Acta Neurochir (Wien) (2008) 150: 165–175
DOI 10.1007/s00701-007-1475-8
Printed in The Netherlands

Acta Neurochirurgica

Review Article

Coagulation disorders after traumatic brain injury

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Received 10 April 2007; Accepted 1 October 2007; Published online 2 January 2008

Summary

Background. Over the past decade new insights in our understanding of coagulation have identified the prominent role of tissue factor. The brain is rich in tissue factor, and injury to the brain may initiate disturbances in local and systemic coagulation. We aimed to review the current knowledge on the pathophysiology, incidence, nature, prognosis and treatment of coagulation disorders following traumatic brain injury (TBI).

Methods. We performed a MEDLINE search from 1966 to April 2007 with various MESH headings, focusing on head trauma and coagulopathy. We identified 441 eligible English language studies. These were reviewed for relevance by two independent investigators. A meta-analysis was performed to calculate the frequencies of coagulopathy after TBI and to determine the association of coagulopathy and outcome, expressed as odds ratios.

Results. Eighty-two studies were relevant for the purpose of this review. Meta-analysis of 34 studies reporting the frequencies of coagulopathy after TBI, showed an overall prevalence of 32.7%. The presence of coagulopathy after TBI was related both to mortality (OR 9.0; 95%CI: 7.3–11.6) and unfavourable outcome (OR 36.3; 95%CI: 18.7–70.5).

Conclusions. We conclude that coagulopathy following traumatic brain injury is an important independent risk factor related to prognosis. Routine determination of the coagulation status should therefore be performed in all patients with traumatic brain injury. These data may have important implications in patient management. Well-performed prospective clinical trials should be undertaken as a priority to determine the beneficial effects of early treatment of coagulopathy.

Keywords: DIC; coagulopathy; meta-analysis; prognosis; review; treatment; traumatic brain injury; head trauma.

Introduction

Disturbances of the haemostatic mechanism are highly relevant in traumatic brain injury (TBI). Micro-haemorrhages occur frequently in the brain parenchyma and a normal coagulation status is important to prevent progression of these to larger haematomas. Haemorrhage is a major cause of in-hospital mortality in patients with TBI [83]. Coagulation abnormalities are not only a result from injury, but may also cause further secondary injury. Coagulation disorders in TBI are complex and can be characterised by a combination of coagulopathy and hypercoagulability. Hypercoagulability is the increased capacity of formation of fibrin in the blood vessels. A hypercoagulable state may be generalised in the case of disseminated intravascular coagulation (DIC) or local with the development of microthrombi in the pen-

All authors were involved in writing the review.

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umbra of a contusion. DIC is characterised by the widespread activation of coagulation, which results in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels [56, 57, 65]. In this review coagulopathy is defined as any coagulation abnormality in TBI as defined by the different criteria of the various studies. Coagulopathy may result from depletion of platelets and clotting factors following blood loss or consumption due to DIC, and may further be enhanced by dilution, acidosis and hypothermia [6]. The resulting disorders of the coagulation status may invoke both bleeding and ischaemia. Many studies have shown progression of parenchymal lesions, particularly in patients with coagulopathy [21, 90, 92–94, 97]. Moreover, the presence of coagulation abnormalities is related to poorer outcome [66, 69, 87]. Disorders of coagulation may be amenable to treatment, and adequate and prompt intervention may prevent secondary complications and poorer outcome [61]. The aim of this review is to summarise the current literature on pathophysiology, incidence, nature, prognosis and treatment of coagulation disorders following TBI.

