clopidogrel) until 1 day before cardiac surgery: responder (*upside*) and “non-responder” (*down*)



(d) Perioperative hemostatic disorders in neurosurgical patients

*Intraoperative hemostatic perturbations*

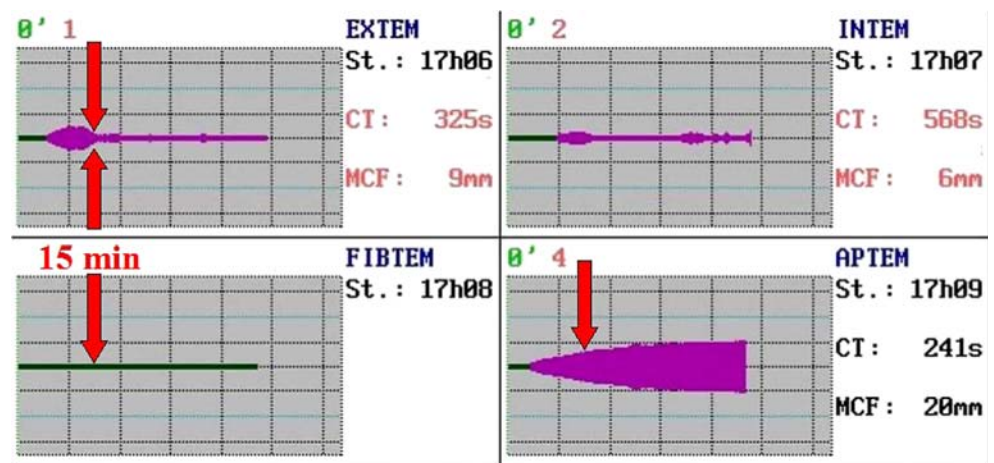
In contrast to patients scheduled for elective neurosurgical procedures, the patient’s history cannot be obtained in emergencies due to an impaired consciousness level or intubation and sedation. In addition, in cases with urgent surgical intervention, a detailed analysis of the hemostatic capacity or an exploration of the fibrinolytic system with conventional methods in the central laboratory is hardly possible. Thus, in non-trauma cases, hemostatic disturbances may not become obvious until surgery is started. Therefore, not only in coagulopathic trauma patients but also in patients with hidden coagulation impairment, the intraoperative therapeutic management can be challenging for both the anaesthesiologist and the neurosurgeon.

Furthermore, results of coagulation tests from the central laboratory are usually available 30–60 min after blood sampling. Therefore, intraoperatively, it is not possible to administer a contemporary and goal-directed therapy based on these laboratory results. Contrary to standard laboratory test point-of-care (POC) tests, like thrombelastometry (ROTEM) and whole-blood impedance aggregometry (Multiplate), enables detection of hyperfibrinolysis, hypofibrinogenaemia, fibrin polymerisation disorders, coagulation factor deficiencies, heparin effects, thrombocytopenia and platelet dysfunction within 10 to 30 min (Figs. 4, 5, 6, 7, 8) [106, 178, 329]. This facilitates a goal-directed therapy with hemostatic drugs, coagulation factor concentrates, and blood components (Fig. 9). Furthermore, POC coagulation monitoring with thrombelastometry has been shown to reduce the transfusion rate as well as costs in liver transplantation, cardiovascular surgery, and trauma surgery [5, 275, 286]. The use of thrombelastometry is mentioned in several recommendations for perioperative coagulation management [64].

Above all, as mentioned earlier, hemostatic impairment may also occur during elective surgery, which can be due to coagulopathy, platelet dysfunction, hyperfibrinolysis, and disseminated intravascular coagulation [15, 100, 240, 277]. Results of a prospective study of patients with unexplained intraoperative coagulopathy showed significantly less FXIII per unit thrombin available at any point in time (i.e., already preoperatively) than patients without such coagulopathy. The consequence is a significant loss of clot firmness associated with an increase in intraoperative blood loss [168, 332]. Some authors consider the intraoperative hemostatic disturbance to be primarily due to hyperfibrinolysis or secondarily to DIC [226, 228, 277], whereas hyperfibrinolysis can easily be detected by thrombelastometry, factor XIII deficiency may be verified partly by thrombelastometry (Figs. 5 and 8) [330]. Impairment of the hemostatic capacity can also exist preoperatively without clinical relevance, but can be amplified during surgery. A new intraoperative coagulopathy can be due to blood loss, dilution and consumption of coagulation factors. Thereby, fibrinogen normally is the first coagulation factor, which achieves a critical value during massive blood loss [126, 209, 276]. The balance between hemostasis and fibrinolysis can also be disturbed by brain tumors [100, 277, 310], after head injury [151, 223] or as a consequence of the operation itself [85]. Data of a retrospective study revealed a significantly higher incidence of postoperative hematomas in patients with higher intraoperative blood loss [335], and that a coagulopathy can be the consequence of excessive bleeding associated with massive transfusion [82, 119].

Hydroxyethyl starch (HES) is commonly used for intravascular volume replacement to achieve hemodynamic stabilization and for resuscitation in trauma patients [253]. In neurosurgical patients, HES is used to expand intravascular volume in patients operated in the semi-sitting position or to induce hypertensive hypervolemic hemodilution therapy (3 H therapy) to treat cerebral vasospasm in patients following SAH [242]. However, there is an

**Fig. 5** ROTEM analysis in a multiple trauma patient with brain and thoracic injury: detection of fulminant hyperfibrinolysis and defibrinogenation within 15 min



ongoing debate about a clinically relevant impairment of hemostasis associated with the administration of HES although the hemostatic impairment was shown in vitro [29] and recently in vivo [211]. The effect on hemostasis seems to be dependent on the molecular weight of HES solutions [171]. In other surgical disciplines it was shown that colloid administration reduces final clot strength more than does Ringer's solution alone. This was due to impaired fibrinogen polymerization, resulting in a decreased fibrinogen part of the clot firmness and reduced clot elasticity [138, 211]. The prolonged administration of HES in patients with cerebrovascular disease was associated with decreased fibrin [315], a drop of platelets [314, 317], and the occurrence of von Willebrand syndrome [316], or a decrease of the von Willebrand factor and coagulation factor VIII (FVIII) [312, 313]. The decrease of the von Willebrand factor and FVIII was seen in healthy people [53, 143, 148] and during surgery [43, 45, 145].

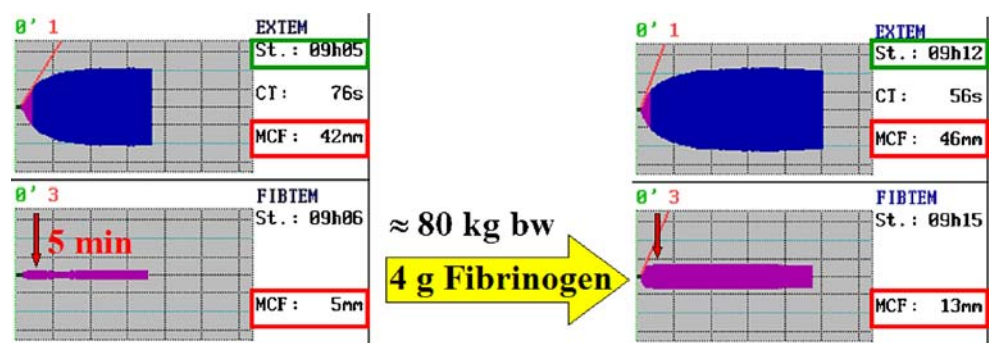
Hypothermia applied to patients with cerebrovascular surgery (aneurysm clipping, bypass surgery) or spontaneous decrease of body temperature after severe trauma and resuscitation may also be a cause of an unpredicted coagulopathy [54, 114]. This is particularly true in combination with severe acidosis [59, 184, 202, 285].

### Postoperative hemostatic perturbations

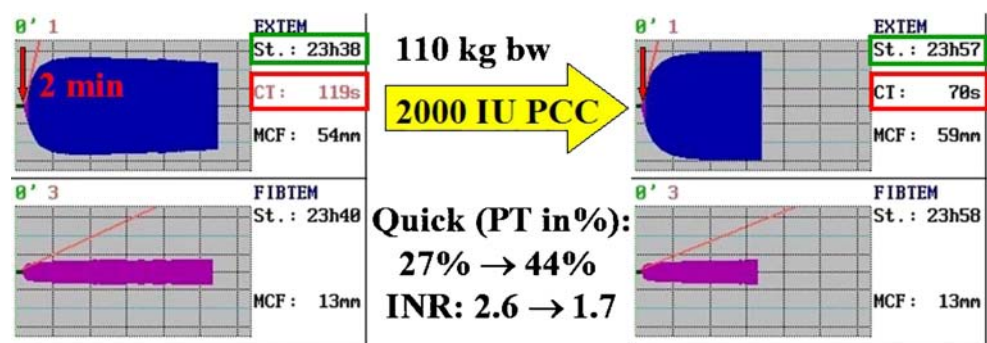
For optimal postoperative care, the neurosurgeon and anaesthesiologist should communicate with the intensivist at the ICU about the intraoperative course, estimated blood loss, the surgeon's impression on hemostasis and abnormal clinical and laboratory findings as well as intraoperative replacement therapy. To detect a postoperative coagulopathy, standard coagulation tests should be performed in addition to the assessment of the patient's neurological status. Patients who only obtain an inadequate level of vigilance after surgery or do not wake up within an appropriate time after cessation of sedation should have a CT scan to rule out any complications. Indications for surgical evacuation of the hematoma are a space-occupying effect and/or a neurological deterioration of the patient.

Postoperative hematomas can occur immediately after surgery or delayed, but were most common within 6 h after surgery [307]. Especially in cases where patients having lesions within the posterior fossa are operated on a postoperative hemorrhage can cause a dramatic deterioration in the patient. Intracranial hematoma can be localized epidural, subdural, intraparenchymal or intraventricular [147]. The risk of postoperative hematoma is highest after

**Fig. 6** ROTEM analysis in a patient with acute bleeding: detection of fibrinogen deficiency within 5 min and therapy with 4 g fibrinogen concentrate (50 mg/kg bw). Control of success is done by a second ROTEM analysis 7 min later



**Fig. 7** ROTEM analysis in a patient with open leg fracture under oral anticoagulation: detection of coagulation factor deficiency within 2 min and therapy with 2,000 IU PCC (20 IU/kg bw). Control of success is done by a second ROTEM analysis 19 min later



surgery for meningiomas (6–8%) [92, 94, 96, 147, 228] and a common association with coagulopathy and thrombocytopenia [39] or platelet dysfunction was seen [92].

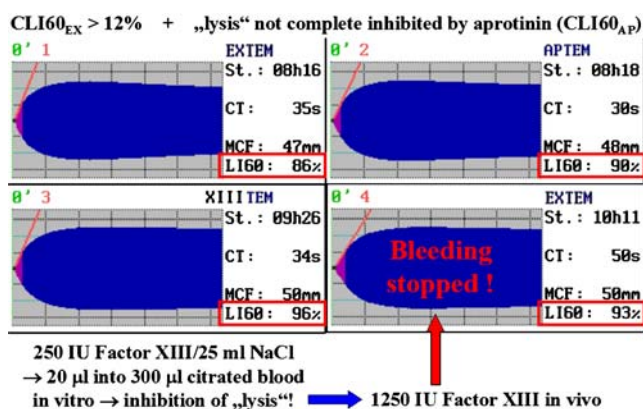
The reported rate of postoperative hematomas varies between 0.7 and 8% [86, 92, 94, 96, 147, 228, 307], depending on the type of surgery (cranial or spinal) and treated pathology. Data from a large retrospective analysis of 6.668 patients showed that 55% of patients with postoperative bleeding complications either died or had an unfavorable outcome [228], and 67% of the patients who suffered from postoperative bleeding had risk factors, which could have been avoided or corrected. Among these, the use of antiplatelet drugs was by far the most common risk factor for postoperative bleeding [228]. A total of 47% of patients who suffered from postoperative hematoma were treated with antiplatelet drugs and another 16% of patients were on oral anticoagulation [228]. These drug effects can be screened contemporary by POC coagulation monitoring with whole-blood impedance aggregometry (Multiplate), respectively, with thrombelastometry (ROTEM) or POC PT measurement (Hemochron Jr. Signature Whole Blood Microcoagulation System). Addi-

tional risk factors associated with postoperative bleeding were thrombocytopenia (14%), coagulation disorders (7%), malignancy (6%), or alcohol abuse (4%) [228]. The occurrence of a preoperative coagulopathy was also a significant risk factor for postoperative hematomas in patients following spinal surgery [170].

(e) Treatment of hemostatic disorders and transfusion strategies

Meticulous surgical hemostasis is the prerequisite to avoid perioperative bleeding complications. In contrast to bleeding from a vascularized tumor or a vessel stump, diffuse bleeding can be an index of a coagulopathy. Identification of the underlining cause and the adequate management can be difficult [15, 90, 226]. Point-of-care diagnostic, based on thrombelastometry (ROTEM) and whole-blood impedance aggregometry (Multiplate), can be helpful in identifying the underlying hemostaseologic disorders and enables a contemporary and goal-directed therapy [106, 178]. Perioperative coagulation management has been shown to be most effective and cost-saving by using algorithms, which closely connect point-of-care diagnostic with rapid available, efficient, and calculable therapeutics [5, 275, 286].

Until now, in neurosurgery no evidence-based recommendations about intraoperative replacement therapy are available for blood products. In contrast to other surgical disciplines, in neurosurgery mechanical measures to stop intraoperative bleeding are limited and only a mild compression can be applied if difficulties are encountered in bipolar coagulation. If intraoperative laboratory tests show a decreased hemostatic capacity with prolonged PTT, prolonged PT, decreased fibrinogen or platelet count, specific replacement therapy should be performed after consultation between the anaesthesiologist and neurosurgeon. Especially in cases with difficulties obtaining sufficient hemostasis and constant oozing the indication for replacement therapy should be liberal. Transfusion of packed red cell units may be supplemented by coagulation factor concentrates—like fibrinogen, PCC and factor XIII - FFP and platelet transfusion depending on the laboratory



**Fig. 8** ROTEM analysis in a patient with diffuse bleeding: clot instability (in EXTEM) is not inhibited by addition of aprotinin (APTEM), but by addition of factor XIII (XIII ITEM) → factor XIII deficiency. Diffuse bleeding stopped after administration of 1,250 IU factor XIII concentrate

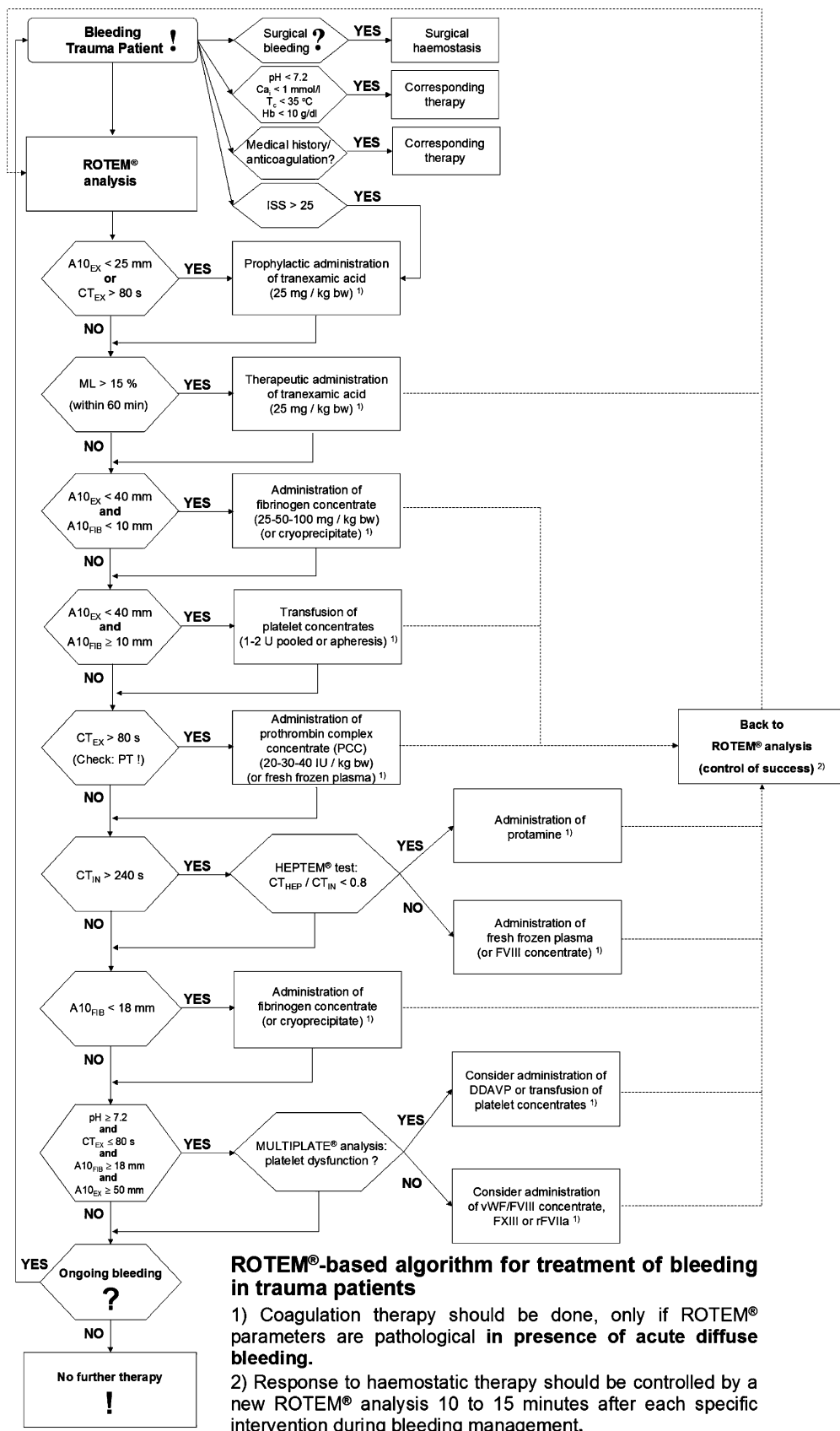


Fig. 9 ROTEM-based algorithm for treatment of bleeding in trauma and neurosurgical patients

findings. Indication and rationale for specific replacement therapy is provided in detail below.

