

Frequencies of TBI-
Coagulopathy

Risk Factors

Outcome

Hypotheses

Treatment

Conclusions

Traumatic Brain Injury- associated Coagulopathy

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Frequencies of coagulopathy after TBI

Review Article

Coagulation disorders after traumatic brain injury

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MEDLINE search 1966-April 2007 with focus
on head trauma and coagulopathy

Meta-Analysis of 34 studies reporting
frequencies of coagulaopathy after TBI

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Frequencies of coagulopathy after TBI

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 <i>et al.</i> [14]	27	17	10	63
Bredbacka and Edner [18]	20	15	5	75
Brohi <i>et al.</i> [19]	1079	256	823	23.7
Carrick <i>et al.</i> [20]	176	60	116	34.1
Chang <i>et al.</i> [21]	113	21	92	18.6
Chiaretti <i>et al.</i> [22]	60	6	54	10
Gando <i>et al.</i> [34]	16	14	2	87.5
Goodnight <i>et al.</i> [39]	26	10	16	38.5
Hulka <i>et al.</i> [43]	159	54	105	34
Hymel <i>et al.</i> [44]	147	40	107	27.2
Kaufmann <i>et al.</i> [45]	14	6	8	42.8
Kearney <i>et al.</i> [48]	36	31	5	86.1
Keller <i>et al.</i> [50]	53	20	33	37.7
Kumura <i>et al.</i> [51]	100	24	76	24
Kuo <i>et al.</i> [52]	61	44	17	72.1
Kushimoto <i>et al.</i> [54]	47	39	8	83
Miner <i>et al.</i> [63]	87	28	59	32
Olson <i>et al.</i> [69]				57.2
Ordog <i>et al.</i> [70]				97.2
Patel <i>et al.</i> [72]				18.4
Pfenninger <i>et al.</i> [75]				24
Piek <i>et al.</i> [76]				18.4
Pondaag [77]				76
Selladurai <i>et al.</i> [87]				75.5
Stein <i>et al.</i> [94]	253	67	186	26.5
Stein <i>et al.</i> [92]	334	102	232	30.5
Takahasi <i>et al.</i> [96]	25	10	15	40
Tan <i>et al.</i> [97]	38	11	27	28.9
Vavilala <i>et al.</i> [106]	69	33	36	34.4
Vecht <i>et al.</i> [107]	40	31	9	77.5
Vecht <i>et al.</i> [109]	6	3	3	50
Vecht and Sibinga [108]	12	6	6	50
Overall	5357	1754	3603	32.7

Overall prevalence 32.7%
(mean frequency)

Frequencies
vary between
10 - 97.5%

Frequencies of coagulopathy after TBI

The presence of coagulopathy after TBI was related to

1. Mortality (OR 9.4; 95%CI: 7.6-11.6)
2. Unfavourable outcome (=OR 33.2; 95%CI: 15.9-69.1)

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 <i>et al.</i> [19]	1079	114	90	142	733	6.5 (4.7–9.1)
Carrick <i>et al.</i> [20]	176	21	13	39	103	4.2 (1.9–9.3)
Hulka <i>et al.</i> [43]	159	21	7	33	98	8.9 (3.5–22.9)
Hymel <i>et al.</i> [44]	147	20	12	20	95	7.9 (3.3–18.8)
Keller <i>et al.</i> [50]	53	6	1	14	32	13.7 (1.5–124.8)
Kumura <i>et al.</i> [51]	100	14	5	10	71	19.9 (5.9–67.1)
Kuo <i>et al.</i> [52]	61	11	0	33	17	n.a.
Miner <i>et al.</i> [63]	87	15	7	13	52	8.6 (2.9–25.3)
Olson <i>et al.</i> [69]	269	85	11	69	104	12.2 (6–24)
Pondaag [77]	46	18	1	17	10	10.6 (21.2–91.8)
Selladurai <i>et al.</i> [87]	143	85	2	23	33	61 (13.6–273)
Takahasi <i>et al.</i> [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.

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Acute Coagulopathy in Isolated Blunt Traumatic Brain Injury

Arasch Wafaisade · Rolf Lefering · Thorsten Tjardes · Sebastian Wutzler ·
Christian Simanski · Thomas Paffrath · Philipp Fischer · Bertil Bouillon ·
Marc Maegele · Trauma Registry of DGU

Aim: To assess the frequency, outcome, and risk factors of acute coagulopathy in isolated blunt TBI

Data: TR-DGU database (retrospective analysis)

Results:

$n = 3,114$ patients w TBI ($AIS_{head} \geq 3$; $AIS_{rest} < 3$)

706 (22.7%) with coagulopathy on ER arrival

Independent risk factors for development of acute coagulopathy in TBI

Risk factor	Odds ratio (CI ₉₅)	P-value
AIS_{HEAD}		
AIS 4	1.36 (0.99–1.88)	0.057
AIS 5	2.25 (1.63–3.10)	<0.001
AIS 6	4.04 (2.14–7.63)	<0.001
GCS ≤ 8 at scene	1.71 (1.38–2.12)	<0.001
SBP ≤ 90 mmHG at scene	1.74 (1.30–2.32)	<0.001
SBP ≤ 90 mmHG at ER	2.34 (1.64–3.34)	<0.001
i.v. fluids pre-hospital		
2,000–2,999 ml	2.15 (1.63–2.84)	<0.001
≥3,000 ml	3.48 (2.13–5.68)	<0.001
Age		
65–74 years	1.31 (0.99–1.73)	0.063
≥75 years	2.30 (1.79–2.96)	<0.001

The logistic regression model was started with eight variables, two variables were excluded by the model (sex; subdural hematoma). *AIS* abbreviated injury scale; *GCS* Glasgow Coma Scale; *SBP* systolic blood pressure

The severity of head injury is associated with increased risk of coagulopathy in combat casualties

Combat casualties with isolated TBI patients ($\text{AIS}_{\text{head}} \geq 3$ + other $\text{AIS} < 2$) were compared with non-TBI patients ($\text{AIS}_{\text{head}} \leq 2$ + other $\text{AIS} \geq 3$) to determine the degree to which TBI is associated with coagulopathy (INR) and to describe characteristics of this population.

Results:

- > 117 TBIs and 1,492 non-TBI injuries
- > Admission INR significantly higher in TBI
- > In stepwise multiple regression BD , GCS , and AIS_{head} were independently associated with coagulopathy by INR

The occurrence of TBI-related coagulopathy increases within the first 24 hrs after impact