Pathogenesis of coagulation disorders in TBI

In healthy individuals, coagulation and fibrinolysis are balanced to prevent excessive haemorrhage or thrombosis [15, 56, 71, 79]. Patients with traumatic brain injury (TBI) are at risk of developing abnormalities of both coagulation and fibrinolysis [43, 76, 85, 101, 105]. The nature of the coagulation abnormalities differs between patients with isolated head injury and patients with multiple injuries. There is evidence that the extent of traumatised brain tissue, rather than traumatic shock or hypoxia, plays an important role in the occurrence of coagulation disorders after TBI [85]. In the early seventies, the release of tissue factor (TF), formerly called thromboplastin or thrombokinase [11], from injured brain tissue was postulated as the cause [49]. Tissue factor is a protein present in subendothelial tissue, platelets, and leukocytes necessary for the initiation of the coagulation cascade that eventually leads to thrombin formation from the zymogen prothrombin. TF is the main physiological initiator of coagulation [35] and its release therefore can also activate the coagulation system excessively in patients with head trauma. It is suggested that this activation depends on the amount of TF released from damage to brain tissue [7, 39, 49, 73]. Recently, Gando and co-workers [33] demonstrated higher levels of TF in head injured patients than in non-head-injured trauma patients. However, this concerns plasma levels of soluble tissue factor antigen and it is yet unclear what these levels mean and its function is totally unknown. In addition, Pathak and co-workers [73] demonstrated increased TF activity in patients with TBI as compared to controls, highlighting the role of TF in coagulation disorders following TBI. Early exposure of TF to both factor VII and VIIa results in the FVIIa/TF complex. This complex forms and generates small amounts of factor Xa and factor IXa. Factor Xa in collaboration with the membrane surface activates a small amount of prothrombin to thrombin. The generation of trace amounts of thrombin will activate platelets and factors V and VIII, that will thereby provide a suitable surface on which the prothrombinase complex can be assembled and which will lead to much more thrombin generation, required for the conversion of fibrinogen to fibrin [55, 58]. This tissue factor-dependent activation of coagulation, formerly known as the extrinsic pathway, causes both micro- and macrovascular fibrin thrombi

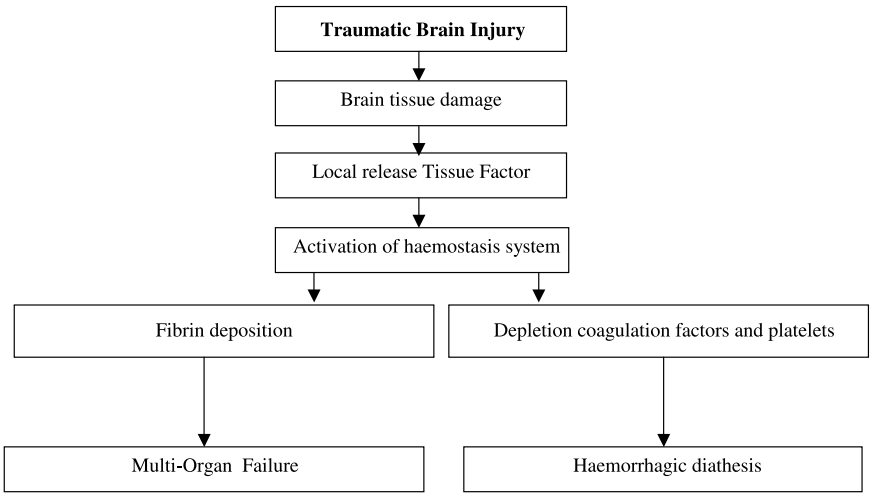

Fig. 1. Schematic diagram of traumatic brain injury and coagulopathy

formation. Control mechanisms, including tissue factor pathway inhibitor (TFPI), the protein C system, antithrombin and glycosamineglycans are active to counter fibrin formation and to localise fibrin formation to the site of injury, but are frequently insufficient after extensive TF exposure. DIC, instigated by TF activation, inhibits these antithrombotic mechanisms through cytokine release and upregulation causing defective physiological anticoagulation pathways. This may cause necrosis and haemorrhage in many organs, eventually leading to multi organ failure (MOF) [45, 56, 57, 63, 79, 104]. Current concepts of haemostasis and DIC, far beyond the scope of this review, were recently reviewed [56, 58, 79]. A schematic diagram of the proposed mechanism of coagulation disorders following TBI is shown in Fig. 1.