### *Platelets*

In adults, normal platelet counts range from 150–400 x 10<sup>9</sup>/l. Spontaneous bleeding is not likely unless the platelet count is less than 5 x 10<sup>9</sup>/l. Although no randomized controlled trials assessed the trigger for prophylactic platelet transfusion, there was a general agreement that a platelet threshold of 10 x 10<sup>9</sup>/l is as safe as higher levels for conservative management of most patients without additional risk factors [46]. These risk factors, which include sepsis, concurrent use of drugs (e.g., antibiotics) and other abnormalities of hemostasis, are indications for a higher threshold. Higher threshold numbers are needed to cover invasive procedures, e.g., line insertions, biopsies or surgical procedures, but there is no consensus on appropriate thresholds.

Patients with bleeding and a platelet count of less than 20 x 10<sup>9</sup>/l and patients at risk of bleeding (petechiae, continuous bleeding from a wound, increasing retinal hemorrhage) and a platelet count of less than 30 x 10<sup>9</sup>/l should receive platelet transfusion [112].

Perioperative bleeding may occur in patients with less than 75 x 10<sup>9</sup>/l platelets or with a normal platelet count but functional impairment [144]. In cardiac surgery platelet function monitored by whole-blood impedance aggregometry (Multiplate), correlates closely with transfusion requirements, whereas platelet count did not [311]. However, threshold platelet counts for transfusions in the perioperative context have not been clearly defined and should be determined by the existence of hemorrhagic risk factors. In case of invasive procedures, it is common practice to transfuse platelets if the count is less than 50 x 10<sup>9</sup>/l, but it is clear that other clinical criteria have to be considered [261]. On the other hand, monitoring of platelet function by ROTEM/Multiplate assumed, low platelet count can be tolerated, e.g., in liver transplantation in case of sufficient clot stability and platelet function [106]. Furthermore, there are increasing data showing that a low platelet count in part can be compensated by elevated fibrinogen levels, since both contribute to mechanical clot stability [325]. Thereby, transfusion rate of platelets could be halved related to liver transplantation at the University Hospital of Essen, Germany, over the last 8 years (unpublished data). This is important because platelet transfusion is closely connected to severe risk of adverse events, like sepsis and thromboembolic incidents [107, 158, 197, 287].

However, in patients scheduled for elective neurosurgical procedures, platelet count should be at least 100 x 10<sup>9</sup>/l, even in patients with normal platelet reactivity [247, 261]. The risk of postoperative hematoma has been shown to be

three-fold increased in thrombocytopenic patients (<150 x 10<sup>9</sup>/l) [96] and thrombocytopenia is a risk factor for the development of a postoperative hematoma [39]. Patients with a platelet count of less than 100 x 10<sup>9</sup>/l, who do not adequately respond to platelet transfusion, are at high risk for severe bleeding complications and adverse outcomes [39]. Moreover, the absolute perioperative decrease of platelets is important. It has been shown that a postoperative hematoma occurred significantly more frequently in patients having an acute drop of their platelet count from normal preoperative numbers to a level between 100 and 124 x 10<sup>9</sup>/l, which means that thrombocytopenic patients with postoperative hematomas had a significantly greater reduction in platelet count than thrombocytopenic patients with no postoperative hematomas [39]. However, considering the risk of bleeding associated with neurological impairment, a more aggressive transfusion management might be more appropriated to achieve a platelet count of 100 x 10<sup>9</sup>/l.

### *Fibrinogen*

The level of fibrinogen required to maintain optimal hemostasis in the perioperative period has not yet been defined. Conservative algorithms suggest replacement of fibrinogen if fibrinogen concentration is below 1.0–1.5 g/l, levels that are far below normal values for fibrinogen [55, 182, 300]. In neurosurgical patients with postoperative bleeding complications, the preoperative fibrinogen was significantly lower compared to patients without bleeding. In the same study, the risk of postoperative hemorrhage was 2.5-fold increased in patients with fibrinogen measuring less than 1.5 g/l [96]. Similarly, fibrinogen levels below 2.0 g/l have been shown to have a positive predictive value of 100% for severe bleeding in postpartum hemorrhage [40]. Furthermore, preoperative fibrinogen levels below 3.8 g/l proved to be predictive for postoperative hemorrhage after cardiac surgery [248, 320]. Administration of fibrinogen concentrate reduced postoperative blood loss by 32% without any clinically detectable adverse events (Karlsson M et al., pers. comm.). Moreover, newer investigations demonstrated reduced clot firmness after colloid infusion, especially after hydroxyethyl starch (HES) solutions. This effect is based on fibrin polymerization disturbances and has been shown to trigger dilutional coagulopathy during orthopaedic surgery. It can be reversed by fibrinogen concentration administration [211]. Furthermore, HES solutions have been shown to interfere significantly with routine photo-optical measurement of fibrinogen concentration by Clauss method or PT derived. This results in a 21 to 92% overestimation of fibrinogen concentration in blood samples diluted with HES, especially in case of low fibrinogen levels [125]. Bearing this in

mind, perioperative fibrinogen level should not be lower than 1.5–2.0 g/l in patients with elective neurosurgery. Maybe higher fibrinogen levels are able to compensate reduced clot stability due to thrombocytopenia or platelet dysfunction [106, 325]. Since thrombelastometry is able to measure clot firmness, and thus capture fibrinogen concentration, platelet count, and function as well as colloid effects, it seems to be superior to conventional laboratory tests for real-time management of fibrinogen substitution [106, 211].

### FXIII

Based on data from a retrospective [93] and prospective [96] study, it was demonstrated that neurosurgical patients had a 6.4-fold increased risk of postoperative hemorrhage with FXIII less than 60%. In patients with additional decreased fibrinogen (<1.5 g/l) or platelets (<150 × 10<sup>9</sup>/l) the risk was even higher (12-fold and 9.7-fold, respectively) [96].

A prospective study of patients with unexplained intraoperative coagulopathy during elective surgery showed significantly less FXIII per unit thrombin available at any point in time (before, during, and after surgery) than patients without such coagulopathy. Fibrinogen and Factor XIII were significantly more rapidly consumed in patients with higher blood loss [332]. The consequence is a significant loss of clot firmness, measured by thrombelastometry, associated with an increase in intraoperative blood loss [168, 332]. The results of this study confirm the rationale for the implementation of preoperative FXIII testing in elective neurosurgical patients to minimize the risk of perioperative bleeding complications [96]. Replacement should be considered in patients with preoperative activity of less than 60%, because the mean decrease of FXIII in major neurosurgical procedures is about 20% [96]. In patients with FXIII activity between 60 and 80%, an intraoperative decision about replacement should be made with respect to the surgeon's judgment of hemostasis and total blood loss. Specific point-of-care measurements, like thrombelastometry, should be performed if available [106, 330].

### Prothrombin complex concentrate (PCC)

Prothrombin complex concentrate (PCC)—in German-speaking countries called PPSB (deduced from the first character of the enclosed coagulation factors)—contains the vitamin K-dependent coagulation factors II, VII, IX, X, and the anticoagulative proteins C and S. Furthermore, in most galenicals small amounts of antithrombin and heparin are enclosed.

PCC, which was first developed for therapy of hemophilia B, is licensed for the treatment of a perioperative

prophylaxis of bleedings in congenital deficiency of any vitamin K-dependent coagulation factor, when purified specific coagulation factor concentrates are not available, and in acquired deficiency of prothrombin complex coagulation factors, when rapid correction is required. PCC has its main field of application in urgent oral anticoagulation reversal (ACR) [72, 102, 117, 179, 191, 225, 241, 252, 305]. Furthermore, PCC can also be used very effectively in significant bleeding situations, which come along with coumarin intoxication, vitamin K deficiency, liver insufficiency, liver transplantation, or massive transfusion [19, 63, 81, 189, 224]. Whereas fresh-frozen plasma (FFP) has been shown to be ineffective in correcting coagulopathy in these situations, PCC offers the possibility of fast, effective, predictable, and safe correction of these coagulopathies [12, 36, 51, 127, 128, 130, 131, 224, 289, 291, 328]. As a rule of thumb a dosage of 1–1.6 IU PCC per kg bodyweight (bw) is required to generate a rise of coagulation factor activity by 1% (measured as PT in % of normal=Quick value).

In cases of severe bleeding with an INR of 1.5–3.0 (Quick value of 50–20 %) an initial bolus of 15–30 IU PCC per kg bw can be recommended. A single bolus of more than 40 IU per kg bw should be avoided [189, 191].

The main advantages of PCC administration compared to FFP transfusion in coagulopathic patients with significant bleeding are the fast, effective, and well-predictable rise in coagulation factor activity and the small volume needed to correct even severe coagulation factor deficiency. Thereby, transfusion associated circulatory overload (TACO) and consecutive acute lung injury (ALI) can be avoided, which is one of the main risks of FFP in these situations [51, 63, 252]. Contrary to this, with FFP, a significant rise in the patient's coagulation factor activity can only be achieved by transfusion of very high plasma volumes (20–30 ml per kg bw, which means 1.6–2.4 l FFP for a person with 80 kg bw) [41]. Furthermore, in contrast to FFP, PCC has no risk of transfusion related acute lung injury (TRALI) and mistransfusion. This is of particular importance because both intricacies are attributed with the highest risks of mortality in connection with blood transfusion [328]. Adverse events after FFP transfusion such as ALI can be responsible for prolongation of postoperative ventilation time and stay at intensive care unit (ICU) [51, 141, 328]. Thereby, secondary costs can be generated [52, 141, 153, 272, 273]. Last but not least, because of the effective viral inactivation by pasteurization and elimination by nanofiltration, to date no case of viral infection has been reported in connection with modern PCC preparations like Beriplex P/N or Octaplex (Rodewald L et al., pers. comm.).

In summary, compared to FFP transfusion, PCC therapy is much more effective in correcting deficiency of vitamin K-dependent coagulation factors. The main risks of FFP

transfusion, such as TRALI, TACO, and mistransfusion, can be eliminated by using coagulation factor concentrates. Compared to rFVIIa, the safety profile of PCC seems to be superior and the drug costs are much lower. Therefore, bodyweight- and PT-adapted administration of PCC enables a fast, effective, well-calculable and safe therapy of coagulopathies based on congenital or acquired deficiency of prothrombin complex coagulation factors. Especially in combination with application of fibrinogen concentrate PCC therapy enables significant reduction of FFP transfusion rate and minimize risk of TRALI, TACO, and mistransfusion in patients with severe bleeding and need for massive transfusion. Thereby, secondary cost for postoperative ICU therapy may be reduced as well.

### *Recombinant FVIIa in neurosurgical patients*

Recombinant FVIIa (rFVIIa) was initially developed as a hemostatic drug for patients with hemophilia A or B and inhibitory antibodies against factors VIII (FVIII) or IX (FIX) [196, 274]. Recombinant FVIIa is licensed for the treatment of bleeding episodes and surgical prophylaxis in patients with hemophilia A and B with inhibitors to FVIII and FIX, hereditary FVII deficiency, and Glanzmann thrombasthenia. It has been shown that the administration of rFVIIa is safe and effective in these patients without increasing the risk of thromboembolic events. Furthermore, many reports of successful nonlicensed use of rFVIIa for rapid correction of a wide variety of coagulopathies are published after the first report from Kenet and Martinowitz [157]. Thereby, during recent years it turned out that also in nonhemophilic patients the administration of rFVIIa can be life-saving in intractable intraoperative bleeding situations [4, 90, 302]. After some promising pilot studies, several randomized placebo-controlled trials with rFVIIa have been done in liver transplantation and trauma patients with disappointing results concerning its efficacy (reduction of transfusion rate by 0–2.6 red blood cell units) [18, 123, 188, 236, 288]. Subsequent randomized and placebo-controlled rFVIIa trials in cardiac surgery and severely injured trauma patients have been terminated over the last months because pre-planned futility analysis predicted a very low likelihood of reaching a successful outcome on the primary efficacy endpoint at the end of the trial. Concerning the risks associated with off-label-use of rFVIIa as a hemostatic agent the analysis of 13 Novo Nordisk-sponsored trials including patients with anticoagulant therapy, cirrhosis, or severe trauma did not show an increased risk of VTE (6.0% in the treatment groups vs. 5.3% in the placebo groups) [183]. On the other hand, two recently published randomized, placebo-controlled trials demonstrated significant efficacy of rFVIIa in elderly, non-hemophilic intracerebral hemorrhage patients, but in these studies the incidence of

thromboembolic events was obviously or even significantly higher in verum than in placebo group (7% vs. 2%;  $p=0.12$  resp. 10 vs. 1%;  $p=0.01$ ) [205, 303]. Myocardial or cerebral ischemia or infarction were the leading types of thromboembolic events in these studies. These data resulted in an FDA alert published in the FDA safety information and adverse event reporting program (MedWatch) against off-label-use of rFVIIa in December 2005. A subsequent review of the FDA compiled the published adverse events after administration of rFVIIa. From March 1999 to December 2004, 185 thromboembolic events were reported in 168 adverse event reports, thereof unlabeled indications accounted for 151 reports. In 72% of the reported deaths, the probable cause of death was the thromboembolic event [221]. Therefore, even though rFVIIa is an option to achieve a rapid increase in thrombin generation and hemostasis in active bleeding situations in neurosurgery, the risk of thromboembolic events, the preconditions for use of rFVIIa, as well as alternatives to obtain hemostasis—like fibrinogen and PCC administration, have to be considered [58, 122, 206, 208, 290].