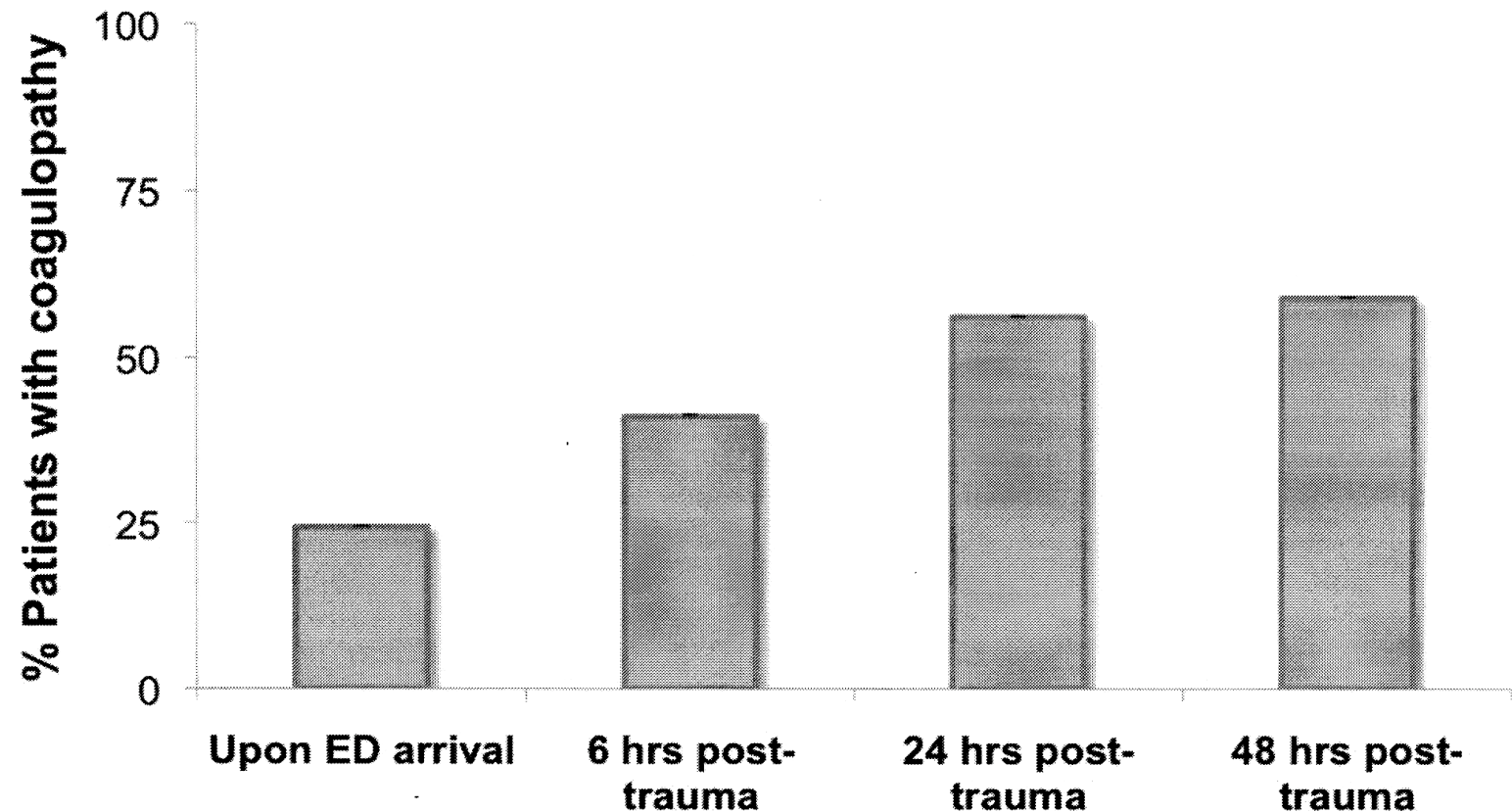
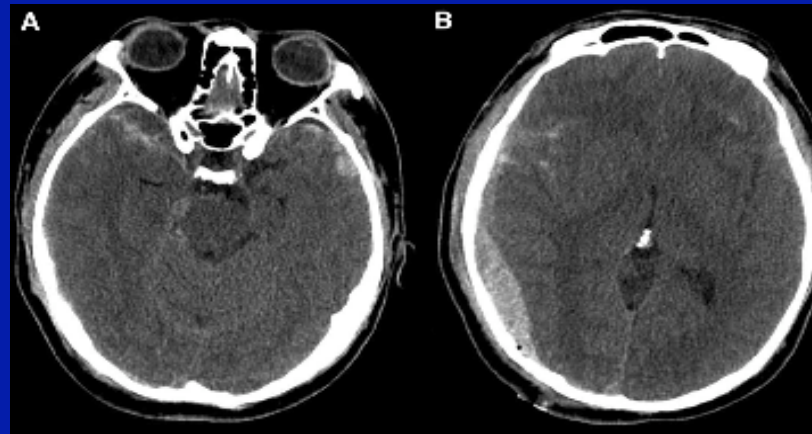


Figure 1 The relative number of patients with a diagnosis of coagulopathy. The relative number of patients with a diagnosis of coagulopathy upon emergency department arrival and at 6, 24 and 48 hours post-trauma.

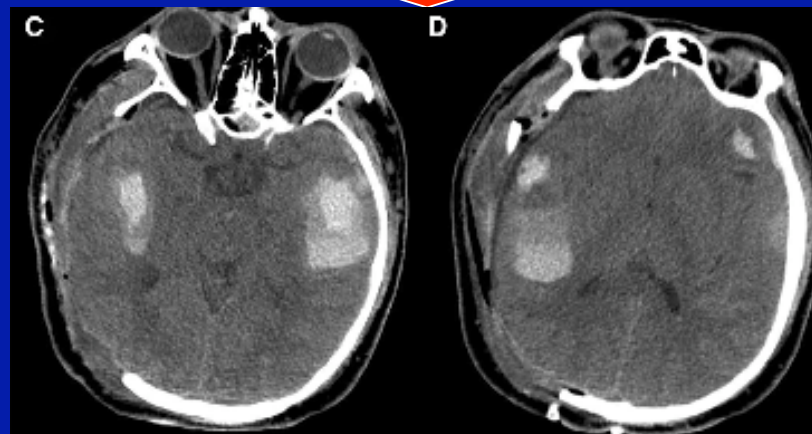
Rapid progression of bilateral hemorrhagic contusion with development of coagulopathy after blunt TBI



23-yrs male with altered mental status after fall 10 m height

CCT: Epidural hematoma right with temporal contusions bilateral

INR in ER: 1.2



Follow-up CCT after evacuation shows progression of bilateral contusions + brain swelling + diffuse bleeding

INR in OR: 1.6

Glasgow Coma Scale as a predictor for hemocoagulative disorders after blunt pediatric traumatic brain injury

Sigune Peiniger, MD; Ulrike Nienaber, MS; Maximilian Braun, MD; Arasch Wafaisade, MD; Matthew A. Borgman, MD; Philip C. Spinella, MD; Marc Maegele, MD; the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie

Frequencies of TBI-
Coagulopathy

Risk Factors

Outcome

Hypotheses

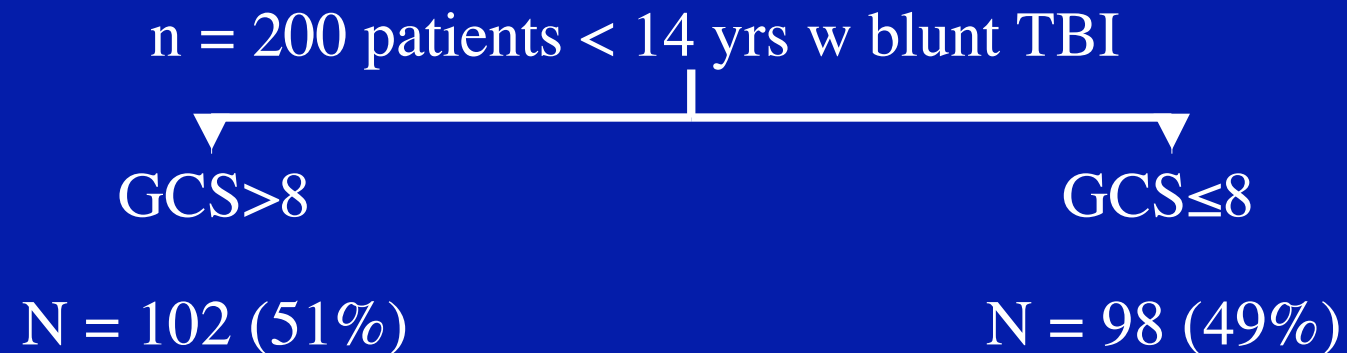
Treatment

Conclusions

Aim: To assess whether neurologic findings reflected by Glasgow Coma Scale at initial resuscitation can predict hemocoagulative disorders resulting from TBI

Data: TR-DGU database (retrospective analysis)

Results:



GCS \leq at scene in children with blunt TBI is associated with increased risk for coagulopathy and mortality

The incidence of coagulopathy (PT/Quick < 70 , PTT > 38 s, platelets $> 100,000$) at ER was higher in GCS ≤ 8 (44% vs 14%; $p < .001$)

Stepwise logistic regression incl. age, gender, physiology, neurology, and injury pattern identified ONLY GCS ≤ 8 at scene as independent risk factor for coagulopathy (odds ratio 3.378)

GCS ≤ 8 at scene in children with blunt TBI is associated with increased risk for coagulopathy and mortality

Mortality in children with GCS ≤ 8 at scene was higher with the presence of coagulation abnormalities at admission compared to children with coagulopathy absent (51,6% vs 5%)