Various studies have confirmed a correlation between the presence of coagulation abnormalities and poorer outcome [66, 69, 87]. The association between clotting abnormalities and delayed intracerebral haemorrhage has become well established [21, 90, 92–94, 97]. Adequate control of haemorrhage remains an important aim in the management of TBI. Considerable controversies, on the diagnosis and treatment of coagulopathy after TBI still exist and it remains uncertain whether initiation of specific treatment in the early hypercoagulable phase may indeed prevent progression of lesions and improve outcome.

Material and methods

We performed a Pubmed search from 1966 to April 2007. First of all, we defined appropriate keywords and subject headings. We combined different keywords and noted the number of studies observed with and without restriction to the English language (Table 1). Since the largest number of studies was observed when combining head trauma and coagulopathy ($n = 429$, Table 1) we used these terms to identify relevant studies. To identify additional eligible studies, the other keyword combinations and the reference list of the selected studies were screened and 12 additional studies were identified. Eventually, this search strategy yielded 441 hits eligible for this study. Two separate reviewers determined the relevance of all titles/abstracts and excluded non-relevant studies. We excluded among others, studies on pharmacologic coagulopathy, chronic subdural haematoma, pre-existing coagulation disorders such as haemophilia and thrombotic thrombocytopenic purpura, spinal trauma and studies on ''non-traumatic'' disorders. This selection resulted in retaining 90 studies. Following a more detailed review we excluded an additional 8 studies since coagulopathy was not studied. In total, this review was therefore based on 82 studies. When available, frequencies of coagulopathy as defined and presented by the authors in relation to outcome were extracted from the studies to create two by two tables. These numbers were used to calculate crude odds ratios with 95% confidence intervals (95%CI). In the second stage, a summary (pooled) estimate is calculated as a weighted average of the effects estimated in the individual studies by using the Mantel Haenszel (MH) method, a widely recognised fixed effect method of meta-analysis.

Results

None of the studies met the criteria for Class I evidence. Many studies had been performed retrospectively and some were limited to case reports. Twenty-six publica-

Table 1. *Pubmed search results*

Keywords	All	English	HITS – review of titles/abstracts/references
Cranio-cerebral trauma coagulopathy	590	414	Exclusion of non-relevant studies, such as
Cranio-cerebral trauma coagulation disorders	516	348	– chronic subdural haematoma
Head trauma coagulation disorders	527	358	– pre-existing coagulation disorders
Head trauma coagulopathy	606	429	– spinal trauma
TBI coagulation disorders	144	78	– non traumatic disorders
TBI coagulopathy	173	107	– non clinical
Closed head injury and coagulation disorders	26	18	possibly relevant studies: 90
Closed head injury and coagulopathy	37	29	detailed review of full manuscripts
			included in systematic review: 82

Table 2. *Epidemiological classification of the studies*

Study design	No. of studies	
Case report	10	[1, 23, 28, 49, 62, 64, 74, 100, 110, 111]
Case-control	10	[9, 34, 45, 51, 75, 84, 85, 96, 114, 117]
Prospective	30	[10, 13, 14, 18, 19, 22, 29, 30, 38, 39, 43, 48, 50, 52–54, 59, 63, 67–69, 89, 92, 93, 99, 101, 107, 108, 113, 115]
Retrospective	16	[20, 21, 31, 37, 44, 46, 52, 70, 72, 76–78, 87, 90, 94, 97, 106]
Cross-sectional	3	[8, 105, 109]
Experimental	1	[104]
Review	5	[42, 47, 81, 88, 91]
Comments	7	[3–5, 25, 26, 95, 103]
Total	82	