In cases of life-threatening intraoperative hemostatic disturbances and bleeding complications, the off-label-use of rFVIIa has been effective in children [121, 213] and adults [76, 90, 149, 154] to control bleeding. Beside the beneficial use to control intraoperative bleeding after conventional hemostatic therapy with FFP failed [90, 149], it has been used in neurosurgical patients with coagulation disorders, trauma [66, 213], intracerebral [205, 207], and subarachnoid hemorrhage [234]. Table 2 depicts recently published data of usage of rFVIIa in neurosurgical patients. In patients with iatrogenic coagulopathy caused by oral anticoagulation in case of prosthetic heart valves, atrial fibrillation or patients with previous venous thromboembolic events rFVIIa readily corrects hemostatic capacity [186, 282, 326], but in most European countries PCC is the labeled and efficient first-line therapy for these indications [72, 179, 191, 241, 252]. Efficacy of rFVIIa has also been demonstrated in patients with coagulopathies due to liver disease [16] and thrombocytopenia [105]. Dosing of rFVIIa has been highly variable and the optimal dose has not yet been established for various indications [122]. A dose of 90–120  $\mu\text{g}/\text{kg}$  body weight is suggested with repeat dosing after 2 h because of the short half-life time of rFVIIa [271]. Some authors recommend to titrate the effect of rFVIIa by giving repeated small doses, whereas others suppose (and recent data suggests) that higher doses are more effective [89, 120, 229, 318]. However, preconditions of rFVIIa administration have to be considered, in order to avoid non-responders to rFVIIa therapy. Among these preconditions rank a pH above 7.2, a platelet count of more than  $50 \times 10^9/\text{l}$  (preferable  $100 \times 10^9/\text{l}$ ), a fibrinogen level of more than 1 g/l (preferably

**Table 2** Summary of clinical studies with the use of rFVIIa in neurosurgical patients: *N.a.* Not applicable; *DIC* Disseminated intravascular coagulation

Authors	Study design	Type of procedure	No. of patients	Indication to use rFVIIa	Dose	VTE	Adverse events
Deveras et al. 2002 [56]	Uncontrolled case series	Intracranial	13	Coagulopathy reversal	15 to 90 µg/kg		
Lin et al. 2003 [186]	Retrospective case series	intracranial spinal	4	Coagulopathy reversal	1.200 µg	0	No
Morenski et al. 2003 [213]	Retrospective case series (pediatric cases)	intracranial	3	Injury induced coagulopathy reversal	90 µg/kg	n.a	No
Park et al. 2003 [230]	Retrospective case series	Intracranial	9	Coagulopathy reversal Liver dysfunction	40-90 µg/kg	0	No
Sorensen et al. 2003 [282]	Retrospective case series	Intracranial	7	Coagulopathy reversal	10-40 µg/kg	0	No
Freeman et al. 2004 [80]	Retrospective case series	Intracranial	7	Coagulopathy reversal	mean 62.1 µg/kg	0	No
Roitberg et al. 2005 [256]	Retrospective controlled series	Intracranial	29	Coagulopathy reversal	1.4 mg	0	0
Brody et al. 2005 [24]	Retrospective case series	Intracranial	12	Coagulopathy reversal		0	1 DIC
Karadimov et al. 2003 [149]	Retrospective case series	Intracranial	3	Intraoperative coagulopathy	1 x 4.8 mg	0	No
Hartmann et al. 2006 [121]	Retrospective case series	Intracranial	2	Intraoperative coagulopathy	2 x 2.4 mg and 4.8 mg	0	Cerebral infarction
Kaw et al. 2004 [154]	Retrospective case series	spinal	4	Intraoperative coagulopathy	48.75 µg/kg	0	0
Pickard et al. 2000	Prospective randomized controlled	Intracranial	5 treatment 5 control Group	Subarachnoid hemorrhage	Placebo 80 µg/kg bolus 80 µg/kg bolus+ 3.5 µg/kg/h 80 µg/kg bolus+7.0 µg/kg/h	0	1 (middle cerebral artery branch thrombosis)
Mayer et al. 2005 [207]	Randomized controlled	None	48	Intracranial hemorrhage	Placebo 10, 20, 40, 80, 120, or 160 µg/kg	2	12
Mayer et al. 2005	Randomized controlled	None	399	Intracranial hemorrhage	Placebo 40, 80, 160 µg		7% vs. 2%

1.5 g/l), as well as the exclusion of heparin effects and hyperfibrinolysis as the underlying cause of bleeding [59, 106, 187, 203, 284, 304, 306]. Specific monitoring of rFVIIa effects or therapeutic efficacy cannot be done by PT or PTT measurements, but some authors recommend thrombelastography/metry for checking preconditions and efficacy of rFVIIa therapy [74, 106, 124, 203, 279–281, 318]. At last, the high cost of rFVIIa compared to other coagulation factor concentrates is a major impediment for a widespread use in daily practice in addition to its still-unclear safety-efficacy ratio in off-label-use [68, 122, 160, 193, 208, 245, 290, 292].

### *Antifibrinolytic Agents*

Only a few studies are subject to determine the effect of antifibrinolytic drugs in neurosurgical patients. A fortiori special attention was paid on the use of aprotinin in cardiac patients during recent months, because these patients showed an increased risk of renal failure requiring dialysis, an increased risk of myocardial infarction or heart failure as well as increased mortality after the use of high-dose aprotinin to limit blood loss [27, 75, 200, 201, 211]. This resulted in an FDA alert and worldwide marketing suspension of aprotinin in 2007. In neurosurgery, aprotinin has been successfully used in patients who underwent cerebrovascular surgery in deep hypothermia and cardiac arrest [109], which was found to be safe and effective. Furthermore, the administration of aprotinin in these patients lead to a reduction of blood loss compared to smaller former studies [180, 251] due to the prevention of hypothermia-associated coagulopathy. Case reports demonstrate the successful administration of aprotinin in patients with assumed or diagnosed hyperfibrinolysis [15, 226], intracranial hemorrhage [165], and head injury [14]. A randomized, double-blind, placebo-controlled trial conducted in two neurosurgical departments showed that the administration of aprotinin (30,000 Kallikrein-inhibiting units (KIU)/kg body weight on induction of anaesthesia followed by continued infusion of 10,000 KIU/kg/h until the surgery was finished, or for a maximum of 8 h) resulted in a halved blood loss in patients with intracranial meningiomas and vestibular schwannomas [227]. Although the study was not designed to evaluate blood loss, blood transfusion requirement was (not significantly) reduced (37 U of blood was used in 11 patients in the aprotinin group and 58 U in 13 patients in the placebo group). No differences were seen for thromboembolic events or other complications [26, 227]. The potential benefit of aprotinin or tranexamic acid in reducing blood loss in major spinal surgery was discussed recently, but no controlled trial proved a benefit for those patients [48, 216, 260]. In case of suspected or detected fibrinolysis tranexamic acid (10–

15 mg/kg initial bolus and 1–5 mg/kg body weight per hour) can be helpful to achieve hemostasis. A recent study demonstrated that rapid administration of a single bolus of tranexamic acid (2 g resp. 25 mg/kg bw over 10 min) resulted in a significantly lower incidence of hematoma growth compared to a prolonged infusion of 1 g tranexamic acid over a period of 6 h in patients with intracerebral hemorrhage [283]. This is consistent with our experience in context with more than 200 hyperfibrinolysis detected by thrombelastometry during liver transplantation. In these patients, recurrence of hyperfibrinolysis occurred in less than 1% of the patients after inhibition of fibrinolysis with a single shot of aprotinin or tranexamic acid [106]. Therefore, a subsequent continuous infusion of tranexamic acid after a bolus of 2 g (25 mg/kg bw) does not seem to have an additional beneficial effect on hemostasis but may increase the risk of thromboembolic events. Anyway, patients in which hyperfibrinolysis is suspected or detected should be monitored closely meshed with thrombelastometry/graphy also after therapy with antifibrinolytic drugs.

### (f) Specific measures to reverse anticoagulation therapy

The time frame to correct impaired hemostatic capacity depends on the urgency to treat neurosurgical patients with associated hemostatic perturbation. Of course, correction of coagulopathy is of pivotal interest in all cases with intracranial hemorrhage either managed conservatively or surgically. However, a challenging situation is a neurosurgical emergency necessitating surgery in patients with abnormal coagulation tests or obvious hemostatic impairment. In these circumstances the question of optimal timing of surgery arises. Therefore, hemostatic management in these patients should be closely coordinated between neurosurgeon and anaesthesiologist. The risks of potential severe intraoperative bleeding or postoperative hematoma have to be weighted against risks (neurological deficits) associated with postponed surgery. Point-of-care tests to evaluate coagulation capacity and platelet function by thrombelastometry (ROTEM) and whole-blood impedance aggregometry (Multiplate) can be helpful for contemporary risk assessment and therapeutic decisions.

### *Antiplatelet drugs*

According to the data of Palmer et al. [228], 47% of patients with postoperative hematomas were treated with antiplatelet drugs, which was therefore the most common risk factor for postoperative hematoma. A few case reports demonstrate the association of perioperative administration of aspirin and bleeding complications [210]. Although aspirin is considered to be a risk factor for postoperative hematomas after intracranial surgery, unfortunately we have

no evidence of when to stop the administration of antiplatelet medication. This is reflected by several surveillances conducted in Germany [166, 167] and England [142], where several attitudes are described.

Because the mechanism of action of most antiplatelet drugs is nonreversible inhibition of the platelet function, it seems to be reasonable to stop medication 7–10 days before elective surgery. In this context, it is an improvement that platelet function can be evaluated within 10 min by whole-blood impedance aggregometry (Multiplate) as a point-of-care test. This test system is sensitive to aspirin and clopidogrel effects as well as for GPIIb/IIIa-receptor antagonists but not optimal for detection of von Willebrand disease [329].

In patients treated with antiplatelet drugs, platelet concentrates should be available and transfused if intraoperative bleeding tendency becomes obvious. Cases with unaffected platelet function (monitored by impedance aggregometry) or uncomplicated intraoperative hemostasis during minor surgical procedures, such as evacuation of a chronic subdural hematoma, might be performed without transfusion. For major surgery platelet transfusion pooled from four single donors provide about  $20\text{--}30 \times 10^9/l$  platelets after transfusion. Platelet function is considerably dependent on duration of storage of platelet concentrates.

Desmopressin acetate (DDAVP)  $0.3 \mu\text{g}/\text{kg}$  body weight diluted in 50–100 ml saline can be infused over 30 min in patients with decreased hemostatic capacity due to antiplatelet agents or von Willebrand disease [119b; 131]. Although the mechanism of action remains incompletely understood, it is known that DDAVP induces an increase in plasma levels of von Willebrand factor (VWF), FVIII, and shortens PTT and bleeding time [78, 152, 181]. In contrast, this compound has no effect on platelet count or aggregation, but enhances platelet adhesion to the vessel wall [255].

#### *Non-steroidal anti-inflammatory drugs (NSAIDs)*

Non steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase and therefore the time of reversible inhibition of platelet function differs with respect to the used agent. Duration of platelet function inhibition is about 3 days with the administration of piroxicam, 2 days with naproxen, indomethacin, and diclofenac and less than 24 h after the administration of ibuprofen [49]. The administration of NSAIDs in patients with subarachnoid hemorrhage (SAH) showed that ketoprofen (but not acetaminophen) impaired platelet function [218]. A study in a small group of 46 neurosurgical patients (evaluated by thromboelastography) showed no significant association between coagulability and aspirin or NSAIDs use or

intraoperative fluid volume [1]. This is not surprising because thromboelastography is not sensitive to aspirin or clopidogrel effects. To evaluate platelet function after medication with antiplatelet drugs or NSAIDs, whole-blood impedance aggregometry (Multiplate) is the adequate tool [265, 329].

#### *Oral anticoagulation*

For patients receiving oral anticoagulation therapy (OAC), there are a number of clinical circumstances that necessitate rapid reversal, e.g., intracranial hemorrhage or trauma associated with head injury. Normalization of hemostasis is a prerequisite to prevent growth of intracranial hematoma and is therefore independent from the indication of surgical intervention. Anticoagulation can be reversed by prothrombin complex concentrate (PCC), which has been shown to be safe [224, 241], calculable, fast, and effective [10, 72, 102, 117, 179, 190, 191, 225, 252, 305, 327]. To reverse oral anticoagulation, PCC is 4–5 times more effective [79] and therefore is superior to fresh-frozen plasma (FFP) [22, 198]. To immediately complete reverse oral anticoagulation a dose of 20–30 IU/kg body weight is recommended. In life-threatening emergencies the doses should be increased up to 30–40 IU/kg KG body weight. The half-life time of oral anticoagulants (phenprocoumon [Marcumar]: 120–150 h; warfarin [Coumadin]: 40–70 h) is much longer than the half-life time of prothrombin complex coagulation factors (4–60 h). Therefore, vitamin K (5–10 mg) has to be administered additionally to avoid a rebound effect. Vitamin K therapy is effective after 12 h using the intravenous and 24 h the oral administration [327]. It is important to monitor and continue the appropriate replacement therapy over the perioperative period.

Although recombinant coagulation factor VII (rFVIIa) is not yet approved for the reversal of oral anticoagulation, in an emergency its “off label” use was very effective in some neurosurgical patients [24, 50, 56, 186, 230, 239, 256, 282, 326], but the very short half-life time of 2 h (numerous repeated applications are required), the missing substitution of the vitamin K-dependent anticoagulative proteins C and S, as well as the high cost have to be considered. In summary, FFP or rFVIIa should only be used for oral anticoagulation reversal (ACR), when PCC is not available. Patients with oral anticoagulation therapy scheduled for elective neurosurgical procedures should stop their medication for normalization of PT. Meanwhile, these patients should be managed with unfractionated heparin (UFH) or low molecular heparin (LMWH) during the pre- and perioperative period. According to the consultation of a cardiologist or neurologist, dosing of UFH or LMWH should be coordinated. The prothrombin time (PT) should be corrected before surgery starts and depending on the

indication (previous stroke or VTE, atrial fibrillation, etc.) the anticoagulation with UFH or LMWH should be stopped 12–24 h before surgery and restarted 12–24 h afterwards. However, management in these patients can be difficult and there is only very limited evidence that suggests when to stop and when to re-start treatment. The management should be individualized and adapted to a specific patient by weighting the risk of postoperative hematoma against the risk of thromboembolic complications. Interactions and synergistical effects of antiplatelet drugs, NSAIDs, antibiotics, antiepileptic drugs, and herbal medicines, such as ginkgo, garlic and ginger, have to be considered because they can aggravate hemostatic dysfunction [84, 135, 140]

#### *Heparin and low-molecular-weight heparin*

Protamine can be used for emergency reversal of unfractionated heparin (UFH) (1 mg neutralizes 100 IE UFH). For low-molecular-weight heparin (LMWH), the administration of protamine is largely ineffective. However, in neurosurgery, preoperative UFH or LMWH should be used only in patients with high risk of thromboembolic complications and should be stopped 12 h before surgery, which was found to be safe in a small group of patients [94].

#### *Antiepileptic drugs*

There is some evidence for adverse events, e.g., thrombocytopenia [177], platelet dysfunction [159], the occurrence of von Willebrand syndrome [97, 172, 270] or decreased coagulation factor XIII activity [237, 309] related to the use of antiepileptic drugs, mainly associated with valproic acid (VPA) [34]. The pathophysiology of these mechanisms is not clear. However, in patients with seizures related to previous head injury or intracranial neoplasm and the need for surgical treatment a potential antiepileptic drug-associated coagulopathy should be considered. In children, the incidence of coagulation disorders related to VPA was nearly 4% [97], which should prompt a distinct alertness for children treated with anticonvulsive medication.

#### *Neurosurgical procedures in patients with known coagulopathy*

Patients with known coagulopathy and the indication for neurosurgical operation should have a preoperative consultation with a hemostaseologist and need extended laboratory workup. According to the deficit, a specific replacement plan has to be available and a consequent factor replacement therapy and laboratory control is a prerequisite for successful surgery. Several reports demonstrate that neurosurgical operations can be performed in patients with hemophilia and cerebrovascular disease [60,

215, 259], head injury [37], or brain tumor [61, 62]. A patient suffering from severe FXIII deficiency and intractable epilepsy was successfully operated on [232] and in a few patients with spontaneous subdural hematoma and FXIII deficiency, surgery was performed without complications [3]. Patients with von Willebrand syndrome can be operated on with and adequate replacement of von Willebrand factor containing FVIII concentrates [73].

#### (g) Aberrations of the coagulation system following head injury

Hemostatic disturbance is quite common in patients with penetrating or blunt head injury (HI). Hypothermia, shock, acidosis, anaemia, consumption or dilutional coagulopathy, and thrombocytopenia can enhance the impairment of hemostasis. Therefore, these preconditions of hemostasis have to be considered in connection with the primary coagulation management [59, 184, 202, 285].

The incidence of a coagulopathy and thrombocytopenia following head injury varies considerably but was found to correlate with the patient's outcome [35, 223, 238]. Piek et al. described the presence of a coagulopathy as a significant independent predictor for the outcome of head injured patients [235], which was confirmed by other authors for adults [87, 155, 175, 268] and children [13, 323]. The association of the severity of trauma and coagulopathy is controversially discussed but not commonly accepted [35, 204].

More than three decades ago, Keimowitz and Annis [156] first discussed an association between the release of tissue factor after head injury and the development of DIC. However, the exact pathophysiological mechanisms still remain unknown and it is still unclear whether the pathological findings after head injury completely fit the DIC criteria [134] or whether they represent different forms of coagulopathy [20, 42, 324]. The difficulty in classifying coagulopathy after HI were extensively reviewed by Stein and Smith [296]. Trauma patients with HI had elevated monocyte TF expression compared to controls for the initial 24-h time period, but they subsequently had a more rapid return of monocyte TF expression to baseline (despite a higher figure in the injury severity score [ISS]) than trauma patients without HI [321]. These authors concluded that the correlation of TF expression with platelet-monocyte interaction suggests that platelet binding may lead to monocyte activation [26, 321].