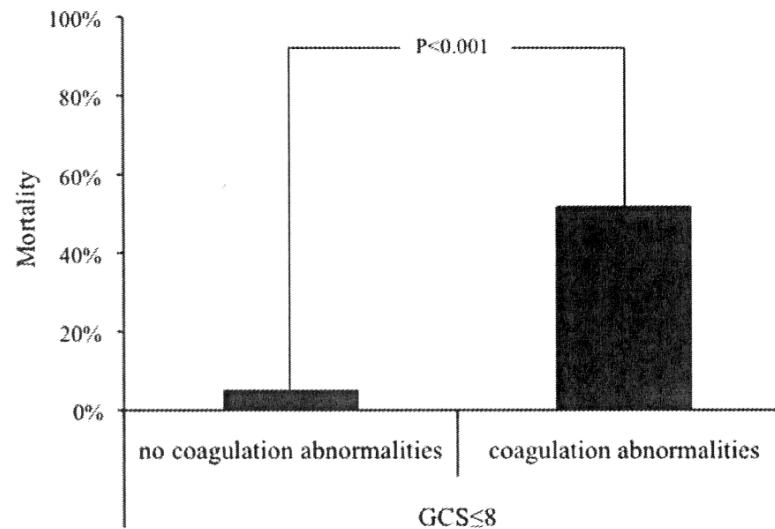
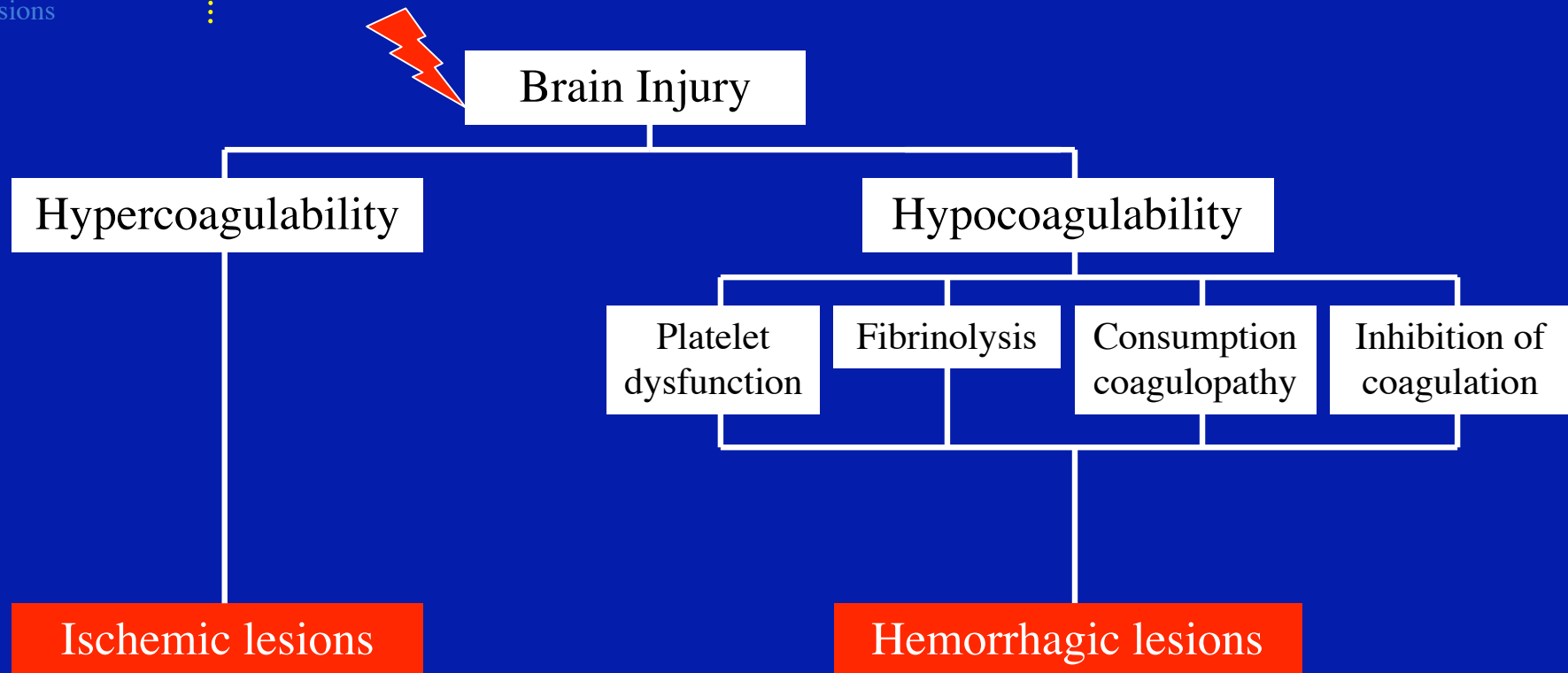


Figure 3. In-hospital mortality of children with Glasgow Coma Scale (GCS) ≤ 8 at scene in presence or absence of coagulation abnormalities upon emergency room admission.

Current hypothesis for the development of coagulopathy after blunt TBI (Coincidence of Hypo-/Hypercoagulation)

A combination of Hypocoagulation and Hypercoagulation triggered by the extent of brain injury will lead to secondary injury by ways of ischemic and hemorrhagic lesions

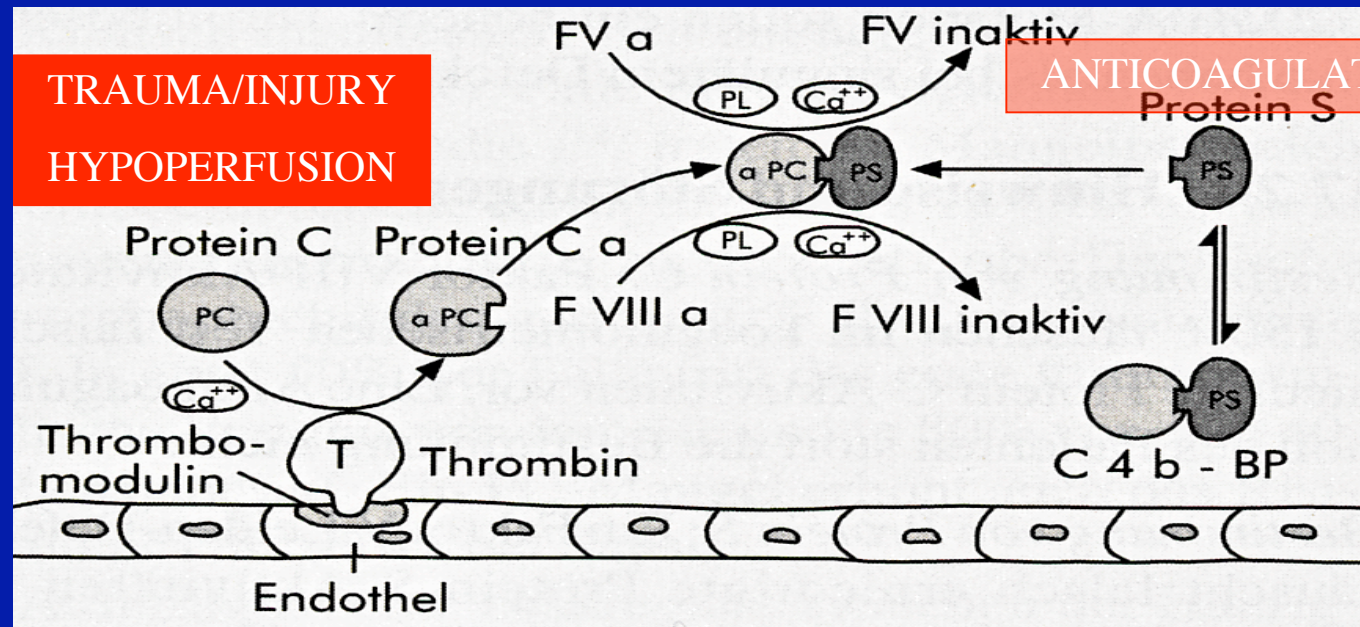


The role of the protein C pathway and hypoperfusion in hypercoagulable and hypocoagulable states

A maldaptive response of protein C to the combination of trauma and hypoperfusion may cause both

- 1. an immediate activated protein C-mediated coagulopathy**
- 2. a chronic protein C depletion-mediated susceptibility to infections and thromboembolic events**

Immediate activated protein-C-mediated coagulopathy / hypocoagulability during hypoperfusion