tions represented prospective series, but some used a nested case control design, in which bias may play an important role. An overview of the studies from an epidemiologic perspective is listed in Table 2. Table 3 shows the characteristics of the studies with frequencies of coagulation disorders, which vary between 10 and 97.5% with a mean of 32.7%. When available, crude odds ratios were calculated for the association between coagulopathy after TBI as defined in the different studies, and mortality or Glasgow Outcome Scale (GOS) 1–3 (bad outcome), versus GOS 4–5 (good outcome). Data for the association between coagulopathy after TBI and the risk of mortality are presented in Table 3A. Odds ratios in the studies vary between 4.2 and 161. Data for the association between coagulopathy after TBI and the risk of bad outcome are presented in Table 3B. In these studies odds ratios vary between 16 and 58. All presented point estimates were statistically significant, although important modifiers (such as age and GCS) were not considered. When the crude data are pooled we find an overall odds ratio for the risk of bad outcome (GOS 1–3) of 33.2 (95%CI: 15.9–69.1) and the risk of mortality of 9.4 (95%CI: 7.6–11.6)

Table 3. *Characteristics of the studies with frequencies of coagulopathy after traumatic brain injury*

Study	No. of patients	Coagulopathy	No coagulopathy	Prevalence of coagulopathy (%)
Auer and Ott [9]	40	15	25	37.5
Avikainen [10]	45	15	30	33
Becker *et al.* [14]	27	17	10	63
Bredbacka and Edner [18]	20	15	5	75
Brohi *et al.* [19]	1079	256	823	23.7
Carrick *et al.* [20]	176	60	116	34.1
Chang *et al.* [21]	113	21	92	18.6
Chiaretti *et al.* [22]	60	6	54	10
Gando *et al.* [34]	16	14	2	87.5
Goodnight *et al.* [39]	26	10	16	38.5
Hulka *et al.* [43]	159	54	105	34
Hymel *et al.* [44]	147	40	107	27.2
Kaufmann *et al.* [45]	14	6	8	42.8
Kearney *et al.* [48]	36	31	5	86.1
Keller *et al.* [50]	53	20	33	37.7
Kumura *et al.* [51]	100	24	76	24
Kuo *et al.* [52]	61	44	17	72.1
Kushimoto *et al.* [54]	47	39	8	83
Miner *et al.* [63]	87	28	59	32
Olson *et al.* [69]	269	154	115	57.2
Ordog *et al.* [70]	180	175	5	97.2
Patel *et al.* [72]	852	157	695	18.4
Pfenninger *et al.* [75]	50	12	38	24
Piek *et al.* [76]	734	135	599	18.4
Pondaag [77]	46	35	11	76
Selladurai *et al.* [87]	143	108	35	75.5
Stein *et al.* [94]	253	67	186	26.5
Stein *et al.* [92]	334	102	232	30.5
Takahasi *et al.* [96]	25	10	15	40
Tan *et al.* [97]	38	11	27	28.9
Vavilala *et al.* [106]	69	33	36	34.4
Vecht *et al.* [107]	40	31	9	77.5
Vecht et al. [109]	6	3	3	50
Vecht and Sibinga [108]	12	6	6	50
Overall	5357	1754	3603	32.7

Table 3A. *Crude odds ratios for the risk of mortality after traumatic brain injury with coagulopathy*

Study	No. of patients	Coagulopathy–no survival	No coagulopathy–no survival	Coagulopathy–survival	No coagulopathy–survival	OR (95%CI)
Auer and Ott [9]	40	14	2	1	23	161 (13.3–1943)
Brohi *et al.* [19]	1079	114	90	142	733	6.5 (4.7–9.1)
Carrick *et al.* [20]	176	21	13	39	103	4.2 (1.9–9.3)
Hulka *et al.* [43]	159	21	7	33	98	8.9 (3.5–22.9)
Hymel *et al.* [44]	147	20	12	20	95	7.9 (3.3–18.8)
Keller *et al.* [50]	53	6	1	14	32	13.7 (1.5–124.8)
Kumura *et al.* [51]	100	14	5	10	71	19.9 (5.9–67.1)
Kuo *et al.* [52]	61	11	0	33	17	n.a.
Miner *et al.* [63]	87	15	7	13	52	8.6 (2.9–25.3)
Olson *et al.* [69]	269	85	11	69	104	12.2 (6–24)
Pondaag [77]	46	18	1	17	10	10.6 (21.2–91.8)
Selladurai *et al.* [87]	143	85	2	23	33	61 (13.6–273)
Takahasi *et al.* [96]	25	9	3	1	12	36 (3.2–405.9)
Overall	2385	433	154	415	1383	9.4 (7.6–11.6)