Endothelial injury and secondary inflammatory processes as well as the release of toxins and ischemia may accelerate the coagulation process and platelet activation [334]. Stein et al. demonstrated that PTT, fibrinogen, fibrin degradation products, and D-dimers have specific changes and the extent of changes varies during the post

trauma course, which could fit with different phases of DIC [296]. D-dimers and fibrin degradation products were elevated within minutes following trauma, indicating a hypercoagulable state. In the very early period after trauma, PTT and PT remain normal, however they increase later and peak after 6 h and normalize within 24 h. The course of fibrinogen changes is opposed with a decrease between 6 and 12 h and a later increase in terms of an acute phase reaction.

Interestingly, Cohen et al. found in a prospective study of patients with HI that coagulopathy already developed about 30 min (early coagulopathy) after head injury, but coagulopathy exclusively occurred in patients with hypoperfusion (base deficit >6) indicated by increased PT, PTT, increased soluble thrombomodulin and decreased inactivated protein C. The authors concluded that the tissue injury, when combined with tissue hypoperfusion, results in a thrombomodulin and endothelial protein C receptor-associated activation of protein C. Unfortunately, they were unable to measure activated protein C, thus their result derives from the finding that inactivated protein C decreases. However, if activated protein C increases, it can inactivate factor Va and factor VIIIa—important accelerators of thrombin generation, leading to coagulopathy. Moreover, activated protein C can consume PAI-1 resulting in a derepression of tPA with consecutive induction of fibrinolysis [25, 44]. Other authors noted during the acute phase of HI a distinct fibrinolysis and fibrinogenolysis with impaired alpha 2- antiplasmin activity [174, 176].

Although most authors did not find prolonged changes after 24–36 h [296], in patients with isolated HI, a significant increase of coagulopathy and thrombocytopenia was found in serial tests within 72 h [35]. In this study, initially 14% of patients had a thrombocytopenia and 21% had a coagulopathy, which significantly increased after 72 h up to 46% and 41%, respectively, and had a significant influence on a patient's outcome [35]. Nekludov et al. demonstrated that patients with traumatic brain injury had a lower platelet count and longer bleeding time, but also dramatically lower platelet responses to arachidonic acid compared to controls [217].

The primary trauma-associated injury to the brain cannot be influenced during the later course. Therefore, all therapeutic measures should prevent secondary brain damage, which can also be caused by hemostatic disturbances [33, 35, 151, 219, 222, 249, 334]. Oertel et al. [222] found a progressive intracranial hemorrhage in 42% of patients with HI. In patients with intraparenchymal contusion, the enlargement was between 51% [222] and 100% [333]. Thus, a serial CT control scan is recommended in cases with initially conservatively managed epidural, subdural and intraparenchymal lesions in adults [31, 32]

and children [65]. Patients with pre-existing coagulation disturbances or antiplatelet medication showed more frequently an increase of the hematoma volume with the need for surgical evacuation. [266]. Re-operation to remove a postoperative hematoma after craniotomy and evacuation of an intracranial hemorrhage was necessary in 6.9% of head injured patients and was significantly more frequent in patients with alcohol abuse or pre-existing coagulopathy [33]. In a smaller series including 340 patients with HI, 91.7% of patients with delayed hematoma (eight patients) or re-bleeding (four patients) had coagulation abnormalities, suggesting disseminated intravascular coagulation and fibrinolysis [151]. These findings are especially noteworthy because patients who are scheduled for so-called minor surgery (external ventriculostomy) are also at risk of developing postoperative bleeding complications associated with an adverse outcome [33, 223]. Patients with minor head injuries and hemostatic abnormalities are also at risk of bleeding complications e.g. development of chronic subdural hematoma (CSDH) [164, 250]. Patients suffering from a recurrence of CSDH had significantly lower platelets [164].

Damage to the brain can also be due to posttraumatic ischemic complications rather than hemorrhagic reasons [110, 111, 297–299]. Causes of ischemia can be manifold. Apart from increased intracranial hypertension with decreased cerebral perfusion pressure, ischemia can be a result of vasospasm or hypotension: however, the direct verification of a specific cause can be difficult [308]. Another possible explanation for the occurrence of ischemia can be the formation of microthrombi, which were more frequent in areas with brain contusions than the contralateral side or in control sections [136, 150, 293, 322]. The formation of these microthrombi was proven histologically and correlated to the ischemic brain regions [293, 294]. Deposition of fibrin on the endothelial cell surface without complete vessel obstruction but reduced oxygen delivery or inflammatory mediators are other mechanisms causing secondary brain damage and are related to DIC [69, 132, 146, 199].

To avoid bleeding complications in patients with HI, there should be a closed observation and laboratory testing of these patients. Thrombelastometry (ROTEM) enables contemporary detection of hyperfibrinolysis, fibrinogen, and coagulation factor deficiency, fibrin polymerization disorders as well as thrombocytopenia [178]. This facilitates a fast and targeted hemostatic therapy with hemostatic drugs, coagulation factor concentrates, and platelets to avoid further brain damage by intracranial hematoma growth. Platelet dysfunction can be detected in time by bedside whole-blood impedance aggregometry (Multiplate). Hence, replacement therapy should be done in patients with hemorrhagic shock, consumption coagulopathy, medication with oral anticoagulants or antiplatelet drugs, or liver

insufficiency with impaired coagulation factor synthesis, to re-establish the full clotting capacity. The potential development of a DIC should be kept in mind in every patient after HI and treated according to the same principles as they are established for DIC treatment due to other reasons. Some authors found the use of FFP beneficial for these patients [104, 137, 204], however, a randomized study comparing FFP vs. placebo in patients with blunt HI did not prove a better outcome in FFP-treated patients [71]. Moreover, the risk of TACCO and TRALI and ALI induced by FFP transfusion has to be considered [51, 63, 141, 158, 197, 289, 328]. Some authors discussed the administration of antithrombin (AT) in head injured patients [133], but there is no evidence of its efficacy in preventing or treating a DIC [113]. In a few cases of life-threatening bleeding situations or massive hemorrhagic disturbance the off-label-use of rFVIIa was reported in children [213] and adults [118, 230].

According to the European guideline for the management of bleeding following major trauma specific replacement therapy should be initiated to achieve the following minimal values: hemoglobin 7–9 g/l, PT 60%, platelets  $100 \times 10^9/l$ , fibrinogen >1.5 g/l [284]. In some patients, higher fibrinogen levels may be required to achieve hemostasis. In case of suspected or detected (ROTEM) hyperfibrinolysis tranexamic acid should be administered prior to substitution of fibrinogen and coagulation factors to stop fibrinolysis [106].

#### (h) Safety and efficacy of pharmacological prophylaxis of VTE

Coagulability increases during neurosurgical procedures as shown for adults [1] and paediatric patients [103] using thromboelastography. Increased clotting starts between the induction of anaesthesia and skin incision and continues to increase throughout surgery, which was more pronounced in patients undergoing craniotomy than patients undergoing spine procedures [1]. Together with the procoagulatoric activation, in some brain neoplasms this could serve as an explanation for the high number of thromboembolic events in neurosurgical patients [116]. Venous thromboembolic events (VTE) can negatively affect the outcome of neurosurgical patients. The incidence of postoperative thromboembolic events in neurosurgical patients is relatively high. Clinically obvious deep venous thrombosis (DVT) occurred between 1.6–4% [2, 83, 116, 269] and asymptomatic DVT, diagnosed in controlled studies, ranged from 26% [220] to 32% [2]. Some authors mentioned an even higher incidence in neurosurgical patients [17, 264]. Pulmonary embolism (PE) occurs between 1.5 and 5% and is associated with high mortality [116]. However, a prospective DVT surveillance in 2,643 neurosurgical

patients revealed acute DVT in 147 (5.6%), being clinically asymptomatic in the vast majority of patients (81%) [77]. VTE are higher after cranial neurosurgical procedures (7.7%) compared to spinal surgery (1.%) [77, 278].

To prevent VTE, various measures with different effectiveness and associated risks are used in neurosurgical patients. A pharmacological VTE- prophylaxis (as performed in most surgical fields) is controversially discussed in neurosurgery [70, 98] or applied in different protocols [26, 243]. Some neurosurgeons refuse the pharmacological prophylaxis because they fear a potential life-threatening postoperative hemorrhage. Therefore, mainly in the United States, the prophylactic protocols are based on mechanically measures using intermittent pneumatic compression boots (IPC) and/or graduated compression stockings (GCS). These measures resulted in a significant reduction of DVT and PE as shown in many studies [8, 30, 319]. Moreover, some authors found that intraoperative unilateral and postoperative bilateral mechanical measures during surgery for brain tumors and motor mapping, were comparable to patients receiving bilateral lower-extremity mechanical VTE prophylaxis [9].

However, recent studies have demonstrated a further reduction of thromboembolic incidents by using unfractionated heparin (UFH) [38, 83, 195, 244] or low-molecular-weight heparin (LMWH) [2, 91, 94, 101, 139, 161, 194, 220] without a significant increased rate of postoperative hemorrhage. Many different protocols using either UFH or LMWH and starting prophylaxis either pre- or postoperatively are published from various institutions. Table 3 summarizes the recently published studies, indicating the different protocols and dose of pharmacological DVT-prophylaxis in neurosurgery. In England, an institutional survey revealed that 32% [301] of neurosurgical units use heparin during elective surgery. A similar postal survey performed in Germany showed that 73% of the neurosurgical centers used UFH or LMWH [243]. Discussing the start of prophylaxis some authors did not see an increase of postoperative bleeding when UFH or LMWH were administered already at the evening before surgery [11, 161, 194, 195, 331]. However, a study that investigated prophylaxis with 30 mg enoxaparin at induction of anaesthesia was terminated prematurely because of excessive bleeding [57], while the use of UFH and dalteparin in a similar study protocol did not increase the rate of postoperative bleeding [194]. The postoperative administration of UFH [38, 83, 244] and LMWH [139] [nadroparin [91, 94, 220]] [enoxaparin [2]], usually beginning at the morning after surgery, was not associated with increased postoperative hematoma, and seems to be appropriate unless the patients have an extraordinary high risk of thromboembolic events, which would justify starting prophylaxis on the day of surgery.

**Table 3** Published series identifying the rate of postoperative hematoma and VTE followed by perioperative administration of UFH or LMWH using different study protocols. *N.a.* Not applicable, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin

Authors	Study design	Type of procedure	Method of prophylaxis	Start	Postop Hematoma Rate study group	Postop Hematoma Rate control group	DVT Rate study group	DVT Rate control group
Boström et al. 1986 [21]	Prospective randomized controlled	Intracranial spinal	2 x 5,000U UFH	2 h before surgery	3/58 (5.2%)	2/46 (4.3%)	5/49 (10%)	5/40 (13%)
Barnett et al. 1977 [11]	Prospective	Intracranial spinal	2 x 5,000U UFH	1 h before surgery	2/150 (1.3%)	No control group	n.a.	n.a.
Cerrato et al. 1978 [38]	Prospective randomized controlled	Intracranial	3 x 5,000U UFH	2 h before surgery	2/50 (4.0%)	1/50 (2.0%)	3/50 (6%)	17/50 (34%)
Dickinson et al. 1998 [57]	Prospective randomized controlled	Intracranial	1 x 30 mg enoxoparin	Before induction of anesthesia	5/46 (10.9%)	0/22 (0%)	1/23 (4.3%)	3/22 (13.6%)
Macdonald et al. 1999 [195]	Prospective	intracranial	2 x 5,000U UFH	Before induction of anesthesia	0/106 (0%)	No control group	3/77 (3.9)	No control group
Macdonald et al. 2003 [194]	Prospective Randomized controlled	Intracranial Spinal	2 x 5,000U UFH 1 x 2,500 units dalteparin	Before induction of anesthesia	1/ 50 (2%) 0/ 50 (0%)	dalteparin vs.UFH	0/ 50 (0%) 2/ 50 (4%)	dalteparin vs. UFH
Wen et al. 1998 [33 1]	Retrospective	Intracranial spinal	2 x 5,000U UFH	Before surgery	3/872 (0.34%)	No control group	No control group	No control group
Kleindienst et al. 2003 [161]	Retrospective	Intracranial Spinal	1 x 3,000U Certoparin	Evening before surgery	3/294 (1.1%)	No control group	0/294 (0%)	No control group
Agnelli et al. 1998 [2]	Prospective randomized controlled	Intracranial spinal	40 mg enoxoparin	<24 h postoperatively	4/153 (2.6%)	4/154 (2.6%)	22/130 (17%)	42/129 (32%)
Frim et al. 1992 [83]	Prospective	Intracranial Spinal	2 x 5000U UFH	<24 h postoperatively	0/138 (0%)	Historical control 1/ 473 (0.2%)	0/138 (0%)	Historical control 15/473 (3.2%)
Nurmohamed et al. 1996 [220]	Prospective randomized double-blind	Intracranial	7500U anti FXa nadroparin	<24 h postoperatively	6/241 (2.5%)	2/244 (0.8%)	31/166 (18.7%)	47/179 (26.3%)
Raabe et al. 2001 [244]	Retrospective	Cranial	3 x 5000 U UFH	<24 h postoperatively	28/1564 (1.8%)	No control group	n.a.	No control group
Goldhaber et al. 2002 [101]	Prospective randomized double blind controlled	Cranial	2 x 5000U UFH 40 mg enoxoparin	<24 h postoperatively	1/75 (1.3%) 2/75 (2.7%)	No control group	5/75 (6.7) 9/ 75 (12%)	No control group
Gerlach et al. 2003 [94]	Prospective	Intracranial	2850U anti FXa	<24 h postoperatively	43/2823 (1.5%)	No control group	7/ 2823 (0.25%)	No control group
Gerlach et al. 2003 [91]	Retrospective	Spinal	2850U anti FXa	<24 h postoperatively	13/ 1954 (0.7%)	No control group	1/ 1954 (0.05%)	No control group

As discussed above, for patients scheduled for elective neurosurgical operations the administration of a pharmacological prophylaxis of thromboembolic events using UFH or LMWH is controversial and a matter of debate in head injured patients. According to our own experience in patients with normal coagulation parameters and excluded massive progression of intracranial hemorrhage by CT, the administration of 0.3 ml nadroparin subcutaneously 1 day after trauma was found to be safe [94]. This was confirmed by other colleagues [47, 162, 173] and decreased the rate of thromboembolic events [47, 162].

It is important to mention that the use of UFH or LMWH in neurosurgical patients is not yet formally approved. Considering available data on prevention of venous thromboembolism in neurosurgery in “The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy”, published in 2004, the following recommendations were given for neurosurgery [88]. Besides the general recommendation for routine thromboprophylaxis in patients undergoing major neurosurgery (IPC with or without GCS), acceptable “alternative options” are prophylaxis with UFH (Grade 2B) or postoperative LMWH (Grade 2A). The authors suggest the combination of mechanical prophylaxis (i.e., GCS and/or IPC) and pharmacologic prophylaxis (i.e., UFH or LMWH) in high-risk neurosurgery patients (Grade 2B)[88]. In the guidelines for the management of severe traumatic brain injury, the following statement was published. “LMWH or low dose unfractionated heparin should be used in combination with mechanical prophylaxis. However there is an increased risk for expansion of intracranial hemorrhage” [23].

## Conclusions

Hemostatic problems in neurosurgery can arise from different origins. Diagnosis and specific treatment can be difficult but appropriate replacement therapy is the prerequisite for the patient’s overall outcome. The management of anticoagulation reversal is discussed on the background of urgency of neurosurgical intervention. The type of intracranial pathology determines the time frame for the correction of hemostatic abnormalities caused either by trauma, medical anticoagulation treatment, or other reasons. Thus in life-threatening neurosurgical emergencies, all methods of replacement therapy should be directed to achieve full clotting capacity and to avoid secondary brain damage due to progressive hemorrhage or re-bleeding after neurosurgical interventions. Especially in emergency situations as well as in case of perioperative hemorrhage, point-of-care tests such as thrombelastometry (ROTEM) and whole-blood impedance aggregometry (Multiplate) enable contemporary detection of the underlying hemostatic

disorders, and thereby facilitate a fast and targeted therapy with hemostatic drugs and coagulation factor concentrates, such as fibrinogen, PCC, factor XIII, or rFVIIa. In contrast to a therapy based on conventional laboratory tests and transfusion of FFP, coagulopathy can be specified in time and corrected effectively and calculable within 30 to 45 min. Furthermore, the risk of FFP induced circulatory overload (TACO) and transfusion related acute lung injury (TRALI) can be avoided.