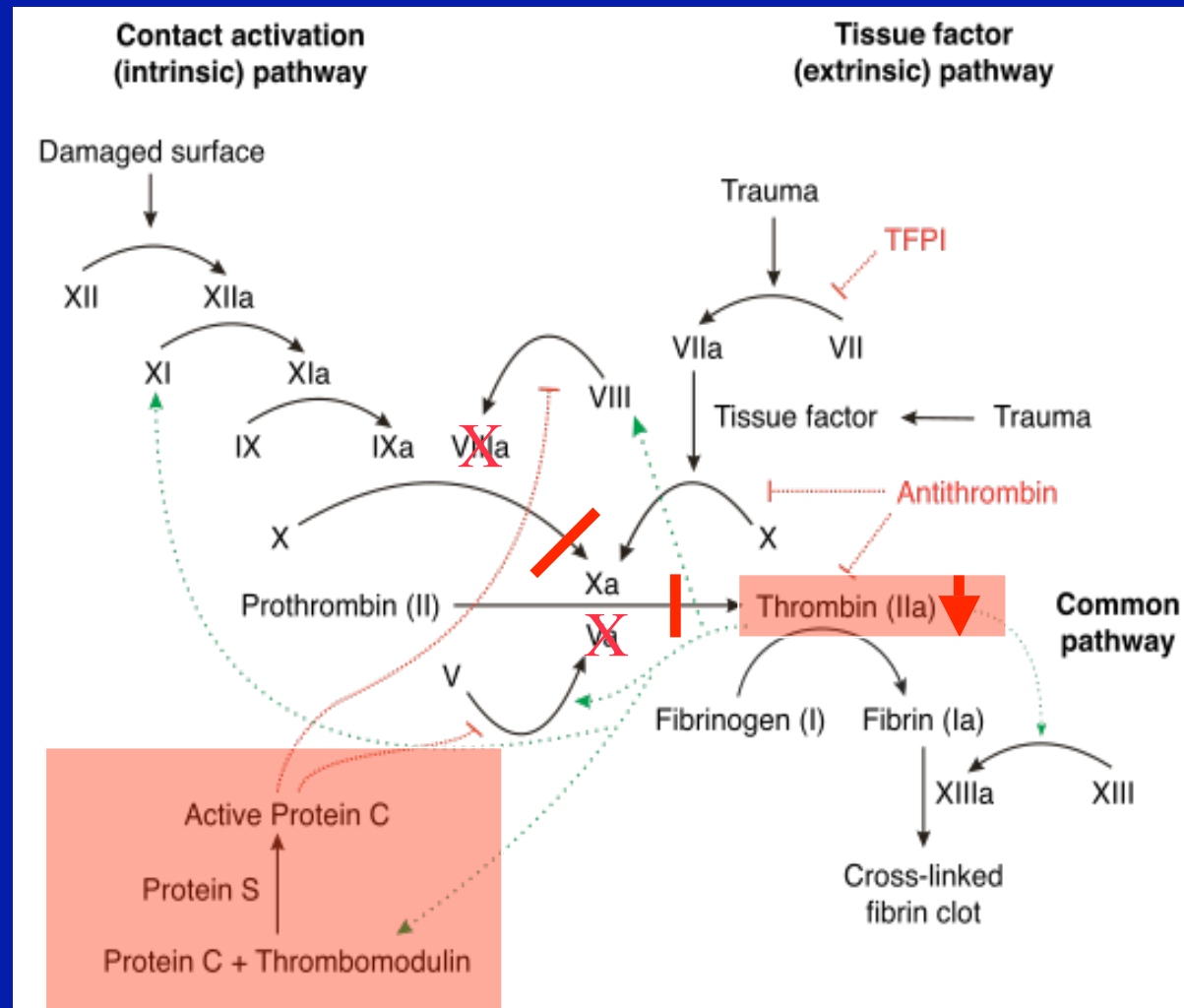


Combined trauma + hypoperfusion could lead to Hypocoagulation via the formation of an anticoagulant complex > thrombin binds to thrombomodulin > thrombin-thrombomodulin-complex

This complex activates protein C in the presence of Ca²⁺

Inactivation of factors 5a and 8a!

Immediate activated protein-C-mediated coagulopathy / hypocoagulability during hypoperfusion



Immediate activated protein-C-mediated coagulopathy / hypocoagulability during hypoperfusion

Frequencies of TBI-Coagulopathy

Risk Factors

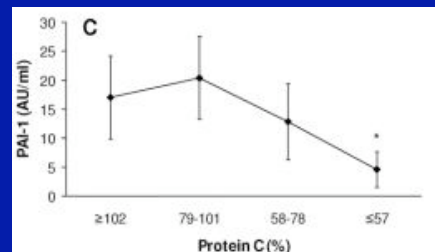
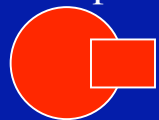
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Hypotheses

Treatment

Conclusions

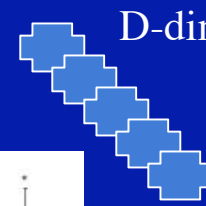
aPC
activated protein C



aPC in surplus consumes PAI-1
(Plasminogen-Activator-Inhibitor-1)

PAI-1

tPA



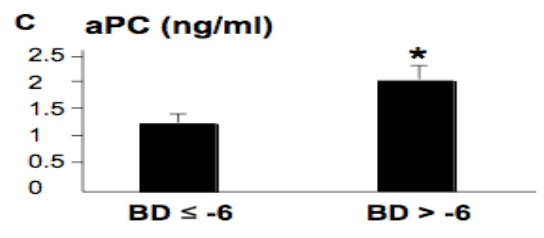
D-dimers

HYPERFIBRINOLYSIS

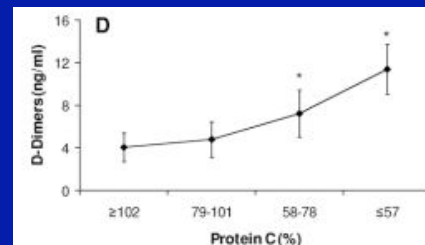
Fibrinolyse ↑

1. tissue plasminogen activator (tPA) ↑

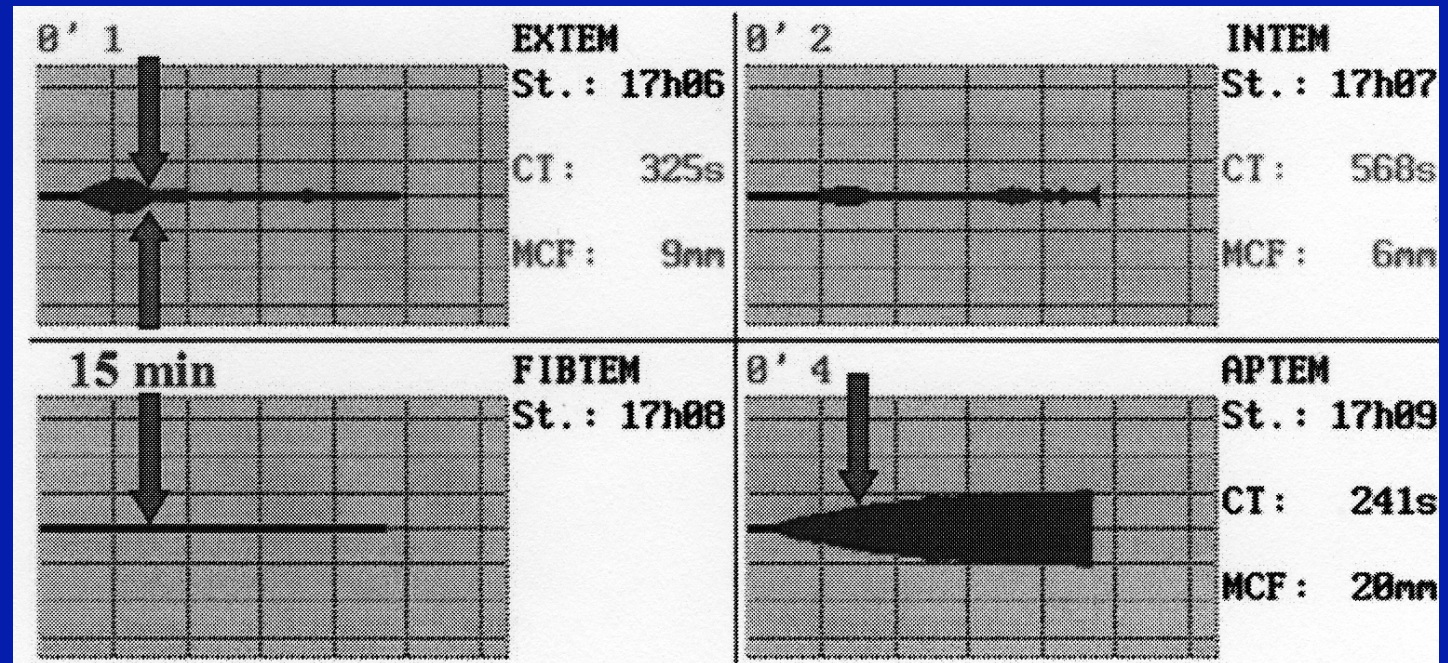
2. D-Dimere ↑



aPC-levels increase with level of shock/hypoperfusion



Hyperfibrinolysis in TBI



4-Chanel ROTEM in a trauma patient with TBI and thoracic injury

1. Fulminant Hyperfibrinolysis (HF) in EXTEM and INTEM
2. NO fibrin generation in FIBTEM (defibrinogenation)
3. APTEM shows clotting when antifibrinolytics were added to EXTEM

Hyperfibrinolysis in TBI

TBI patients may be prone for the development of HF but incidence rates are still speculative (Kushimoto et al., J Neurotrauma 2003; Schoechl et al., Hämostaseologie 2012)

Estimated 2.5-7% of trauma/TBI patients present with HF (Levrat et al., Br J Anaesth 2008; Tauber et al., Br J Anaesth 2011; Schoechl et al., Hämostaseologie 2012)

Presence of HF associated with worse outcome

„Hyperfibrinolysis increased fatality rates“ (Tauber et al., Br J Anaesth 2011)

„HF only observed in TBI non-survivors“ (Schoechl et al., Hämostaseologie 2012)

„Fulminante (<30 min), intermediate (30-60 min), or late HF (>60 min) resulted in 100%, 91%, or 73% mortality“ (Schoechl et al., J Trauma 2009)

„The actual overall mortality of HF (88%) exceeded the predicted trauma and ISS mortality (70%)“ (Schoechl et al., J Trauma 2009)

The level of plasma D-dimer after TBI suggested as predictor of progressive hemorrhagic injury/intra-cranial hemorrhage (PIH) (Tian et al., Neurosurg Rev 2010; Tong et al., Brain Injury 2012)

Vice-versa.....