OR odds ratio, *95%CI* 95% confidence interval, *n.a.* not applicable.

Table 3B. *Crude odds ratios for the risk of bad outcome according to GOS after TBI and coagulopathy*

Study	No. of patients	Coagulopathy GOS1-3	No coagulopathy 3 GOS1-3	Coagulopathy GOS > 3	No coagulopathy GOS > 3	OR (95%CI)
Bredbacka and Edner [18]	20	12	1	3	4	16 (1.3–200.9)
Goodnight *et al.* [39]	26	9	4	1	12	27 (2.6–284.7)
Kushimoto *et al.* [54]	47	17	4	0	26	n.a.
Pfenninger *et al.* [75]	50	9	6	3	32	16 (3.3–77)
Tan *et al.* [97]	38	10	8	1	19	23.8 (2.6–218)
Vavilala *et al.* [106]	69	29	4	4	32	58.3 (13–253)
Overall	250	86	27	12	125	33.2 (15.9–69.1)

GOS Glasgow Outcome Scale, *TBI* traumatic brain injury, *OR* odds ratio, *95% CI* 95% confidence interval, *n.a.* not applicable.

after TBI and coagulopathy. Using the Mantel-Haenszel method, the odds ratio for the risk of bad outcome (GOS 1–3) is 36.3 (95%CI: 8.7–70.5) and 9.0 (95%CI: 7.3–11.6) for the risk of mortality.

Discussion

Incidence of coagulation disorders

The incidence of coagulopathy in TBI is high, but actual numbers vary considerably between studies. The wide variation in frequency is not striking because different study designs and definitions for coagulopathy have been used. The definitions of coagulopathy have been changed over time, and in addition, other techniques for measuring DIC have become available in the last decade. Recently the International Society of Thrombosis and Haemostasis (ISTH) simplified the laboratory diagnosis of DIC by calculating a DIC score based on platelet count, elevated fibrin-related marker, prolonged prothrombin time and fibrinogen level [98]. However, none of the studies included in our review have used this score, but instead were mainly based on other parameters, including fibrinogen, fibrinogen degradation products and antithrombin levels. Overall, in this review, one out of three patients with TBI have signs of coagulopathy (Table 3) and according to the literature it occurs in more than 60% of patients with severe TBI [8, 24, 42]. In mild TBI coagulopathy is probably less than one percent [37]. Kuo and colleagues [52] reported an incidence of coagulopathy in 100% of patients dying from head injury whereas Chiaretti and colleagues [22] presented a frequency of 10% in patients with TBI. Studies from the late 1970's already reported a decrease of platelets and fibrinogen during the first five days after injury, indicating consumptive coagulopathy [8, 9], but could not confirm the presence of DIC. Later studies, utilising more sensitive laboratory techniques for detecting a hypercoagulable state, reported an increased frequency of DIC following head injury up to 76% [51, 63, 69, 77, 104]. According to some authors 15–40% of patients with severe TBI meet the criteria for symp-

tomatic DIC [18, 41, 63, 94], however as indicated above different criteria for DIC were used. DIC seems to occur most frequently in patients with acute subdural haematoma, or parenchymal contusions [51]. Haemostatic activation may be more prominent in cerebrovascular blood than in peripheral blood [67]. The presence of local cerebral intravascular coagulation has been confirmed in surgical specimens of human cerebral contusions, and cerebral contusions of rats and pigs [90].