In patients scheduled for elective neurosurgery any coagulation abnormality should be excluded by thorough history evaluation and standard tests before surgery. If any uncertainty evolves, the operation should be postponed until a consultation with a hemostaseologist has excluded any bleeding tendency. The indication of anticoagulation medications needs to be evaluated carefully and changed to UFH or LMWH at an appropriate time. Patients with known hemostatic abnormalities need a sufficient replacement therapy during the whole perioperative course. Postoperative prophylaxis of VTE using a combination of mechanical (IPC, GCS) and pharmacological measures (UFH, LMWH) is safe and does not increase the risk of postoperative hematoma. Besides its usefulness for perioperative bleeding management, thrombelastometry (ROTEM) may be helpful in assessing hypercoagulability after neurosurgery and the therewith associated risk of thromboembolic events.

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## References

1. Abrahams JM, Torchia MB, McGarvey M, Putt M, Baranov D, Sinson GP (2002) Perioperative assessment of coagulability in neurosurgical patients using thromboelastography. *Surg Neurol* 58:5–11
2. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D’Angelo A, Beltrametti C, Damiani M, Andrioli GC, Pugliese R, Iorio A, Brambilla G (1998) Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *N Engl J Med* 339:80–85
3. Albanese A, Tuttolomondo A, Anile C, Sabatino G, Pompucci A, Pinto A, Licata G, Mangiola A (2005) Spontaneous chronic

- subdural hematomas in young adults with a deficiency in coagulation factor XIII. Report of three cases. *J Neurosurg* 102:1130–1132
4. Aldouri M (2002) The use of recombinant factor VIIa in controlling surgical bleeding in non-haemophilic patients. *Pathophysiol Haemost Thromb* 32(Suppl 1):41–46
  5. Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W (2006) An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. *Transfus Med* 16:31–39
  6. Arai Y, Kubota T, Nakagawa T, Kabuto M, Sato K, Kobayashi H (1998) Production of urokinase-type plasminogen activator (u-PA) and plasminogen activator inhibitor-1 (PAI-1) in human brain tumours. *Acta Neurochir (Wien)* 140:377–385
  7. Astrup T (1965) Assay and content of tissue thromboplastin in different organs. *Thromb Diath Haemorrh* 14:401–416
  8. Auguste KI, Quinones-Hinojosa A, Berger MS (2004) Efficacy of mechanical prophylaxis for venous thromboembolism in patients with brain tumors. *Neurosurg Focus* 17:E3
  9. Auguste KI, Quinones-Hinojosa A, Gadhary C, Zada G, Lamborn KR, Berger MS (2003) Incidence of venous thromboembolism in patients undergoing craniotomy and motor mapping for glioma without intraoperative mechanical prophylaxis to the contralateral leg. *J Neurosurg* 99:680–684
  10. Baglin TP, Keeling DM, Watson HG (2006) Guidelines on oral anticoagulation (warfarin): third edition–2005 update. *Br J Haematol* 132:277–285
  11. Barnett HG, Clifford JR, Llewellyn RC (1977) Safety of mini-dose heparin administration for neurosurgical patients. *J Neurosurg* 47:27–30
  12. bdel-Wahab OI, Healy B, Dzik WH (2006) Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion* 46:1279–1285
  13. Becker S, Schneider W, Kreuz W, Jacobi G, Scharrer I, Nowak-Gottl U (1999) Post-trauma coagulation and fibrinolysis in children suffering from severe cerebro-cranial trauma. *Eur J Pediatr* 158(Suppl 3):S197–S202
  14. Benzer H, Blümel G, Brenner H (1963) Ueber Blutgerinnungsstörungen nach Hirnverletzungen und Hirnverletzungen. *Wien Klin Wochenschr* 75:725–726
  15. Berger MM, Ravussin P, Vielle G, Fankhauser H (1995) Life-threatening hemorrhagic diathesis due to disseminated intravascular coagulation during elective brain tumor surgery. *J Neurosurg Anesthesiol* 7:26–29
  16. Bernstein DE, Jeffers L, Erhardtson E, Reddy KR, Glazer S, Squiban P, Bech R, Hedner U, Schiff ER (1997) Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology* 113:1930–1937
  17. Black PM, Baker MF, Snook CP (1986) Experience with external pneumatic calf compression in neurology and neurosurgery. *Neurosurgery* 18:440–444
  18. Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 59:8–15
  19. Bohrer H (1999) Prothrombin complex concentrate substitution during liver transplantation. *Thromb Res* 95:S71–S74
  20. Bonnemaïson J, Thicoipe M, Dixmerias F, Guerin V (1998) Coagulopathy suggestive of a primary fibrinolysis after head injuries with brain death. *Ann Fr Anesth Reanim* 17:275–277
  21. Bostrom S, Holmgren E, Jonsson O, Lindberg S, Lindstrom B, Winso I, Zachrisson B (1986) Post-operative thromboembolism in neurosurgery. A study on the prophylactic effect of calf muscle stimulation plus dextran compared to low-dose heparin. *Acta Neurochir (Wien)* 80:83–89
  22. Boulis NM, Bobek MP, Schmaier A, Hoff JT (1999) Use of factor IX complex in warfarin-related intracranial hemorrhage. *Neurosurgery* 45:1113–1118
  23. Bratton SL, Chestnut RM, Ghajar J, Connell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW (2007) Guidelines for the management of severe traumatic brain injury. V. Deep vein thrombosis prophylaxis. *J Neurotrauma* 24(Suppl 1):S32–S36
  24. Brody DL, Aiyagari V, Shackelford AM, Diringner MN (2005) Use of recombinant factor VIIa in patients with warfarin-associated intracranial hemorrhage. *Neurocrit Care* 2:263–267
  25. Brohi K, Cohen MJ, Davenport RA (2007) Acute coagulopathy of trauma: mechanism, identification and effect. *Curr Opin Crit Care* 13:680–685
  26. Browd SR, Ragel BT, Davis GE, Scott AM, Skalabrin EJ, Couldwell WT (2004) Prophylaxis for deep venous thrombosis in neurosurgery: a review of the literature. *Neurosurg Focus* 17:E1
  27. Brown JR, Birkmeyer NJ, O'Connor GT (2007) Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 115:2801–2813
  28. Brozna JP (1990) Cellular regulation of tissue factor. *Blood Coagul Fibrinolysis* 1:415–426
  29. Brummel-Ziedins K, Whelihan MF, Ziedins EG, Mann KG (2006) The resuscitative fluid you choose may potentiate bleeding. *J Trauma* 61:1350–1358
  30. Bucci MN, Papadopoulos SM, Chen JC, Campbell JA, Hoff JT (1989) Mechanical prophylaxis of venous thrombosis in patients undergoing craniotomy: a randomized trial. *Surg Neurol* 32:285–288
  31. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, Servadei F, Walters BC, Wilberger J (2006) Surgical management of traumatic parenchymal lesions. *Neurosurgery* 58:S25–S46
  32. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, Servadei F, Walters BC, Wilberger JE (2006) Surgical management of acute epidural hematomas. *Neurosurgery* 58:S7–15
  33. Bullock R, Hanemann CO, Murray L, Teasdale GM (1990) Recurrent hematomas following craniotomy for traumatic intracranial mass. *J Neurosurg* 72:9–14
  34. Cannizzaro E, Albisetti M, Wohrlab G, Schmutz M (2007) Severe bleeding complications during antiepileptic treatment with valproic acid in children. *Neuropediatrics* 38:42–45
  35. Carrick MM, Tyroch AH, Youens CA, Handley T (2005) Subsequent development of thrombocytopenia and coagulopathy in moderate and severe head injury: support for serial laboratory examination. *J Trauma* 58:725–729
  36. Casbard AC, Williamson LM, Murphy MF, Rege K, Johnson T (2004) The role of prophylactic fresh-frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. *Anaesthesia* 59:550–558
  37. Cermelj M, Negro F, Schijman E, Ferro AM, Acerenza M, Pollola J (2004) Neurosurgical intervention in a haemophilic child with a subdural and intracerebral haematoma. *Haemophilia* 10:405–407
  38. Cerrato D, Ariano C, Fiacchino F (1978) Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. *J Neurosurg* 49:378–381
  39. Chan KH, Mann KS, Chan TK (1989) The significance of thrombocytopenia in the development of postoperative intracranial hematoma. *J Neurosurg* 71:38–41
  40. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, de PD (2007) The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 5:266–273

41. Chowdhury P, Saayman AG, Paulus U, Findlay GP, Collins PW (2004) Efficacy of standard dose and 30 ml/kg fresh-frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol* 125:69–73
42. Churliaev IuA, Lychev VG, Epifantseva NN, Redkokasha LIU (1999) [Clinico-pathogenetic variants of DIC syndrome in patients with severe craniocerebral trauma]. *Anesteziol Reanimatol* (6):27–29
43. Claes Y, Van Hemelrijck J, Van Gerven M, Arnout J, Vermeylen J, Weidler B, Van Aken H (1992) Influence of hydroxyethyl starch on coagulation in patients during the perioperative period. *Anesth Analg* 75:24–30
44. Cohen MJ, Brohi K, Ganter MT, Manley GT, Mackersie RC, Pittet JF (2007) Early coagulopathy after traumatic brain injury: the role of hypoperfusion and the protein C pathway. *J Trauma* 63:1254–1261
45. Conroy JM, Fishman RL, Reeves ST, Pinosky ML, Lazarchick J (1996) The effects of desmopressin and 6% hydroxyethyl starch on factor VIII:C. *Anesth Analg* 83:804–807
46. Contreras M (1998) Consensus conference on platelet transfusion. Final statement. *Transfus Sci* 19:111–114
47. Cothren CC, Smith WR, Moore EE, Morgan SJ (2007) Utility of once-daily dose of low-molecular-weight heparin to prevent venous thromboembolism in multisystem trauma patients. *World J Surg* 31:98–104
48. Cravens GT, Brown MJ, Brown DR, Wass CT (2006) Antifibrinolytic therapy use to mitigate blood loss during staged complex major spine surgery: Postoperative visual color changes after tranexamic acid administration. *Anesthesiology* 105:1274–1276
49. Cronberg S, Wallmark E, Soderberg I (1984) Effect on platelet aggregation of oral administration of 10 non-steroidal analgesics to humans. *Scand J Haematol* 33:155–159
50. Da'as N, Misgav M, Kalish Y, Varon D (2006) Recombinant factor VIIa for rapid reversal of anticoagulant effect in patients with intracranial hemorrhage: the Israeli experience and review of the literature. *Isr Med Assoc J* 8:807–811
51. Dara SI, Rana R, Afessa B, Moore SB, Gajic O (2005) Fresh-frozen plasma transfusion in critically ill medical patients with coagulopathy. *Crit Care Med* 33:2667–2671
52. Dasta JF, McLaughlin TP, Mody SH, Piech CT (2005) Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med* 33:1266–1271
53. de Jonge E, Levi M, Buller HR, Berends F, Kesecioglu J (2001) Decreased circulating levels of von Willebrand factor after intravenous administration of a rapidly degradable hydroxyethyl starch (HES 200/0.5/6) in healthy human subjects. *Intensive Care Med* 27:1825–1829
54. Deloughery TG (2004) Coagulation defects in trauma patients: etiology, recognition, and therapy. *Crit Care Clin* 20:13–24
55. Despotis GJ, Goodnough LT (2000) Management approaches to platelet-related microvascular bleeding in cardiothoracic surgery. *Ann Thorac Surg* 70:S20–S32
56. Deveras RA, Kessler CM (2002) Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med* 137:884–888
57. Dickinson LD, Miller LD, Patel CP, Gupta SK (1998) Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 43:1074–1081
58. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, Broderick JP (2008) Risk of thromboembolic events in controlled trials of rFVIIa in spontaneous intracerebral hemorrhage. *Stroke* 39:850–856
59. Dirkmann D, Hanke AA, Gorlinger K, Peters J (2008) Hypothermia and acidosis synergistically impair coagulation in human whole blood. *Anesth Analg* 106:1627–1632
60. Donmez A, Turker H, Sekerci S, Kayhan Z, Ozbek N (1999) Dealing with a hemophilia-A patient undergoing cerebral aneurysm surgery. *J Neurosurg Anesthesiol* 11:214–215
61. Doughty HA, Coles J, Parmar K, Bullock P, Savidge GF (1995) The successful removal of a bleeding intracranial tumour in a severe haemophilic using an adjusted dose continuous infusion of monoclonal factor VIII. *Blood Coagul Fibrinolysis* 6:31–34
62. Doughty HA, Northeast A, Sklair L, Roques T, Young AE, Savidge GF, Hunt BJ (1995) The use of recombinant factor VIIa in a patient with acquired haemophilia A undergoing surgery. *Blood Coagul Fibrinolysis* 6:125–128
63. Drews RE (2003) Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. *Clin Chest Med* 24:607–622
64. Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U, Nashef SA (2008) Guideline on antiplatelet and anticoagulation management in cardiac surgery. *Eur J Cardiothorac Surg* 34:73–92
65. Durham SR, Liu KC, Selden NR (2006) Utility of serial computed tomography imaging in pediatric patients with head trauma. *J Neurosurg* 105:365–369
66. Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM (2004) Factor VIIa for correction of traumatic coagulopathy. *J Trauma* 57:709–718
67. Dzik WH (2004) Predicting hemorrhage using preoperative coagulation screening assays. *Curr Hematol Rep* 3:324–330
68. Earnshaw SR, Joshi AV, Wilson MR, Rosand J (2006) Cost-effectiveness of recombinant activated factor VII in the treatment of intracerebral hemorrhage. *Stroke* 37:2751–2758
69. Edwards RL, Rickles FR (1992) The role of leukocytes in the activation of blood coagulation. *Semin Hematol* 29:202–212
70. Epstein NE (2005) A review of the risks and benefits of differing prophylaxis regimens for the treatment of deep venous thrombosis and pulmonary embolism in neurosurgery. *Surg Neurol* 64:295–301
71. Etemadzezaie H, Baharvahdat H, Shariati Z, Lari SM, Shakeri MT, Ganjeifar B (2007) The effect of fresh-frozen plasma in severe closed head injury. *Clin Neurol Neurosurg* 109:166–171
72. Evans G, Luddington R, Baglin T (2001) Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding. *Br J Haematol* 115:998–1001
73. Federici AB (2005) Management of von Willebrand disease with factor VIII/von Willebrand factor concentrates: results from current studies and surveys. *Blood Coagul Fibrinolysis* 16(Suppl 1):S17–S21
74. Fenger-Eriksen C, Ingerslev J, Tønnesen E, Sørensen B (2009) Citrate artificially masks the haemostatic effect of recombinant factor VIIa in dilutional coagulopathy. *Ann Hematol* 88(3):255–260
75. Fergusson DA, Hebert PC, Mazer CD, Fries S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Cote D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R (2008) A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med* 358:2319–2331
76. Fewel ME, Park P (2004) The emerging role of recombinant-activated factor VII in neurocritical care. *Neurocrit Care* 1:19–29
77. Flinn WR, Sandager GP, Silva MB Jr, Benjamin ME, Cerullo LJ, Taylor M (1996) Prospective surveillance for perioperative venous thrombosis. Experience in 2,643 patients. *Arch Surg* 131:472–480
78. Franchini M (2007) The use of desmopressin as a hemostatic agent: a concise review. *Am J Hematol* 82:731–735
79. Fredriksson K, Norrving B, Stromblad LG (1992) Emergency reversal of anticoagulation after intracerebral hemorrhage. *Stroke* 23:972–977