J Trauma. 2010 May;68(5):1072-7.

Low plasma D-dimer concentration predicts the absence of traumatic brain injury in children.

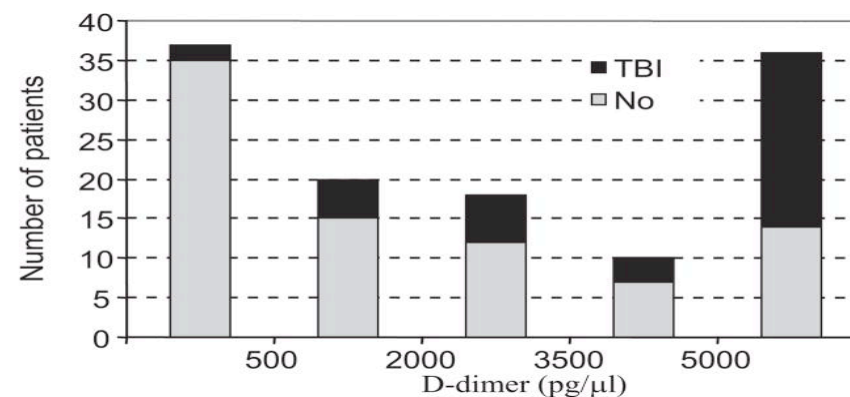
Swanson CA, Burns JC, Peterson BM.

Sutter Memorial Hospital, Sacramento, California, USA. cswanson@stanfordalumni.org

Retrospective cohort of 57 consecutive patients

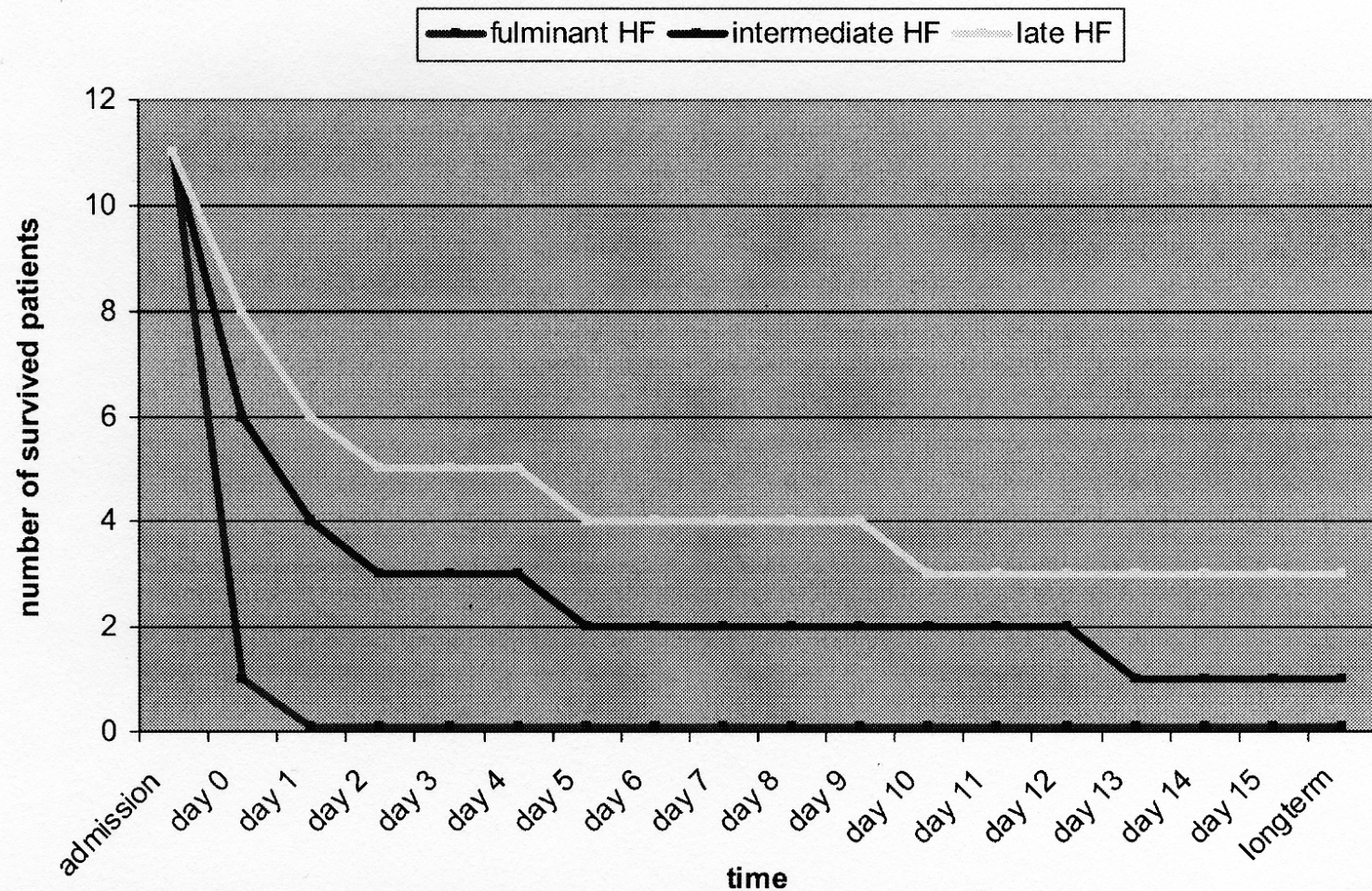
RESULTS: All patients generally met common clinical criteria (such as the CHALICE criteria 4) for head CT after trauma. Plasma levels of D-dimer were associated with TBI on head CT by univariate analysis ($p < 0.001$). Other markers including prothrombin time, partial thromboplastin time, and s100beta were not. D-dimer also had the strongest association in multivariate analysis ($p = 0.02$). This association was independent of and stronger than the baseline Glasgow Coma Scale ($p = 0.08$). A D-dimer level cut-off of 500 pg/microl had 94% negative predictive value ($p < 0.001$) for brain injury on head CT. The discriminatory capacity of this D-dimer level was confirmed in the independent retrospective cohort.

CONCLUSIONS: In children who meet clinical criteria for a head CT scan after trauma, low plasma d-dimer suggests the absence of significant brain injury.