Severity of TBI and coagulopathy

Hypercoagulability after injury is most prevalent during the first 24 h and more pronounced in women [86]. Children with a glasgow coma score (GCS) <14 after TBI are at greater risk for coagulopathy and this risk is even more increased at lower GCS levels [50]. Several studies have demonstrated that fibrin degradation product (FDP) levels correlate positively with the degree of brain damage [46, 51, 69, 102]. Stein and colleagues [92] found that almost 50% of patients with TBI developed delayed brain injury, as defined by the occurrence of new intracranial lesions or progression of lesions initially present on admission. In that study, abnormalities in the prothrombin time, partial thromboplastin time, or platelet count at admission were present in 55% of patients with evidence of delayed injury, versus only 9% of patients without delayed injury. In particular, mean prothrombin time and partial thromboplastin time at admission were significantly longer in patients developing delayed injury. More recently, Yokota and colleagues [116], found that Von Willebrand factor (vWF) and thrombomodulin (TM) are useful indicators of cerebral endothelial injury and that increased TM levels predict delayed brain injury.

Prognosis

The presence of coagulopathy is not only related to the risk for developing delayed injury, but also to a poorer outcome. Continued bleeding is one factor, but not the only one responsible for a poorer outcome. As mentioned above, DIC, which involves, by definition, ''intravascular coagulation'', causes multiple organ failure by thromboembolic ischaemia and may also be responsible for a bad outcome. Similarly, the DIC after TBI causes intravascular coagulation-induced cerebral ischaemia and may be related to a bad prognosis. It is striking that the risk of mortality in patients with coagulopathy after TBI is approximately ten times higher than in these patients without coagulopathy (Table 3A). The risk of bad outcome in patients with coagulopathy after TBI is even more than thirty times higher than in these patients without coagulopathy (Table 3B). We are aware that bias plays an important role in these studies and the various prevalences cannot be compared due to different criteria of coagulopathy in each of the studies. Moreover, the parameters of coagulopathy in these studies differ and this variation will lead to clinical heterogeneity. This is an important limitation of our study. However, these results are consistent with the findings of two similar studies [69, 87] in which logistic regression models with adjustment of different parameters were used to calculate the probability of a bad outcome after TBI and coagulopathy. Various large clinical studies have demonstrated that DIC is an important predictor of poor outcome in head injury [46, 63, 94]. This relationship was absent in only one of the presented studies [67]. Kushimoto and colleagues [53] studied the clinical significance of fibrinolysis and fibrinogenolysis in patients with closed head injury and found that indices of fibrinolytic activity like fibrinogen degradation products (FDP), and fibrin degradation products (FbDP) were correlated to outcome. A limitation of this study is that they did not adjust for confounders such as gender, age or extent of brain tissue damage. The interpretation of different studies on the predictive value of coagulation parameters and outcome is complex due to differences in study design, population and definitions of DIC. Some studies have a relatively small sample size and short follow up periods whereas others only present cross-sectional data. Some authors claim that laboratory values for coagulation status may be a better predictor of mortality than midline shift or pupillary reactivity [52], but only few have investigated the predictive value of coagulopathy adjusted for other predictors. Olson and colleagues [69] and Selladurai and colleagues [87] studied the predictive value of coagulopathy in TBI with logistic regression models. Both studies found that high FDP levels predict poor outcome independently of other variables and that prognosis worsens as the level of FDP increases. In patients with mild head injury, this high FDP level may lead to a rapid deterioration and eventually to death. In patients with an intermediate level of severity of brain injury, the activated partial thromboplastin time (APTT) appeared to be of greater prognostic value. Increased plasma concentrations of FDP and plasmin-alpha2-plasmin inhibitor complex and decreased fibrinogen levels are associated with a high percentage of unfavourable outcome three months after injury. Similar

results have also been reported in children [106]. Very recently, results from the IMPACT (International Mission for Prognosis And Clinical Trial) study showed that the prothrombin time is a powerful independent prognostic factor after TBI [66].