80. Freeman WD, Brott TG, Barrett KM, Castillo PR, Deen HG Jr, Czervionek LF, Meschia JF (2004) Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. *Mayo Clin Proc* 79:1495–1500
81. Fries D, Haas T, Klingler A, Streif W, Klima G, Martini J, Wagner-Berger H, Innerhofer P (2006) Efficacy of fibrinogen and prothrombin complex concentrate used to reverse dilutional coagulopathy—a porcine model. *Br J Anaesth* 97:460–467
82. Fries D, Streif W, Haas T, Kuhbacher G (2004) Dilutional coagulopathy, an underestimated problem? *Anesthesiol Intensivmed Notfallmed Schmerzther* 39:745–750
83. Frim DM, Barker FG, Poletti CE, Hamilton AJ (1992) Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. *Neurosurgery* 30:830–832
84. Fugh-Berman A (2000) Herb-drug interactions. *Lancet* 355:134–138
85. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O (1994) Serial changes in hemostasis after intracranial surgery. *Neurosurgery* 35:26–33
86. Fukamachi A, Koizumi H, Nukui H (1985) Postoperative intracerebral hemorrhages: a survey of computed tomographic findings after 1,074 intracranial operations. *Surg Neurol* 23:575–580
87. Gando S, Nakanishi Y, Tedo I (1995) Cytokines and plasminogen activator inhibitor-1 in posttrauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. *Crit Care Med* 23:1835–1842
88. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG (2004) Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126:338S–400S
89. Gelsomino S, Lorusso R, Romagnoli S, Bevilacqua S, De CG, Bille G, Stefano P, Gensini GF (2008) Treatment of refractory bleeding after cardiac operations with low-dose recombinant activated factor VII (NovoSeven): a propensity score analysis. *Eur J Cardiothorac Surg* 33:64–71
90. Gerlach R, Marquardt G, Wissing H, Scharrer I, Raabe A, Seifert V (2002) Application of recombinant activated factor VII during surgery for a giant skull base hemangiopericytoma to achieve safe hemostasis. Case report. *J Neurosurg* 96:946–948
91. Gerlach R, Raabe A, Beck J, Woszczyk A, Seifert V (2004) Postoperative nadroparin administration for prophylaxis of thromboembolic events is not associated with an increased risk of hemorrhage after spinal surgery. *Eur Spine J* 13(1):9–13
92. Gerlach R, Raabe A, Scharrer I, Meixensberger J, Seifert V (2004) Post-operative hematoma after surgery for intracranial meningiomas: causes, avoidable risk factors and clinical outcome. *Neurol Res* 26:61–66
93. Gerlach R, Raabe A, Zimmermann M, Siegemund A, Seifert V (2000) Factor XIII deficiency and postoperative hemorrhage after neurosurgical procedures [In Process Citation]. *Surg Neurol* 54:260–266
94. Gerlach R, Scheuer T, Beck J, Woszczyk A, Seifert V, Raabe A (2003) Risk of postoperative hemorrhage after intracranial surgery after early nadroparin administration: results of a prospective study. *Neurosurgery* 53:1028–1035
95. Gerlach R, Scheuer T, Bohm M, Beck J, Woszczyk A, Raabe A, Scharrer I, Seifert V (2003) Increased levels of plasma tissue factor pathway inhibitor in patients with glioblastoma and intracerebral metastases. *Neurol Res* 25:335–338
96. Gerlach R, Tolle F, Raabe A, Zimmermann M, Siegemund A, Seifert V (2002) Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity: implications of a prospective study. *Stroke* 33:1618–1623
97. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, König S (2006) Valproate-associated coagulopathies are frequent and variable in children. *Epilepsia* 47:1136–1143
98. Gnanalingham KK, Holland JP (2003) Attitudes to the use of prophylaxis for thrombo-embolism in neurosurgical patients. *J Clin Neurosci* 10:467–469
99. Goh KY, Poon WS, Chan DT, Ip CP (2005) Tissue plasminogen activator expression in meningiomas and glioblastomas. *Clin Neurol Neurosurg* 107:296–300
100. Goh KY, Tsoi WC, Feng CS, Wickham N, Poon WS (1997) Haemostatic changes during surgery for primary brain tumours. *J Neurol Neurosurg Psychiatry* 63:334–338
101. Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM (2002) Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest* 122:1933–1937
102. Goldstein JN, Rosand J, Schwamm LH (2008) Warfarin reversal in anticoagulant-associated intracerebral hemorrhage. *Neurocrit Care* 9(2):277–283
103. Goobie SM, Soriano SG, Zurakowski D, McGowan FX, Rockoff MA (2001) Hemostatic changes in pediatric neurosurgical patients as evaluated by thrombelastograph. *Anesth Analg* 93:887–892
104. Goodnight SH, Kenoyer G, Rapaport SI, Patch MJ, Lee JA, Kurze T (1974) Defibrination after brain-tissue destruction: a serious complication of head injury. *N Engl J Med* 290:1043–1047
105. Goodnough LT (2004) Experiences with recombinant human factor VIIa in patients with thrombocytopenia. *Semin Hematol* 41:25–29
106. Gorlinger K (2006) Coagulation management during liver transplantation. *Hamostaseologie* 26:S64–S76
107. Gosseye S, van OL, Weynand B, Scheiff JM, Moulin D, de GJ de Ville, Otte JB (1991) Platelet aggregates in small lung vessels and death during liver transplantation. *Lancet* 338:532–534
108. Grady RE, Oliver WC Jr, Abel MD, Meyer FB (2002) Aprotinin and deep hypothermic cardiopulmonary bypass with or without circulatory arrest for craniotomy. *J Neurosurg Anesthesiol* 14:137–140
109. Grady RE, Oliver WC Jr, Abel MD, Meyer FB (2002) Aprotinin and deep hypothermic cardiopulmonary bypass with or without circulatory arrest for craniotomy. *J Neurosurg Anesthesiol* 14:137–140
110. Graham DI, Adams JH (1971) Ischaemic brain damage in fatal head injuries. *Lancet* 1:265–266
111. Graham DI, Ford I, Adams JH, Doyle D, Teasdale GM, Lawrence AE, McLellan DR (1989) Ischaemic brain damage is still common in fatal non-missile head injury. *J Neurol Neurosurg Psychiatry* 52:346–350
112. Greenberg MS (1997) Hematology. In: Greenberg MS (ed) *Handbook of neurosurgery*, 4th edn. Greenberg Graphics Inc., Lakeland, Florida, pp 491–523
113. Grenander A, Bredbacka S, Rydvall A, Aroch R, Edner G, Koskinen LO, Olivecrona M (2001) Antithrombin treatment in patients with traumatic brain injury: a pilot study. *J Neurosurg Anesthesiol* 13:49–56
114. Grounds M (2003) Recombinant factor VIIa (rFVIIa) and its use in severe bleeding in surgery and trauma: a review. *Blood Rev* 17 (Suppl 1):S11–S21
115. Guan M, Su B, Lu Y (2002) Quantitative reverse transcription-PCR measurement of tissue factor mRNA in glioma. *Mol Biotechnol* 20:123–129
116. Hamilton MG, Hull RD, Pineo GF (1994) Venous thromboembolism in neurosurgery and neurology patients: a review. *Neurosurgery* 34:280–96, discussion 296
117. Hanley JP (2004) Warfarin reversal. *J Clin Pathol* 57:1132–1139
118. Hansen MK, Jensen MK, Andersen C (2006) Uncontrollable bleeding in a patient with head trauma treated with blood component therapy guided by thromboelastography. *Ugeskr Laeger* 168:3535–3536

119. Hardy JF, de Moerloose P, Samama M (2004) Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth* 51:293–310
120. Harrison TD, Laskosky J, Jazaeri O, Pasquale MD, Cipolle M (2005) “Low-dose” recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. *J Trauma* 59:150–154
121. Hartmann M, Sucker C, Messing M (2006) Recombinant activated factor VII in the treatment of near-fatal bleeding during pediatric brain tumor surgery. Report of two cases and review of the literature. *J Neurosurg* 104:55–58
122. Hawryluk GW, Cusimano MD (2006) The role of recombinant activated factor VII in neurosurgery: hope or hype? *J Neurosurg* 105:859–868
123. Hendriks HG, Meijer K, de Wolf JT, Klomp maker IJ, Porte RJ, de Kam PJ, Hagenaaers AJ, Melsen T, Slooff MJ, der MJ van (2001) Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation* 71:402–405
124. Hendriks HG, Meijer K, de Wolf JT, Porte RJ, Klomp maker IJ, Lip H, Slooff MJ, van der MJ (2002) Effects of recombinant activated factor VII on coagulation measured by thromboelastography in liver transplantation. *Blood Coagul Fibrinolysis* 13:309–313
125. Hiippala ST (1995) Dextran and hydroxyethyl starch interfere with fibrinogen assays. *Blood Coagul Fibrinolysis* 6:743–746
126. Hiippala ST, Myllyla GJ, Vahtera EM (1995) Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 81:360–365
127. Ho AM, Dion PW, Cheng CA, Karmakar MK, Cheng G, Peng Z, Ng YW (2005) A mathematical model for fresh-frozen plasma transfusion strategies during major trauma resuscitation with ongoing hemorrhage. *Can J Surg* 48:470–478
128. Ho AM, Karmakar MK, Dion PW (2005) Are we giving enough coagulation factors during major trauma resuscitation? *Am J Surg* 190:479–484
129. Hoffman M, Monroe DM (2007) Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am* 21:1–11
130. Holland LL, Brooks JP (2006) Toward rational fresh-frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. *Am J Clin Pathol* 126:133–139
131. Holland LL, Foster TM, Marlar RA, Brooks JP (2005) Fresh-frozen plasma is ineffective for correcting minimally elevated international normalized ratios. *Transfusion* 45:1234–1235
132. Holmin S, Soderlund J, Biberfeld P, Mathiesen T (1998) Intracerebral inflammation after human brain contusion. *Neurosurgery* 42:291–298
133. Hoots WK (1997) Experience with antithrombin concentrates in neurotrauma patients. *Semin Thromb Hemost* 23(Suppl 1):3–16
134. Hoots WK (1997) Experience with antithrombin concentrates in neurotrauma patients. *Semin Thromb Hemost* 23(Suppl 1):3–16
135. Hu Z, Yang X, Ho PC, Chan SY, Heng PW, Chan E, Duan W, Koh HL, Zhou S (2005) Herb-drug interactions: a literature review. *Drugs* 65:1239–1282
136. Huber A, Dorn A, Witzmann A, Cervos-Navarro J (1993) Microthrombi formation after severe head trauma. *Int J Legal Med* 106:152–155
137. Hulka F, Mullins RJ, Frank EH (1996) Blunt brain injury activates the coagulation process. *Arch Surg* 131:923–927
138. Innerhofer P, Fries D, Margreiter J, Klingler A, Kuhbacher G, Wachter B, Oswald E, Salner E, Frischhut B, Schobersberger W (2002) The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. *Anesth Analg* 95:858–65
139. Iorio A, Agnelli G (2000) Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. *Arch Intern Med* 160:2327–2332
140. Izzo AA, Ernst E (2001) Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 61:2163–2175
141. Jackson WL Jr, Shorr AF (2005) Blood transfusion and the development of acute respiratory distress syndrome: more evidence that blood transfusion in the intensive care unit may not be benign. *Crit Care Med* 33:1420–1421
142. James DN, Fernandes JR, Calder I, Smith M (1997) Low-dose aspirin and intracranial surgery. A survey of the opinions of consultant neuroanaesthetists in the UK. *Anaesthesia* 52:169–172
143. Jamnicki M, Bombeli T, Seifert B, Zollinger A, Camenzind V, Pasch T, Spahn DR (2000) Low- and medium-molecular-weight hydroxyethyl starches: comparison of their effect on blood coagulation. *Anesthesiology* 93:1231–1237
144. Jellinek DA, Robin F (2000) Perioperative Care. In: Kaye Andrew H et al (eds) *Operative neurosurgery*. Churchill Livingstone, London, pp 15–32
145. Jones SB, Whitten CW, Despotis GJ, Monk TG (2003) The influence of crystalloid and colloid replacement solutions in acute normovolemic hemodilution: a preliminary survey of hemostatic markers. *Anesth Analg* 96:363–8
146. Kalabalikis P, Papazoglou K, Gouriotis D, Papadopoulos N, Kardara M, Papageorgiou F, Papadatos J (1999) Correlation between serum IL-6 and CRP levels and severity of head injury in children. *Intensive Care Med* 25:288–292
147. Kalfas IH, Little JR (1988) Postoperative hemorrhage: a survey of 4,992 intracranial procedures. *Neurosurgery* 23:343–347
148. Kapiotis S, Quehenberger P, Eichler HG, Schwarzinger I, Partan C, Schneider B, Lechner K, Speiser W (1994) Effect of hydroxyethyl starch on the activity of blood coagulation and fibrinolysis in healthy volunteers: comparison with albumin. *Crit Care Med* 22:606–612
149. Karadimov D, Binev K, Nachkov Y, Platikanov V (2003) Use of activated recombinant factor VII (NovoSeven) during neurosurgery. *J Neurosurg Anesthesiol* 15:330–332
150. Kaufman HH, Hui KS, Mattson JC, Borit A, Childs TL, Hoots WK, Bernstein DP, Makela ME, Wagner KA, Kahan BD (1984) Clinicopathological correlations of disseminated intravascular coagulation in patients with head injury. *Neurosurgery* 15:34–42
151. Kaufman HH, Moake JL, Olson JD, Miner ME, duCret RP, Pruessner JL, Gildenberg PL (1980) Delayed and recurrent intracranial hematomas related to disseminated intravascular clotting and fibrinolysis in head injury. *Neurosurgery* 7:445–449
152. Kaufmann JE, Vischer UM (2003) Cellular mechanisms of the hemostatic effects of desmopressin (DDAVP). *J Thromb Haemost* 1:682–689
153. Kaushal R, Bates DW, Franz C, Soukup JR, Rothschild JM (2007) Costs of adverse events in intensive care units. *Crit Care Med* 35:2479–2483
154. Kaw LL Jr, Coimbra R, Potenza BM, Garfin SR, Hoyt DB (2004) The use of recombinant factor VIIa for severe intractable bleeding during spine surgery. *Spine* 29:1384–1387
155. Kearney TJ, Benth L, Grode M, Lee S, Hiatt JR, Shabot MM (1992) Coagulopathy and catecholamines in severe head injury. *J Trauma* 32:608–611
156. Keimowitz RM, Annis BL (1973) Disseminated intravascular coagulation associated with massive brain injury. *J Neurosurg* 39:178–180
157. Kenet G, Walden R, Eldad A, Martinowitz U (1999) Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 354:1879
158. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O (2007) Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 131:1308–1314