Hyperfibrinolysis

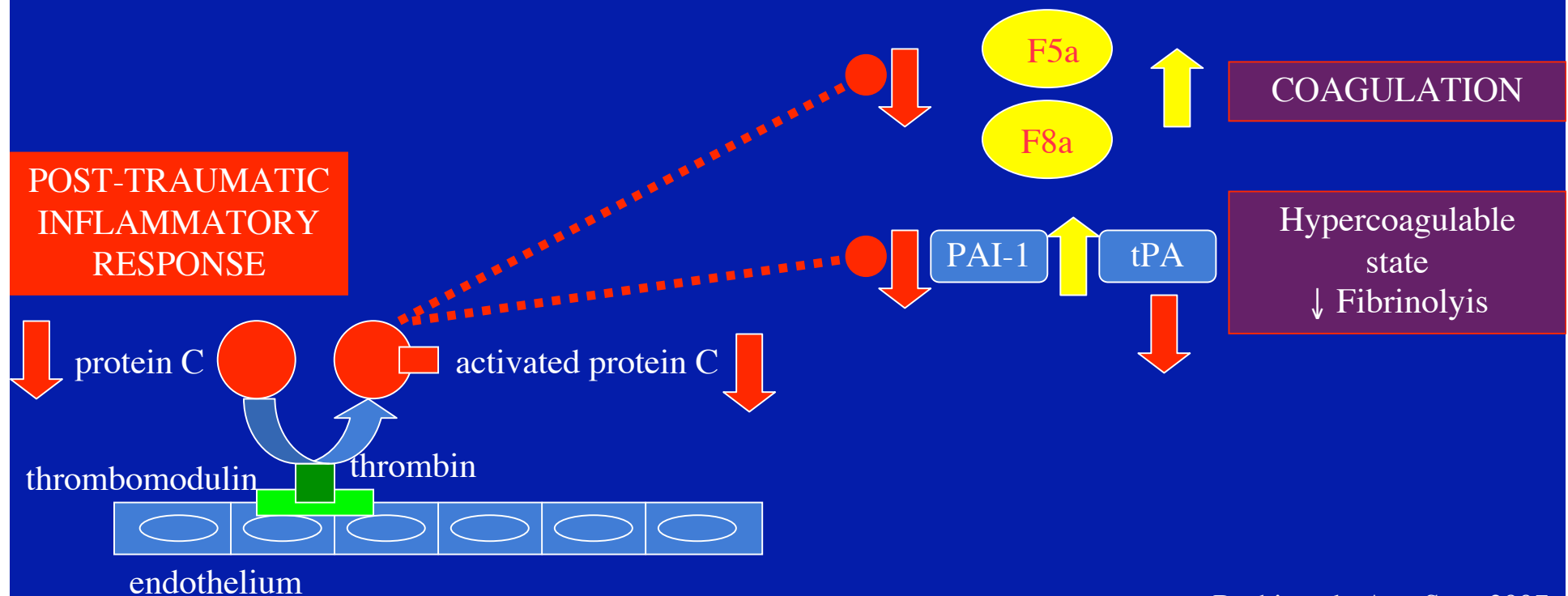
Mortality



Surviving patients at different time points after admission group by severity of HF

Hypercoagulability state secondary to protein-C depletion

Chronic protein C depletion-mediated susceptibility to infectious and thromboembolic events



Hypercoagulability state secondary to protein-C depletion

Chronic protein C depletion-mediated susceptibility to infectious and thromboembolic events

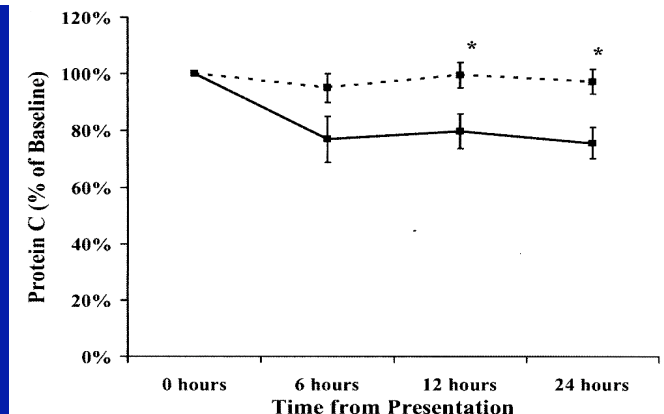
Critical trauma patients have an early activation of the PC pathway with a rapid decrease in plasma levels of this protein and increase in EPCR (soluble endothelial PC receptor).

Plasma levels of PC return to normal levels within 24 hours in most patients.

A substantial number of trauma patients present with significantly lower plasma levels of PC within 24 hours after injury, suggesting a possible consumption of this vitamin K-dependent protein and an inhibition of its activation by inflammatory mediators.

Protein C Depletion Early After Trauma Increases the Risk of Ventilator-Associated Pneumonia

Mitchell J. Cohen, MD, Natasha Bir, MD, Pamela Rahn, BS, Rachel Dotson, MD, Karim Brohi, FRCS, FRCA, Brian B. Chesebro, MD, Robert Mackersie, MD, Michel Carles, MD, Jeanine Wiener-Kronish, MD, and Jean-François Pittet, MD



Significantly lower Protein-C levels at 6, 12 and 24 hours in patients with complications (VAP-pneumonia) compared to non-infected patients

Soluble endothelial PC receptor (sEPCR) levels were also lower at 24 hours

**Protein-C depletion is associated with complications!
(for example VAP-pneumonia)**

Cohen et al., J Trauma 2009
Cohen et al., Ann Surg 2012

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Treatment Option for Coagulopathy after TBI

Fresh Frozen Plasma

Antifibrinolytics

rFVIIa

Reversal of Hypercoagulation

Volume (Hypertonic Saline-Dextran)

Fresh Frozen Plasma

Administration of FFP in coagulopathic patients is part of the standard treatment in traumatology (Lucas et al., Am J Surg 1996; Kashuk et al., Ann Surg 2010)

Prophylactic administration in TBI patients has not proven to be beneficial in reversing coagulopathy or improving outcome (Winter et al., 1989)

Fresh Frozen Plasma



ELSEVIER

Clinical Neurology and Neurosurgery 109 (2007) 166–171

Clinical Neurology
and Neurosurgery

www.elsevier.com/locate/clineuro

The effect of fresh frozen plasma in severe closed head injury

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Abstract

Objective: Traumatic brain injury (TBI) is one of the most common causes of morbidity and mortality. Coagulopathy, commonly occurring after severe TBI, is associated with poor outcome and secondary complications, especially delayed traumatic intracerebral hematoma (DTICH). In this study we evaluated the effect of fresh frozen plasma (FFP) on the reduction in the incidence of DTICH in severe closed head injury victims.

Methods: This study was carried out as a double-blind randomized clinical trial. Ninety patients were entered in two parallel groups taking either FFP or normal saline (N/S). Patients' selection criteria for both groups were: severe closed head injury (Glasgow coma scale ≤ 8), no mass lesion required evacuation and no history of coagulopathy. The clinical findings, laboratory data, computed tomography (CT) scans and Glasgow outcome scale after 1 month were assessed and compared in two groups.

Results: Out of 90 patients, 44 received FFP and 46 received N/S. The development of new intracerebral hematoma in follow-up CT scans were more common in the FFP group than the N/S group ($p=0.012$). Both groups showed similar frequency of poor outcome ($p=0.343$).

~~The mortality was significantly more common in the FFP group than in the N/S group (63% versus 35%, $p=0.006$).~~

Conclusion: The result of this study revealed that early empirical infusion of FFP in patients with severe head injury may lead to adverse effects, such as an increase in the frequency of DTICH and an increase in the mortality.

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Peiniger et al., Crit Care 2011
Spinella et al., J Trauma 2011

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Fresh Frozen Plasma

Antifibrinolytics

rFVIIa

Reversal of Hypercoagulation

Volume (Hypertonic Saline-Dextran)

Antifibrinolytics (Tranexamic acid)

BMJ

BMJ 2011;343:d3795 doi: 10.1136/bmj.d3795

Page 1 of 11

Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study)

Objective To assess the effect of tranexamic acid (which reduces bleeding in surgical patients and reduces mortality due to bleeding in trauma patients) on intracranial haemorrhage in patients with traumatic brain injury.

Methods A nested, randomised, placebo controlled trial. All investigators were masked to treatment allocation. All analyses were by intention to treat.

Patients 270 adult trauma patients with, or at risk of, significant extracranial bleeding within 8 hours of injury, who also had traumatic brain injury.

Interventions Patients randomly allocated to tranexamic acid (loading dose 1 g over 10 minutes, then infusion of 1 g over 8 hours) or matching placebo.

Main outcome measures Intracranial haemorrhage growth (measured by computed tomography) between hospital admission and then 24–48 hours later, with adjustment for Glasgow coma score, age, time from injury to the scans, and initial haemorrhage volume.

Results Of the 133 patients allocated to tranexamic acid and 137 allocated to placebo, 123 (92%) and 126 (92%) respectively provided information on the primary outcome. All patients provided information on clinical outcomes. The mean total haemorrhage growth was 5.9 ml (SD 26.8) and 8.1 mL (SD 29.2) in the tranexamic acid and placebo groups respectively (adjusted difference –3.8 mL (95% confidence interval –11.5 to 3.9)). New focal cerebral ischaemic lesions occurred in 6 (5%) patients in the tranexamic acid group versus 12 (9%) in the placebo group (adjusted odds ratio 0.51 (95% confidence interval 0.18 to 1.44)). There were 14 (11%) deaths in the tranexamic acid group and 24 (18%) in the placebo group (adjusted odds ratio 0.47 (0.21 to 1.04)).

Conclusions This trial shows that neither moderate benefits nor moderate harmful effects of tranexamic acid in patients with traumatic brain injury can be excluded. However, the analysis provides grounds for further clinical trials evaluating the effect of tranexamic acid in this population.