Treatment

Guidelines for the treatment of coagulopathy following TBI do not exist. No randomized studies have been performed to study any intervention such as infusion of fresh frozen plasma (FFP), antithrombotic drugs or antithrombotic coagulation factor concentrates after TBI. Therefore opinions on preferred approaches vary. These differences reflect the complexity of the problem and the strong heterogeneity in type, degree and phase of coagulation disturbances. In general, the therapy of coagulation disturbances should be aimed at treating the primary cause. Stein and colleagues [91] recently argued that the objectives of treatment should be to combat coagulation, to lyse existing clots, to replete clotting factors and reverse hyperfibrinolysis. Fresh frozen plasma and platelet concentrates are recommended for patients with active bleeding. May and colleagues [60] have advocated the use of FFP as resuscitation fluid in patients with a GCS $\leq$7. However, Winter and co-workers [113] did not find any benefit on outcome with the use of FFP. Keller and colleagues [50] propose administration of FFP to all children presenting the GCS <8 in an attempt to combat coagulation disorders and prevent progression of lesions. According to Rubin and Colman [82] heparin anticoagulation followed by aggressive replacement with platelets and FFP is indicated as a treatment of patients with DIC in general. This treatment might be extrapolated to DIC in TBI. However, administration of these products may carry a risk of enhancing coagulation by adding procoagulant factors. Rubin and Colman [82] proposed administration of heparin in therapeutic doses, sufficient to overcome the coagulant forces that may have produced a relative heparin-resistant state in the blood. Most clinicians treating TBI however will be extremely reluctant to administer heparin for fear of increasing intracranial haemorrhage and in view of the lack of clinical evidence we consider this approach, although theoretically sound, debatable [27].

DIC also occurs frequently in sepsis where activated protein C, a potent anticoagulant and profibrinolytic agent, has shown to improve coagulation disturbances and improve outcome in septic patients, who developed multiple organ failure [32]. Nevertheless, an increased risk of bleeding has been observed with the administration of protein C to patients with sepsis [16, 32] and in children it may even cause serious bleeding events [36]. To date, no such studies have been performed in patients with TBI. Various other approaches have been explored to correct coagulopathy in TBI. The early administration of antithrombin III (AT III) to patients with TBI could inhibit or significantly shorten the time of coagulopathy. Grenander and colleagues [40] described a marginal reduction of hypercoagulation parameters following administration of AT III but could not confirm a benefit on progression of lesions, on outcome or on length of ICU stay. Antifibrinolytic agents like aprotinin, tranexamic acid and [epsilon]-aminocaproic acid are commonly used in cardiac surgery. The role of antifibrinolytic agents in trauma patients with massive blood loss is yet not clear. The CRASH-2 (Clinical Randomisation of Antifibrinolytic in Significant Haemorrhage) trial is a World Health Organization (WHO) supported large international multi-centre randomised placebo controlled trial of the effects of the antifibrinolytic agent tranexamic acid on death and transfusion requirements in adult trauma patients with significant haemorrhage. In this large study, recruitment is expected to be completed in December 2009 and will provide us more insight in the use of antifibrinolytic agents in trauma patients [80]. To our knowledge, no randomised data are available on the administration of antifibrinolytics after traumatic brain injury. Preliminary data indicate that recombinant factor VIIa (rFVIIa) provides a rapid and successful correction of coagulopathy in the head-injured patient which may suggest an alternative strategy for treating coagulopathy in TBI [64]. Interestingly, treatment with rFVIIa within four hours after the onset of intracerebral haemorrhage limits the growth of the haematoma, reduces mortality, and improves functional outcomes at 90 days [61]. Very recently, however, a completed phase 3, randomised, controlled trial involving 821 patient presented on the 16th European Stroke Conference Glasgow, United Kingdom 2007, showed that there was a significant reduction in the size of the intracerebral haematoma but no effect on mortality and severe disability on day 90 (unpublished data). Since TBI is commonly associated with cerebral contusions and haemorrhage [2] these results may be extrapolated to TBI as was reported recently [112]. However, rFVIIa should be administered with caution due to the increased risk of thromboembolic complications [61]. To date there is only one published randomised placebo-controlled trial of the use of rFVIIa in trauma [17]. The authors showed