159. Kis B, Szupera Z, Mezei Z, Gecse A, Telegdy G, Vecsei L (1999) Valproate treatment and platelet function: the role of arachidonate metabolites. *Epilepsia* 40:307–310
160. Kissela BM, Eckman MH (2008) Cost-effectiveness of recombinant factor VIIa for treatment of intracerebral hemorrhage. *BMC Neurol* 8:17
161. Kleindienst A, Harvey HB, Mater E, Bronst J, Flack J, Herenz K, Haupt WF, Schon R (2003) Early antithrombotic prophylaxis with low-molecular-weight heparin in neurosurgery. *Acta Neurochir (Wien)* 145:1085–1090
162. Knudson MM, Morabito D, Paiement GD, Shackelford S (1996) Use of low-molecular-weight heparin in preventing thromboembolism in trauma patients. *J Trauma* 41:446–459
163. Koizume S, Jin MS, Miyagi E, Hirahara F, Nakamura Y, Piao JH, Asai A, Yoshida A, Tsuchiya E, Ruf W, Miyagi Y (2006) Activation of cancer cell migration and invasion by ectopic synthesis of coagulation factor VII. *Cancer Res* 66:9453–9460
164. König SA, Schick U, Dohnert J, Goldammer A, Vitzthum HE (2003) Coagulopathy and outcome in patients with chronic subdural haematoma. *Acta Neurol Scand* 107:110–116
165. Koos W, Kraus H, Blumel G, Bock F (1970) Mode of action of proteinase inhibitors (Trasyolol) in intracranial hemorrhages. *Neurochirurgie* 16:548–550
166. Korinth MC (2006) Low-dose aspirin before intracranial surgery—results of a survey among neurosurgeons in Germany. *Acta Neurochir (Wien)* 148:1189–1196
167. Korinth MC, Gilsbach JM, Weinzierl MR. (2007) Low-dose aspirin before spinal surgery: results of a survey among neurosurgeons in Germany. *Eur Spine J* 16(3):365–372
168. Korte W (2006) Fibrin monomer and factor XIII: a new concept for unexplained intraoperative coagulopathy. *Hamostaseologie* 26:S30–S35
169. Koscielny J, Ziemer S, Radtke H, Schmutzler M, Pruss A, Sinha P, Salama A, Kiesewetter H, Latza R (2004) A practical concept for preoperative identification of patients with impaired primary hemostasis. *Clin Appl Thromb Hemost* 10:195–204
170. Kou J, Fischgrund J, Biddinger A, Herkowitz H (2002) Risk factors for spinal epidural hematoma after spinal surgery. *Spine* 27:1670–1673
171. Kozek-Langenecker SA (2005) Effects of hydroxyethyl starch solutions on hemostasis. *Anesthesiology* 103:654–660
172. Kreuz W, Linde R, Funk M, Meyer-Schrod R, Foll E, Nowak-Gottl U, Jacobi G, Vigh Z, Scharrer I (1992) Valproate therapy induces von Willebrand disease type I. *Epilepsia* 33:178–184
173. Kurtoglu M, Yanar H, Bilsel Y, Guloglu R, Kizilirmak S, Buyukkurt D, Granit V (2004) Venous thromboembolism prophylaxis after head and spinal trauma: intermittent pneumatic compression devices versus low-molecular-weight heparin. *World J Surg* 28:807–811
174. Kushimoto S, Shibata Y, Yamamoto Y (2003) Implications of fibrinogenolysis in patients with closed head injury. *J Neurotrauma* 20:357–363
175. Kushimoto S, Yamamoto Y, Shibata Y, Sato H, Koido Y (2001) Implications of excessive fibrinolysis and alpha(2)-plasmin inhibitor deficiency in patients with severe head injury. *Neurosurgery* 49:1084–1089
176. Kushimoto S, Yamamoto Y, Shibata Y, Sato H, Koido Y (2001) Implications of excessive fibrinolysis and alpha(2)-plasmin inhibitor deficiency in patients with severe head injury. *Neurosurgery* 49:1084–1089
177. Lackmann GM (2004) Valproic-acid-induced thrombocytopenia and hepatotoxicity: discontinuation of treatment? *Pharmacology* 70:57–58
178. Lang T, von DM (2006) Possibilities and limitations of thrombelastometry/-graphy. *Hamostaseologie* 26:S20–S29
179. Lankiewicz MW, Hays J, Friedman KD, Tinkoff G, Blatt PM (2006) Urgent reversal of warfarin with prothrombin complex concentrate. *J Thromb Haemost* 4:967–970
180. Lawton MT, Raudzens PA, Zabramski JM, Spetzler RF (1998) Hypothermic circulatory arrest in neurovascular surgery: evolving indications and predictors of patient outcome. *Neurosurgery* 43:10–20
181. Leithauer B, Zielske D, Seyfert UT, Jung F (2008) Effects of desmopressin on platelet membrane glycoproteins and platelet aggregation in volunteers on clopidogrel. *Clin Hemorheol Microcirc* 39:293–302
182. Levy JH (2006) Massive transfusion coagulopathy. *Semin Hematol* 43:S59–S63
183. Levy JH, Fingerhut A, Brott T, Langbakke IH, Erhardtson E, Porte RJ (2006) Recombinant factor VIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury: review of safety profile. *Transfusion* 46:919–933
184. Lier H, Kampe S, Schroder S (2007) Prerequisites of a functional haemostasis. What must be considered at the scene of an accident, in the emergency room and during an operation? *Anaesthesist* 56:239–251
185. Lillcrap D, Nair SC, Srivastava A, Rodeghiero F, Pabinger I, Federici AB (2006) Laboratory issues in bleeding disorders. *Haemophilia* 12(Suppl 3):68–75
186. Lin J, Hanigan WC, Tarantino M, Wang J (2003) The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. *J Neurosurg* 98:737–740
187. Lisman T, Leebeek FW, Meijer K, van der MJ, Nieuwenhuis HK, de Groot PG (2002) Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology* 35:616–621
188. Lodge JP, Jonas S, Jones RM, Olausson M, Mir-Pallardo J, Soefelt S, Garcia-Valdecasas JC, McAlister V, Mirza DF (2005) Efficacy and safety of repeated perioperative doses of recombinant factor VIIa in liver transplantation. *Liver Transpl* 11:973–979
189. Lorenz R, Kienast J, Otto U, Egger K, Kiehl M, Schreiter D, Kwasny H, Haertel S, Barthels M (2003) Efficacy and safety of a prothrombin complex concentrate with two virus-inactivation steps in patients with severe liver damage. *Eur J Gastroenterol Hepatol* 15:15–20
190. Lorenz R, Kienast J, Otto U, Kiehl M, Schreiter D, Haertel S, Barthels M (2007) Successful emergency reversal of phenprocoumon anticoagulation with prothrombin complex concentrate: a prospective clinical study. *Blood Coagul Fibrinolysis* 18:565–570
191. Lubetsky A, Hoffman R, Zimlichman R, Eldor A, Zvi J, Kostenko V, Brenner B (2004) Efficacy and safety of a prothrombin complex concentrate (Octaplex) for rapid reversal of oral anticoagulation. *Thromb Res* 113:371–378
192. Luxembourg B, Krause M, Lindhoff-Last E (2007) Blood clotting disorders. *Deutsches Ärzteblatt* 104:1489–1498
193. Lyseng-Williamson KA, Plosker GL (2007) Recombinant factor VIIa (eptacog alfa): a pharmacoeconomic review of its use in haemophilia in patients with inhibitors to clotting factors VIII or IX. *Pharmacoeconomics* 25:1007–1029
194. Macdonald RL, Amidei C, Baron J, Weir B, Brown F, Erickson RK, Hekmatpanah J, Frim D (2003) Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. *Surg Neurol* 59:363–372

195. Macdonald RL, Amidei C, Lin G, Munshi I, Baron J, Weir BK, Brown F, Erickson RK, Hekmatpanah J (1999) Safety of perioperative subcutaneous heparin for prophylaxis of venous thromboembolism in patients undergoing craniotomy. *Neurosurgery* 45:245–251
196. Macik BG, Lindley CM, Lusher J, Sawyer WT, Bloom AL, Harrison JF, Baird-Cox K, Birch K, Glazer S, Roberts HR (1993) Safety and initial clinical efficacy of three dose levels of recombinant activated factor VII (rFVIIa): results of a phase I study. *Blood Coagul Fibrinolysis* 4:521–527
197. MacLennan S, Williamson LM (2006) Risks of fresh-frozen plasma and platelets. *J Trauma* 60:S46–S50
198. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF (1997) Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh-frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost* 77:477–480
199. Malham GM, Souter MJ (2001) Systemic inflammatory response syndrome and acute neurological disease. *Br J Neurosurg* 15:381–387
200. Mangano DT, Rieves RD, Weiss KD (2006) Judging the safety of aprotinin. *N Engl J Med* 355:2261–2262
201. Mangano DT, Tudor IC, Dietzel C (2006) The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 354:353–365
202. Martini WZ, Pusateri AE, Uscilowicz JM, Delgado AV, Holcomb JB (2005) Independent contributions of hypothermia and acidosis to coagulopathy in swine. *J Trauma* 58:1002–1009
203. Martinowitz U, Michaelson M (2005) Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 3:640–648
204. May AK, Young JS, Butler K, Bassam D, Brady W (1997) Coagulopathy in severe closed head injury: is empiric therapy warranted? *Am Surg* 63:233–236
205. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T (2005) Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 352:777–785
206. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T (2008) Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 358:2127–2137
207. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T (2005) Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke* 36:74–79
208. Mazer CD, Leong-Poi H, Mahoney J, Latter D, Strauss BH, Teitel JM (2007) Vascular injury and thrombotic potential: a note of caution about recombinant factor VIIa. *Semin Cardiothorac Vasc Anesth* 11:261–264
209. McLoughlin TM, Fontana JL, Alving B, Mongan PD, Bunger R (1996) Profound normovolemic hemodilution: hemostatic effects in patients and in a porcine model. *Anesth Analg* 83:459–465
210. Merriman E, Bell W, Long DM (1979) Surgical postoperative bleeding associated with aspirin ingestion. Report of two cases. *J Neurosurg* 50:682–684
211. Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P (2007) Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. *Anesth Analg* 105:905–17
212. Monroe DM, Hoffman M, Roberts HR (2002) Platelets and thrombin generation. *Arterioscler Thromb Vasc Biol* 22:1381–1389
213. Morenski JD, Tobias JD, Jimenez DF (2003) Recombinant activated factor VII for cerebral injury-induced coagulopathy in pediatric patients. Report of three cases and review of the literature. *J Neurosurg* 98:611–616
214. Munro J, Booth A, Nicholl J (1997) Routine preoperative testing: a systematic review of the evidence. *Health Technol Assess* 1:i–iv
215. Nakau H, Maruishi M, Takiguchi H, Shima K (1998) Successful surgical removal of a large arteriovenous malformation in a patient with hemophilia: case report. *Neurosurgery* 43:1459–1461
216. Neilipovitz DT (2004) Tranexamic acid for major spinal surgery. *Eur Spine J* 13(Suppl 1):S62–S65
217. Nekludov M, Bellander BM, Blomback M, Wallen HN (2007) Platelet dysfunction in patients with severe traumatic brain injury. *J Neurotrauma* 24:1699–1706
218. Niemi T, Tanskanen P, Taxell C, Juvela S, Randell T, Rosenberg P (1999) Effects of nonsteroidal anti-inflammatory drugs on hemostasis in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 11:188–194
219. Ninchoji T, Uemura K, Shimoyama I, Hinokuma K, Bun T, Nakajima S (1984) Traumatic intracerebral haematomas of delayed onset. *Acta Neurochir (Wien)* 71:69–90
220. Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d’Azemar P, Buller HR, ten Cate JW, Hoek JA, van der MJ, van der HC, Turpie AG, Haley S, Sicurella A, Gent M (1996) low-molecular-weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. *Thromb Haemost* 75:233–238
221. O’Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM (2006) Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 295:293–298
222. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, Gravori T, Obukhov D, McBride DQ, Martin NA (2002) Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *J Neurosurg* 96:109–116
223. Olson JD, Kaufman HH, Moake J, O’Gorman TW, Hoots K, Wagner K, Brown CK, Gildenberg PL (1989) The incidence and significance of hemostatic abnormalities in patients with head injuries. *Neurosurgery* 24:825–832
224. Ostermann H, Haertel S, Knaub S, Kalina U, Jung K, Pabinger I (2007) Pharmacokinetics of Beriplex P/N prothrombin complex concentrate in healthy volunteers. *Thromb Haemost* 98:790–797
225. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H (2008) Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. *J Thromb Haemost* 6:622–631
226. Palmer JD, Francis DA, Roath OS, Francis JL, Iannotti F (1995) Hyperfibrinolysis during intracranial surgery: effect of high dose aprotinin. *J Neurol Neurosurg Psychiatry* 58:104–106
227. Palmer JD, Francis JL, Pickard JD, Iannotti F (2003) The efficacy and safety of aprotinin for hemostasis during intracranial surgery. *J Neurosurg* 98:1208–1216
228. Palmer JD, Sparrow OC, Iannotti F (1994) Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. *Neurosurgery* 35:1061–1064
229. Parameswaran R, Shapiro AD, Gill JC, Kessler CM (2005) Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 11:100–106
230. Park P, Fewel ME, Garton HJ, Thompson BG, Hoff JT (2003) Recombinant activated factor VII for the rapid correction of coagulopathy in nonhemophilic neurosurgical patients. *Neurosurgery* 53:34–38

231. Pathak A, Dutta S, Marwaha N, Singh D, Varma N, Mathuriya SN (2005) Change in tissue thromboplastin content of brain following trauma. *Neurol India* 53:178–182
232. Pernod G, Barro C, Arnutti B, Blanc-Jouvan F, Garrel S, Kahn P, Minotti L, Koudsie A, Benabid AL, Wroblewski I, Joannard A, Polack B (2003) Surgery in severe factor XIII deficiency: report of a case of epilepsy neurosurgery and review. *Haemophilia* 9:121–124
233. Pfanner G, Koscielny J, Pernerstorfer T, Gutl M, Perger P, Fries D, Hofmann N, Innerhofer P, Kneifl W, Neuner L, Schochl H, Kozek-Langenecker SA (2007) Preoperative evaluation of the bleeding history. Recommendations of the working group on perioperative coagulation of the Austrian Society for Anaesthesia, Resuscitation and Intensive Care. *Anaesthesist* 56:604–611
234. Pickard JD, Kirkpatrick PJ, Melsen T, Andreasen RB, Gelling L, Fryer T, Matthews J, Minhas P, Hutchinson PJ, Menon D, Downey SP, Kendall I, Clark J, Carpenter TA, Williams E, Persson L (2000) Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. *Blood Coagul Fibrinolysis* 11(Suppl 1):S117–20 S117–S120
235. Pick J, Chesnut RM, Marshall LF, Berkum-Clark M, Klauber MR, Blunt BA, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA (1992) Extracranial complications of severe head injury. *J Neurosurg* 77:901–907
236. Planinsic RM, van der MJ, Testa G, Grande L, Candela A, Porte RJ, Ghobrial RM, Isoniemi H, Schelde PB, Erhardtens E, Klintmalm G, Emre S (2005) Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease. *Liver Transpl* 11:895–900
237. Pohlmann-Eden B, Peters CN, Wennberg R, Dempfle CE (2003) Valproate induces reversible factor XIII deficiency with risk of perioperative bleeding. *Acta Neurol Scand* 108:142–145
238. Pondaag W (1979) Disseminated intravascular coagulation related to outcome in head injury. *Acta Neurochir Suppl (Wien)* 28:98–102
239. Powner DJ, Hartwell EA, Hoots WK (2005) Counteracting the effects of anticoagulants and antiplatelet agents during neurosurgical emergencies. *Neurosurgery* 57:823–831
240. Prasad KS, Sharma BS, Marwaha N, Sarode RS, Kak VK (1994) Haemostatic derangement in patients with intracranial tumours. *Br J Neurosurg* 8:695–702
241. Preston FE, Laidlaw ST, Sampson B, Kitchen S (2002) Rapid reversal of oral anticoagulation with warfarin by a prothrombin complex concentrate (Beriplex): efficacy and safety in 42 patients. *Br J Haematol* 116:619–624
242. Raabe A, Beck J, Keller M, Vatter H, Zimmermann M, Seifert V (2005) Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg* 103:974–981
243. Raabe A, Gerlach R, Zimmermann M, Seifert V (2000) Practice of perioperative thromboembolic prophylaxis in neurosurgery: results of a German survey. *Zentralbl Neurochir* 61:103–110
244. Raabe A, Gerlach R, Zimmermann M, Seifert V (2001) The risk of haemorrhage associated with early postoperative heparin administration after intracranial surgery. *Acta Neurochir (Wien)* 143:1–7
245. Ranucci M, Isgro G, Soro G, Conti D, De TB (2008) Efficacy and safety of recombinant activated factor vii in major surgical procedures: systematic review and meta-analysis of randomized clinical trials. *Arch Surg* 143:296–304
246. Rao JS, Rayford A, Morantz RA, Festoff BW, Sawaya R (1993) Increased levels of plasminogen activator inhibitor-1 (PAI-1) in human brain tumors. *J Neurooncol* 17:215–221
247. Rebullá P (2001) Platelet transfusion trigger in difficult patients. *Transfus Clin Biol* 8:249–254
248. Reinhofer M, Brauer M, Franke U, Barz D, Marx G, Losche W (2008) The value of rotation thromboelastometry to monitor disturbed perioperative haemostasis and bleeding risk in patients with cardiopulmonary bypass. *Blood Coagul Fibrinolysis* 19:212–219
249. Resnick DK, Marion DW, Darby JM (1994) The effect of hypothermia on the incidence of delayed traumatic intracerebral hemorrhage. *Neurosurgery* 34:252–255
250. Reymond MA, Marbet G, Radu EW, Gratzl O (1992) Aspirin as a risk factor for hemorrhage in patients with head injuries. *Neurosurg Rev* 15:21–25
251. Richards PG, Marath A, Edwards JM, Lincoln C (1987) Management of difficult intracranial aneurysms by deep hypothermia and elective cardiac arrest using cardiopulmonary bypass. *Br J Neurosurg* 1:261–269
252. Riess HB, Meier-Hellmann A, Motsch J, Elias M, Kursten FW, Dempfle CE (2007) Prothrombin complex concentrate (Octaplex) in patients requiring immediate reversal of oral anticoagulation. *Thromb Res* 121:9–16
253. Rizoli SB (2003) Crystalloids and colloids in trauma resuscitation: a brief overview of the current debate. *J Trauma* 54:S82–S88
254. Rodas RA, Fenstermaker RA, McKeever PE, Blaivas M, Dickinson LD, Papadopoulos SM, Hoff JT, Hopkins LN, Duffy-Fronckowiak M, Greenberg HS (1998) Correlation of intraluminal thrombosis in brain tumor vessels with postoperative thrombotic complications: a preliminary report. *J Neurosurg* 89:200–205
255. Rodeghiero F, Castaman G (2005) Treatment of von Willebrand disease. *Semin Hematol* 42:29–35
256. Roitberg B, Emechebe-Kennedy O, Amin-Hanjani S, Mucksavage J, Tesoro E (2005) Human recombinant factor VII for emergency reversal of coagulopathy in neurosurgical patients: a retrospective comparative study. *Neurosurgery* 57:832–836
257. Rong Y, Durden DL, Van Meir EG, Brat DJ (2006) 'Pseudopalisading' necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis. *J Neuropathol Exp Neurol* 65:529–539
258. Rong Y, Hu F, Huang R, Mackman N, Horowitz JM, Jensen RL, Durden DL, Van Meir EG, Brat DJ (2006) Early growth response gene-1 regulates hypoxia-induced expression of tissue factor in glioblastoma multiforme through hypoxia-inducible factor-1-independent mechanisms. *Cancer Res* 66:7067–7074
259. Saito N, Yamazaki M, Kobayashi S, Teramoto A (2006) Resection of arteriovenous malformation in a patient with hemophilia type A. *Neurol Med Chir (Tokyo)* 46:191–193
260. Samama CM (2004) Aprotinin and major orthopedic surgery. *Eur Spine J* 13(Suppl 1):S56–S61
261. Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF (2005) Perioperative platelet transfusion: recommendations of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) 2003. *Can J Anaesth* 52:30–37
262. Sawaya R, Cummins CJ, Kornblith PL (1984) Brain tumors and plasmin inhibitors. *Neurosurgery* 15:795–800
263. Sawaya R, Ramo OJ, Glas-Greenwalt P, Wu SZ (1991) Plasma fibrinolytic profile in patients with brain tumors. *Thromb Haemost* 65:15–19
264. Sawaya R, Zuccarello M, Elkalliny M, Nishiyama H (1992) Postoperative venous thromboembolism and brain tumors: Part I. Clinical profile. *J Neurooncol* 14:119–125
265. Scharbert G, Gebhardt K, Sow Z, Duris M, Deusch E, Kozek-Langenecker S (2007) Point-of-care platelet function tests: detection of platelet inhibition induced by nonopioid analgesic drugs. *Blood Coagul Fibrinolysis* 18:775–780
266. Schuster R, Waxman K (2005) Is repeated head computed tomography necessary for traumatic intracranial hemorrhage? *Am Surg* 71:701–704
267. Sciacca FL, Ciusani E, Silvani A, Corsini E, Frigerio S, Pogliani S, Parati E, Croci D, Boiardi A, Salmaggi A (2004) Genetic and