Antifibrinolytics (Tranexamic acid)

BMJ

BMJ 2011;343:d3795 doi: 10.1136/bmj.d3795

Page 1 of 11

Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study)

What did the study add:

1. First randomised, placebo controlled trial to evaluate the effects of antifibrinolytic TXA in patients with TBI
2. Non-significant trends to beneficial effects justify a randomised controlled trial to evaluate the effectiveness of the early administration of TXA in TBI > CRASH-3 trial
3. An early short course of TXA seems to be safe (in relation to new ischemic brain lesions) in patients with trauma with extracranial significant bleeding and concomitant TBI

Antifibrinolytics (Tranexamic acid)

if administered > „give it early!“

Ⓜ The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH-2 collaborators*

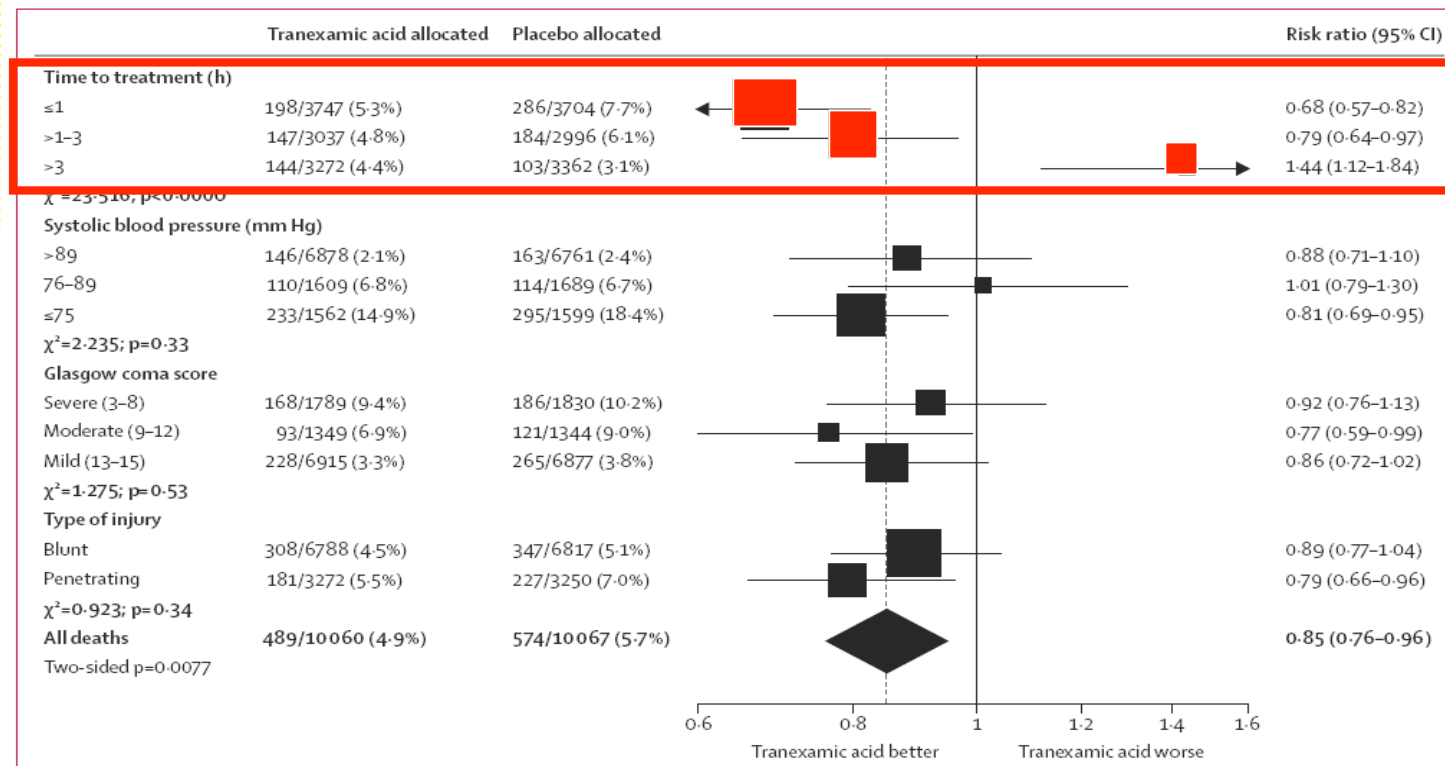


Figure 1: Mortality due to bleeding by subgroups

Antifibrinolytics (Tranexamic acid)

if administered > „give it early!“

Neurosurgery. 2005 Nov;57(5):837-44.

Rapid administration of antifibrinolytics and strict blood pressure control for intracerebral hemorrhage.

Sorimachi T, Fujii Y, Morita K, Tanaka R.

Department of Neurosurgery, Nishiogi-chuo Hospital, Tokyo, Japan. sorimachi-t@h2.dion.ne.jp

Abstract

OBJECTIVE: Hematoma growth is a major cause of poor outcome in patients with intracerebral hemorrhage. We evaluated the efficacy of a combination of rapid antifibrinolytic therapy and strict blood pressure control for prevention of hematoma growth in this retrospective study.

METHODS: Systolic blood pressure was strictly controlled below 150 mm Hg by use of intravenously administered nicardipine (BPC). Prolonged infusion of antifibrinolytic therapy was given by intravenous administration of 1 g tranexamic acid over a period of 6 hours (PAF). Rapid administration of antifibrinolytic therapy was given by intravenous administration of 2 g tranexamic acid over a period of 10 minutes (RAF). Immediately after diagnosis of intracerebral hemorrhage on computed tomographic scan, 156 patients who were admitted within 24 hours of onset were treated with either a combination of PAF and BPC (PAF group) or a combination of RAF and BPC (RAF group). The incidence of hematoma growth determined by a second computed tomographic scan the day after admission was compared between the PAF and the RAF groups.

RESULTS: Hematoma growth was observed in 11 (17.5%) of 63 patients in the PAF group and 4 (4.3%) of 93 patients in the RAF group using a 20% cutoff value for hematoma enlargement. The RAF group showed a significantly low incidence of hematoma growth compared with the PAF group ($P < 0.05$). Between the two groups, there was no significant difference in any of the other factors reported to affect hematoma growth.

CONCLUSION: The combination of rapid administration of antifibrinolytics and strict blood pressure control may prevent hematoma growth in patients with intracerebral hemorrhage.

Frequencies of TBI-
Coagulopathy

Risk Factors

Outcome

Hypotheses

Treatment

Conclusions

Treatment Option for Coagulopathy after TBI

Fresh Frozen Plasma

Antifibrinolytics

rFVIIa

Reversal of Hypercoagulation

Volume (Hypertonic Saline-Dextran)

Recombinant Factor VIIa (rFVIIa)

Neurosurgery. 2008 Apr;62(4):776-86; discussion 786-8.

Recombinant factor VIIa in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial.

Narayan RK, Maas AI, Marshall LF, Servadei F, Skolnick BE, Tillinger MN; rFVIIa Traumatic ICH Study Group.

Collaborators (6)

Department of Neurosurgery, University of Cincinnati, Cincinnati, Ohio, USA.

Aim: To evaluate the safety and preliminary effectiveness of rFVIIa to limit traumatic intracerebral hemorrhage progression

M/M:

1. Prospective, randomized, placebo-controlled, dose escalation study
2. Inclusion tICH lesions 2 ml on a baseline CT obtained within 6 hrs of injury
3. rFVIIa or placebo within 2.5 hrs of CT and < 7 hrs of injury
4. CTs repeated at 24 and 72 hrs
5. 5 escalating doses (40, 80, 120, 160, 200 microg/kg rFVIIa)
6. Clinical evaluations/adverse events recorded until d15

Recombinant Factor VIIa (rFVIIa)

Results:

NO difference in mortality or number/type adverse events

A nonsignificant trend for rFVIIa dose-response to limit traumatic intracranial hemorrhage volume progression was observed (placebo, 21.0 ml; rFVIIa, 10.1 ml).

Asymptomatic deep vein thrombosis, detected on routinely performed ultrasound at day 3 more frequently in the rFVIIa treatment group (placebo, 3%; rFVIIa, 8%; not significant)

Recombinant Factor VIIa (rFVIIa)

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Review

A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia

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ABSTRACT

Hematoma growth is common in intracerebral hemorrhage (ICH) and is associated with a poor outcome for patients. To evaluate the efficacy and safety of recombinant activated factor VII (rFVIIa) used as a hemostatic agent in patients with ICH without hemophilia, we searched Medline, Scopus, the Cochrane Library, Clinicaltrials.gov and the Stroke Trials Directory. Five randomized controlled trials were selected for analysis. Although rFVIIa can reduce the change in ICH volume, there was no significant difference in mortality, modified Rankin Scale (mRS) score or extended Glasgow Outcome Scale (GOS-E) score in patients treated with rFVIIa or placebo. There was a significant increase in arterial thromboembolic adverse events (TAE) in patients treated with rFVIIa. There was an increase in deep vein thrombosis in patients with spontaneous ICH and traumatic ICH. In conclusion, the use of rFVIIa reduces the growth of the hematoma but does not improve patient survival or functional outcome after ICH; in addition,

In conclusion, the use of rFVIIa reduces the growth of the hematoma but does not improve patient survival or functional outcome after intracranial hemorrhage; in addition, rVIIa increases the incidence of arterial thrombembolic events!