that rFVIIa resulted in a significant reduction in red blood cell transfusion in severe blunt trauma. Investigating the beneficial effect of early treatment of coagulation disorders in TBI in well-performed blinded randomised trials should be a priority for future research.

Conclusions and recommendations

- Coagulopathy occurs frequently in TBI.
- Coagulopathy is more pronounced in patients with severe injuries.
- Progressive brain injury seems to occur more frequently in patients with coagulopathy.
- The presence of coagulopathy after TBI is related to poor prognosis.
- Coagulopathy following TBI may be amenable to treatment.

We conclude that coagulopathy following traumatic brain injury is an important independent risk factor related to prognosis and routine determination of the coagulation status should therefore be performed in all patients with traumatic brain injury. This status should specifically include tests focused on hypercoagulopathy and DIC. Guidelines regarding specific DIC scores [12, 98] recommend that D-dimer or FDP, platelet count, prothrombin time and fibrinogen offer the best DIC diagnostic test panel. These data may have important implications in patient management. Well-performed prospective clinical trials on coagulopathy in TBI patients should have priority to determine beneficial effects of early treatment of coagulopathy in TBI.

Acknowledgement

There was no financial support or conflict of interest with the current work.

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Comment

Harhangi and colleagues have done a thorough search of the TBI literature for links between coagulopathy and outcome. They use meta-analytic techniques to combine the results of many different studies to generate pooled estimates and thereby strengthen their conclusions. Among these conclusions are the very strong links between coagulopathy and both unfavorable outcome and mortality after TBI. Both *n*-weighted and variance-weighted pooled estimates are in close agreement.

None of this is entirely new. Indeed, many of the investigators cited by the present authors have made similar assertions. However, the pooled data presented here are compelling and demand further exploration of the process. The implications of these findings are potentially crucial. Firstly, coagulopathy often appears within minutes of TBI, and so will usually already be present on hospital admission. Hence it is a convenient marker of potential risk. If the coagulopathy can be reversed or ameliorated pharmacologically, outcomes may be improved, perhaps substantially.

Harhangi *et al.* provide a thorough review of the pathogenesis of coagulopathy in TBI. I have a minor quibble with them about this. During their discussion of this process in the Introduction, they state that tissue factor (TF), *released* by TBI, initiates the clotting process. TF, a transmembrane protein which is especially prevalent on the adventitial surface of cerebral vessels, is *activated* by exposure to blood; initiation of clotting does not require its release. The authors also provide an excellent discussion of the complexities of TBI-induced DIC. Multiple processes are occurring both simultaneously and in sequence: hypercoagulability, intravascular coagulation, clotting factor and platelet consumption, as well as fibrinolysis. Therapy which addresses only one process or which is given at the wrong stage of the cycle may have unintended and adverse consequences. For example, the authors mention the CRASH-2 trial involving many TBI patients, in which patients randomly receive either the antifibrinolytic tranexamic acid or placebo. Another randomized, controlled, multicenter trial of recombinant factor VIIa for TBI has been completed but has not yet been reported. It is hoped that both studies will be carefully scrutinized for the occurrence of medication-induced cerebral ischemia, a possible side effect of both treatments.

Harhangi and colleagues are to be congratulated on a well-prepared and interesting report. I hope that their paper will generate a dialogue about novel ways in which we can advance treatment for TBI.

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