- plasma markers of venous thromboembolism in patients with high grade glioma. *Clin Cancer Res* 10:1312–1317
268. Selladurai BM, Vickneswaran M, Duraisamy S, Atan M (1997) Coagulopathy in acute head injury—a study of its role as a prognostic indicator. *Br J Neurosurg* 11:398–404
  269. Semrad TJ, O'Donnell R, Wun T, Chew H, Harvey D, Zhou H, White RH (2007) Epidemiology of venous thromboembolism in 9,489 patients with malignant glioma. *J Neurosurg* 106:601–608
  270. Serdaroglu G, Tutuncuoglu S, Kavakli K, Tekgul H (2002) Coagulation abnormalities and acquired von Willebrand's disease type 1 in children receiving valproic acid. *J Child Neurol* 17:41–43
  271. Seremetis S (2003) Dose optimization of recombinant factor VIIa in the treatment of acute bleeding in haemophilia-associated inhibitors. *Blood Coagul Fibrinolysis* 14(Suppl 1):S29–S30
  272. Shander A (2007) Financial and clinical outcomes associated with surgical bleeding complications. *Surgery* 142:S20–S25
  273. Shander A, Hofmann A, Gombotz H, Theusinger OM, Spahn DR (2007) Estimating the cost of blood: past, present, and future directions. *Best Pract Res Clin Anaesthesiol* 21:271–289
  274. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA (1998) Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 80:773–778
  275. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA (1999) Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 88:312–319
  276. Singbartl K, Innerhofer P, Radvan J, Westphalen B, Fries D, Stogbauer R, Van AH (2003) Hemostasis and hemodilution: a quantitative mathematical guide for clinical practice. *Anesth Analg* 96:929–935
  277. Singh VP, Jain D, Mohan R, Bhatia R, Bhargava M (1990) Haemostatic abnormalities in brain tumours. *Acta Neurochir (Wien)* 102:103–107
  278. Smith SF, Simpson JM, Sekhon LH (2004) Prophylaxis for deep venous thrombosis in neurosurgical oncology: review of 2779 admissions over a 9-year period. *Neurosurg Focus* 17:E4
  279. Sorensen B, Ingerslev J (2004) Thromboelastography and recombinant factor VIIa-hemophilia and beyond. *Semin Hematol* 41:140–144
  280. Sorensen B, Ingerslev J (2005) Tailoring haemostatic treatment to patient requirements—an update on monitoring haemostatic response using thrombelastography. *Haemophilia* 11(Suppl 1):1–6
  281. Sorensen B, Ingerslev J (2006) A direct thrombin inhibitor studied by dynamic whole blood clot formation. Haemostatic response to ex-vivo addition of recombinant factor VIIa or activated prothrombin complex concentrate. *Thromb Haemost* 96:446–453
  282. Sorensen B, Johansen P, Nielsen GL, Sorensen JC, Ingerslev J (2003) Reversal of the international normalized ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. *Blood Coagul Fibrinolysis* 14:469–477
  283. Sorimachi T, Fujii Y, Morita K, Tanaka R (2005) Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage. *Neurosurgery* 57:837–844
  284. Spahn DR, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Gordini G, Stahel PF, Hunt BJ, Komadina R, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R (2007) Management of bleeding following major trauma: a European guideline. *Crit Care* 11:R17
  285. Spahn DR, Rossaint R (2005) Coagulopathy and blood component transfusion in trauma. *Br J Anaesth* 95:130–139
  286. Spalding GJ, Hartrumpf M, Sierig T, Oesberg N, Kirschke CG, Albes JM (2007) Cost reduction of perioperative coagulation management in cardiac surgery: value of “bedside” thrombelastography (ROTEM). *Eur J Cardiothorac Surg* 31:1052–1057
  287. Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S, Murkin J, Nadel A (2004) Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. *Transfusion* 44:1143–1148
  288. Squizzato A, Ageno W (2007) Recombinant activated factor VII as a general haemostatic agent: evidence-based efficacy and safety. *Current Drug Safety* 2:155–161
  289. Stanworth SJ (2007) The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. *Hematology Am Soc Hematol Educ Program* 2007:179–186
  290. Stanworth SJ, Birchall J, Doree CJ, Hyde C (2007) Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev*: CD005011
  291. Stanworth SJ, Brunskill SJ, Hyde CJ, McClelland DB, Murphy MF (2004) Is fresh-frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 126:139–152
  292. Steen CK, Astermark J, Donfield S, Berntorp E (2008) Cost and outcome: comparisons of two alternative bypassing agents for persons with haemophilia A complicated by an inhibitor. *Thromb Haemost* 99:1060–1067
  293. Stein SC, Chen XH, Sinson GP, Smith DH (2002) Intravascular coagulation: a major secondary insult in nonfatal traumatic brain injury. *J Neurosurg* 97:1373–1377
  294. Stein SC, Graham DI, Chen XH, Smith DH (2004) Association between intravascular microthrombosis and cerebral ischemia in traumatic brain injury. *Neurosurgery* 54:687–691
  295. Stein SC, Smith DH (2004) Coagulopathy in traumatic brain injury. *Neurocrit Care* 1:479–488
  296. Stein SC, Smith DH (2004) Coagulopathy in traumatic brain injury. *Neurocrit Care* 1:479–488
  297. Stein SC, Spettell C, Young G, Ross SE (1993) Delayed and progressive brain injury in closed-head trauma: radiological demonstration. *Neurosurgery* 32:25–30
  298. Stein SC, Spettell CM (1995) Delayed and progressive brain injury in children and adolescents with head trauma. *Pediatr Neurosurg* 23:299–304
  299. Stein SC, Young GS, Talucci RC, Greenbaum BH, Ross SE (1992) Delayed brain injury after head trauma: significance of coagulopathy. *Neurosurgery* 30:160–165
  300. Steiner ME, Despotis GJ (2007) Transfusion algorithms and how they apply to blood conservation: the high-risk cardiac surgical patient. *Hematol Oncol Clin North Am* 21:177–184
  301. Stephens PH, Healy MT, Smith M, Jewkes DA (1995) Prophylaxis against thromboembolism in neurosurgical patients: a survey of current practice in the United Kingdom. *Br J Neurosurg* 9:159–163
  302. Stratmann G, Russell IA, Merrick SH (2003) Use of recombinant factor VIIa as a rescue treatment for intractable bleeding following repeat aortic arch repair. *Ann Thorac Surg* 76:2094–2097
  303. Sugg RM, Gonzales NR, Matherne DE, Ribo M, Shaltoni HM, Baraniuk S, Noser EA, Grotta JC (2006) Myocardial injury in patients with intracerebral hemorrhage treated with recombinant factor VIIa. *Neurology* 67:1053–1055
  304. Taketomi T, Szlam F, Levy JH, Tanaka KA (2008) Warfarin reversal with prothrombin complex concentrate confers better antifibrinolytic activity compared with recombinant activated factor VII. *Blood Coagul Fibrinolysis* 19:106–108
  305. Tanaka KA, Szlam F, Dickneite G, Levy JH (2008) Effects of prothrombin complex concentrate and recombinant activated factor VII on vitamin K antagonist induced anticoagulation. *Thromb Res* 122:117–123
  306. Tanaka KA, Taketomi T, Szlam F, Calatzis A, Levy JH (2008) Improved clot formation by combined administration of activat-

- ed factor VII (NovoSeven) and fibrinogen (Haemocomplettan P). *Anesth Analg* 106:732–8
307. Taylor WA, Thomas NW, Wellings JA, Bell BA (1995) Timing of postoperative intracranial hematoma development and implications for the best use of neurosurgical intensive care [see comments]. *J Neurosurg* 82:48–50
  308. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B (1998) Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *J Neurotrauma* 15:587–597
  309. Teich M, Longin E, Dempfle CE, Konig S (2004) Factor XIII deficiency associated with valproate treatment. *Epilepsia* 45:187–189
  310. Thoron L, Arbit E (1994) Hemostatic changes in patients with brain tumors. *J Neurooncol* 22:87–100
  311. Toth O, Calatzis A, Penz S, Losonczy H, Siess W (2006) Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. *Thromb Haemost* 96:781–788
  312. Treib J, Haass A, Pindur G (1997) Coagulation disorders caused by hydroxyethyl starch. *Thromb Haemost* 78:974–983
  313. Treib J, Haass A, Pindur G, Grauer MT, Jung F, Wenzel E, Schimrigk K (1997) Increased haemorrhagic risk after repeated infusion of highly substituted medium molecular weight hydroxyethyl starch. *Arzneimittelforschung* 47:18–22
  314. Treib J, Haass A, Pindur G, Grauer MT, Treib W, Wenzel E, Schimrigk K (1996) Influence of low and medium molecular weight hydroxyethyl starch on platelets during a long-term hemodilution in patients with cerebrovascular diseases. *Arzneimittelforschung* 46:1064–1066
  315. Treib J, Haass A, Pindur G, Grauer MT, Wenzel E, Schimrigk K (1996) Decrease of fibronectin following repeated infusion of highly substituted hydroxyethyl starch. *Infusionsther Transfusionsmed* 23:71–75
  316. Treib J, Haass A, Pindur G, Miyachita C, Grauer MT, Jung F, Wenzel E, Schimrigk K (1996) Highly substituted hydroxyethyl starch (HES200/0.62) leads to Type-I von Willebrand syndrome after repeated administration. *Haemostasis* 26:210–213
  317. Treib J, Haass A, Pindur G, Treib W, Wenzel E, Schimrigk K (1996) Influence of intravascular molecular weight of hydroxyethyl starch on platelets. *Eur J Haematol* 56:168–172
  318. Trowbridge CC, Stammers AH, Ciccarelli N, Klayman M (2006) Dose titration of recombinant factor VIIa using thromboelastograph monitoring in a child with hemophilia and high titer inhibitors to factor VIII: a case report and brief review. *J Extra Corpor Technol* 38:254–259
  319. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J (1989) Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 149:679–681
  320. Ucar HI, Oc M, Tok M, Dogan OF, Oc B, Aydin A, Farsak B, Guvener M, Yorgancioglu AG, Dogan R, Demircin M, Pasaoglu I (2007) Preoperative fibrinogen levels as a predictor of postoperative bleeding after open heart surgery. *Heart Surg Forum* 10:E392–E396
  321. Utter GH, Owings JT, Jacoby RC, Gosselin RC, Paglieroni TG (2002) Injury induces increased monocyte expression of tissue factor: factors associated with head injury attenuate the injury-related monocyte expression of tissue factor. *J Trauma* 52:1071–1077
  322. van der Sande JJ, Veltkamp JJ, Boekhout-Mussert RJ, Bouwhuis-Hoogerwerf ML (1978) Head injury and coagulation disorders. *J Neurosurg* 49:357–365
  323. Vavilala MS, Dunbar PJ, Rivara FP, Lam AM (2001) Coagulopathy predicts poor outcome following head injury in children less than 16 years of age. *J Neurosurg Anesthesiol* 13:13–18
  324. Vecht CJ, Sibinga CT, Minderhoud JM (1975) Disseminated intravascular coagulation and head injury. *J Neurol Neurosurg Psychiatry* 38:567–571
  325. Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, Klima G, Martinowitz U, Fries D (2007) The effect of fibrinogen concentrate on thrombocytopenia. *J Thromb Haemost* 5:1019–1025
  326. Veshchev I, Elran H, Salame K (2002) Recombinant coagulation factor VIIa for rapid preoperative correction of warfarin-related coagulopathy in patients with acute subdural hematoma. *Med Sci Monit* 8:CS98–100
  327. Vigue B, Ract C, Tremey B, Engrand N, Leblanc PE, Decaux A, Martin L, Benhamou D (2007) Ultra-rapid management of oral anticoagulant therapy-related surgical intracranial hemorrhage. *Intensive Care Med* 33:721–725
  328. Wallis JP, Dzik S (2004) Is fresh-frozen plasma overtransfused in the United States? *Transfusion* 44:1674–1675
  329. Weber AA, Adamzik M, Bachmann HS, Gorlinger K, Grandoch M, Leineweber K, Muller-Beissenhirtz H, Wenzel F, Naber C (2008) Methods to evaluate the pharmacology of oral antiplatelet drugs. *Herz* 33:287–296
  330. Weber CF, Jambor C, Marquardt M, Gorlinger K, Zwissler B (2008) Thrombelastometric detection of factor XIII deficiency. *Anaesthesist* 57:487–490
  331. Wen DY, Hall WA (1998) Complications of subcutaneous low-dose heparin therapy in neurosurgical patients. *Surg Neurol* 50:521–525
  332. Wettstein P, Haeberli A, Stutz M, Rohner M, Corbetta C, Gabi K, Schnider T, Korte W (2004) Decreased factor XIII availability for thrombin and early loss of clot firmness in patients with unexplained intraoperative bleeding. *Anesth Analg* 99:1564–1569
  333. Yamaki T, Hirakawa K, Ueguchi T, Tenjin H, Kuboyama T, Nakagawa Y (1990) Chronological evaluation of acute traumatic intracerebral haematoma. *Acta Neurochir (Wien)* 103:112–115
  334. Yokota H, Naoe Y, Nakabayashi M, Unemoto K, Kushimoto S, Kurokawa A, Node Y, Yamamoto Y (2002) Cerebral endothelial injury in severe head injury: the significance of measurements of serum thrombomodulin and the von Willebrand factor. *J Neurotrauma* 19:1007–1015
  335. Zetterling M, Ronne-Engstrom E (2004) High intraoperative blood loss may be a risk factor for postoperative hematoma. *J Neurosurg Anesthesiol* 16:151–155

## Comment

This is a major and very up-to-date overview about hemostatic and hemorrhagic disorders and problems encountered in neurosurgical disease and procedures. It also covers very nicely the postoperative problems, for example in the ICU, and gives clues for preoperative easy evaluation. It may turn out to become a very valuable reference paper in neurosurgical wards, with guidelines highlighted on plastic cards for daily use. Very recent developments are also covered, like the use of rF VII, including costs and cost-effectiveness. The authors give strong arguments for the routine use of modern test equipment like the ROTEM and the Multiplate test. In the subchapters, the reader can find all the necessary information on most if not all details one should like to know about specific situations. The bottom line is: the variety in the clotting and its disturbances is large, and the right tests should be used for the right things. Recommendable, especially for the education and training of residents, and not only in neurosurgery!

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