Recombinant Factor VIIa (rFVIIa)

Summary

Recombinant Factor VIIa:

1. may limit progression of traumatic intracranial hemoatoma/hematoma growth
2. may rapidly and effectively reverse coagulopathy (INR > 1.4) in patients with severe TBI thus decreasing the time to intervention/surgery and the use of blood products
3. does not improve outcome (survival/functional outcome)
4. is associated with a lower total cost of hospitalization compared with standard reversal with FFP
5. Appears to be safe but safety data are somewhat conflicting

Bartal et al., J Trauma 2007
Kluger et al., Crit Care 2007
Narayan et al., Neurosurgery 2008
Stein et al., J Trauma 2008
Stein et al., J Trauma 2009
Yuan et al., J Clin Neurosc 2010

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Reversal of Hypercoagulation

The administration of antithrombin III concentrate, a procoagulant blocker, has not been shown to improve outcome or to have clinical benefit in TBI

Antiplatelet therapy and anticoagulation with heparin are well-established treatments for thrombembolic diseases but their use after TBI is counterintuitive given the high risk of hemorrhagic progression

Antiplatelet compounds have been shown to diminish the size of cortical lesions and microthrombi in animal models of TBI but have never been tested in humans

Hoots, Semin Thromb Hemost 1997

Owings, Gosselin, Thromb hemost (Suppl) 1997

Granander et al., J Neurosurg Anaesthesiol 2001

Betzner et al., J Neurotrauma 2001

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J Neuroinflammation. 2010 Jan 18;7:5.

Prehospital resuscitation with hypertonic saline-dextran modulates inflammatory, coagulation and endothelial activation marker profiles in severe traumatic brain injured patients.

Rhind SG, Crnko NT, Baker AJ, Morrison LJ, Shek PN, Scarpelini S, Rizoli SB.

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Abstract

BACKGROUND: Traumatic brain injury (TBI) initiates interrelated inflammatory and coagulation cascades characterized by wide-spread cellular activation, induction of leukocyte and endothelial cell adhesion molecules and release of soluble pro/antiinflammatory cytokines and thrombotic mediators. Resuscitative care is focused on optimizing cerebral perfusion and reducing secondary injury processes. Hypertonic saline is an effective osmotherapeutic agent for the treatment of intracranial hypertension and has immunomodulatory properties that may confer neuroprotection. This study examined the impact of hypertonic fluids on inflammatory/coagulation cascades in isolated head injury.

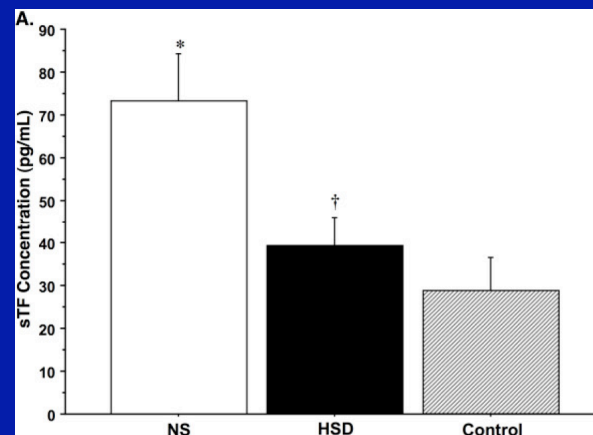
METHODS: Using a prospective, randomized controlled trial we investigated the impact of prehospital resuscitation of severe TBI (GCS < 8) patients using 7.5% hypertonic saline in combination with 6% dextran-70 (HSD) vs 0.9% normal saline (NS), on selected cellular and soluble inflammatory/coagulation markers. Serial blood samples were drawn from 65 patients (30 HSD, 35 NS) at the time of hospital admission and at 12, 24, and 48-h post-resuscitation. Flow cytometry was used to analyze leukocyte cell-surface adhesion (CD62L, CD11b) and degranulation (CD63, CD66b) molecules. Circulating concentrations of soluble (s)L- and sE-selectins (sL-, sE-selectins), vascular and intercellular adhesion molecules (sVCAM-1, sICAM-1), pro/antiinflammatory cytokines [tumor necrosis factor (TNF)-alpha and interleukin (IL-10)], tissue factor (sTF), thrombomodulin (sTM) and D-dimers (D-D) were assessed by enzyme immunoassay. Twenty-five healthy subjects were studied as a control group.



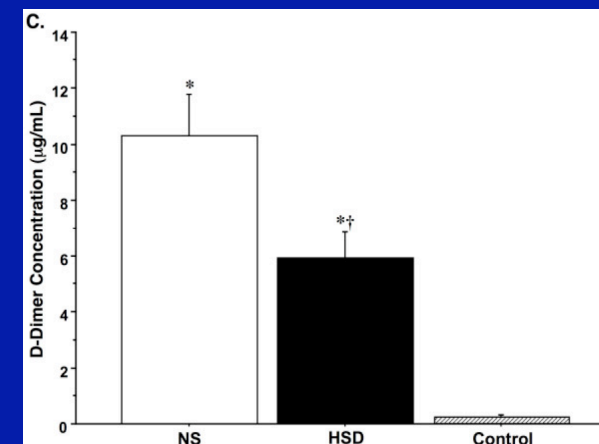
Volume (Hypertonic Saline-Dextran)

RESULTS: TBI provoked marked alterations in a majority of the inflammatory/coagulation markers assessed in all patients. Relative to control, NS patients showed up to a 2-fold higher surface expression of CD62L, CD11b and CD66b on polymorphonuclear neutrophils (PMNs) and monocytes that persisted for 48-h. HSD blunted the expression of these cell-surface activation/adhesion molecules at all time-points to levels approaching control values. Admission concentrations of endothelial-derived sVCAM-1 and sE-selectin were generally reduced in HSD patients. Circulating sL-selectin levels were significantly elevated at 12 and 48, but not 24 h post-resuscitation with HSD. TNF-alpha and IL-10 levels were elevated above control throughout the study period in all patients, but were reduced in HSD patients. Plasma sTF and D-D levels were also significantly lower in HSD patients, whereas sTM levels remained at control levels.

Tissue factor in HSD



D-dimers in HSD



Plasma concentrations of tissue factor (sTF) and D-dimers in TBI patients resuscitated with normal saline (NS, n = 30) or hypertonic saline-dextran (HSD, n = 25) at the time of ED admission

Conclusions (I)

- Coagulopathy following TBI is frequent and an important independent risk factor related to prognosis
- The complex mechanisms that lead to the development of coagulopathy after TBI are still poorly defined and the early events after TBI must be studied in greater detail to identify the main triggers
- The use of functional assays such as viscoelastic testing should be encouraged because they can help to direct individualized treatments and allow a more targeted goal-orientated therapy

Conclusions (II)

- HF in patients with severe brain injury is infrequent but, if present, associated with high mortality
- Shock (acidosis) and further hypoperfusion should be prevented (systolic blood pressure < 150 mmHg!)
- Plasma/FFP should be given only when there is evidence of coagulation abnormalities (risk stratification via scoring systems/algorithms (TASH)?) > NO empirical infusion of FFP in TBI patients!!

Conclusions (III)

- Have not talked about LyoPlasma (freeze dried-plasma)!
- Survival benefit for high platelet:pRBC has been demonstrated retrospectively (Thrombocytopenia on admission linked to progression of intracranial hemorrhage)
- Short course of TXA seems to be safe (in relation to new ischemic brain lesions) in patients with trauma and concomitant TBI > should be given early!!
- Non-significant trends to beneficial effects justify a randomised controlled trial to evaluate the effectiveness of early TXA in TBI > CRASH-3 trial

Conclusions (IV)

- Effectiveness of rFVIIa needs to be replicated and further validated in a prospective randomized controlled trial
- Fibrinogen (F1) > little data, 7% hypofibrinogenemia in TBI (Chhabra et al. 2010)
- Attempts to reverse hypercoagulation are either counterintuitive or still experimental
- Hypertonic saline-dextran has important modulatory potential in attenuating the up-regulation of leukocyte/endothelial cell pro-inflammatory/prothrombotic mediators and may help to ameliorate secondary brain injury

Thank you very much for your attention

DO YOU HAVE
THE BLEEDING
UNDER CONTROL
???



Das Buch zum Fest !!

