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Short Communication

Trauma-Induced Coagulopathy: Standard Coagulation Tests, Biomarkers of Coagulopathy, and Endothelial Damage in Patients with Traumatic Brain Injury

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Abstract

It remains to be debated whether traumatic brain injury (TBI) induces a different coagulopathy than does non-TBI. This study investigated traditional coagulation tests, biomarkers of coagulopathy, and endothelial damage in trauma patients with and without TBI. Blood from 80 adult trauma patients was sampled (median of 68 min [IQR 48–88] post-injury) upon admission to our trauma center. Plasma/serum were retrospectively analyzed for biomarkers reflecting sympathoadrenal activation (adrenaline, noradrenaline), coagulation activation/inhibition and fibrinolysis (protein C, activated protein C, tissue factor pathway inhibitor, antithrombin, prothrombin fragment 1 + 2, thrombin/antithrombin complex, von Willebrand factor, factor XIII, d-dimer, tissue-type plasminogen activator, plasminogen activator inhibitor-1), immunology (interleukin [IL]6), endothelial cell/glycocalyx damage (soluble thrombomodulin, syndecan-1), and vasculogenesis (angiopoietin-1, -2). Patients were stratified according to: 1) isolated severe head/neck injuries (Abbreviated Injury Score [AIS]-head/neck ≥ 3, AIS-other < 3) (isoTBI); 2) severe head/neck and extracranial injuries (AIS-head/neck ≥ 3, AIS-other > 3) (sTBI + other); and 3) injuries without significant head/neck injuries (AIS-head/neck < 3, including all AIS-other scores) (non-TBI). Twenty-three patients presented with isoTBI, 15 with sTBI + other and 42 with non-TBI. Acute coagulopathy of trauma shock, defined as activated partial thromboplastin time (APTT) and/or international normalized ratio (INR) > 35 sec and > 1.2, was found in 13%, 47%, and 5%, respectively ($p = 0.000$). sTBI + other had significantly higher plasma levels of adrenaline, noradrenaline, annexin V, d-dimer, IL-6, syndecan-1, soluble thrombomodulin, and reduced protein C and factor XIII levels (all $p < 0.05$). No significant biomarker differences were found between isoTBI and non-TBI patients. Injury Severity Scale (ISS) rather than the presence or absence of head/neck injuries determined the hemostatic and biomarker response to the injury. The coagulopathy identified thus reflected the severity of injury rather than its localization.

Key words: coagulopathy; pathogenesis; TBI; trauma

Introduction

Trauma-induced coagulopathy (TIC) has been introduced as a term describing the multifactorial coagulopathy following trauma.[1] TIC covers the endogenous acute coagulopathy of trauma, which occurs immediately after injury, and is attributed to activation of endogenous inflammatory and hemostatic (including fibrinolysis, and pro- and anticoagulation) cascades. Further, TIC is exacerbated by shock, hemorrhage, hypothermia, acidosis, and transfusions, and genetic factors are also important.[2]

The definition of TIC varies between studies, but minor increases in activated partial thromboplastin time (APTT) and international normalized ratio (INR) predict increased mortality in trauma patients, including those with isolated brain injuries,[3] and TIC is an independent predictor of mortality[4,5] and is positively correlated with the injury severity score (ISS).[6]

TIC pathogenesis in traumatic brain injury (TBI) remains elusive, although extensive tissue factor (TF) release from the brain parenchyma, described in the 1970s,[7] has been proposed. Cohen et al. suggested that activation of the protein C system may be of importance,[8] similar to the findings by Brohi et al. who introduced the ''acute coagulopathy of trauma shock'' (ACoTS) covering trauma patients with an established coagulopathy on admission to the emergency room.[9] ACoTS is identified by prolonged plasma-based

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coagulation tests such as prothrombin time (PT) or partial thromboplastin time (PTT).[9,10] ACoTS is present on admission to the emergency room[10] and is proposed to be driven by trauma, shock, and tissue hypoperfusion induced protein C activation and hyperfibrinolysis,[5] and is reported in 25–35% of trauma patients with severe injuries.[5,9] Recently, we reported of an association between sympathoadrenal activation,[6] endothelial cell/glycocalyx damage,[11] hypocoagulability, and poor outcome in trauma patients, suggesting that the degree of tissue injury and the sympathoadrenal activation elicited was the main driver of coagulopathy and poor outcome.

It remains to be debated whether TBI induces pronounced coagulopathy compared to non-TBI. In a study from 2007, including 5357 TBI patients, Harhangi et al. reported a prevalence of coagulopathy in patients with TBI to one third of the patients, when defining coagulopathy as any coagulation abnormality reported in the various studies.[12] Similarly, in a retrospective analysis from 2009, Wafaisade et al. found, in 3114 TBI patients (Abbreviated Injury Score [AIS]-head ≥ 3 and AIS-other < 3), that $\sim 25\%$ had coagulopathy, defined as ''prothrombin time test'' (Quick's value) $< 70\%$ and/or platelets $< 100.000\ \mu$L, upon admission. Further, a positive correlation between the severity of the brain injury and coagulopathy was found.[13] The purpose of the present study was to investigate the hemostatic response to isolated severe TBI (isoTBI), severe TBI including other severe body-injuries (sTBI + other) and injury without severe TBI (non-TBI), assessed by traditional coagulation tests, biomarkers of coagulopathy and endothelial damage.

Methods

Study design

A prospective observational cohort study of trauma patients was admitted directly to a level I equivalent trauma center (TC) at Rigshospitalet (Copenhagen, Denmark). The study was part of an ongoing multicenter study, Activation of Coagulation and Inflammation after Trauma 3 (ACIT3), approved by the Regional Ethics Committee (H-4-2009-139), the Danish Data Protection Agency, and conducted in accordance with the Second Declaration of Helsinki.

Patients were stratified into three groups according to their AIS score (www.trauma.org): isoTBI (AIS-head/neck ≥ 3 and AIS-other < 3), sTBI + other (AIS-head/neck ≥ 3 and AIS-other ≥ 3), and non-TBI (AIS-head/neck < 3 including all AIS-other scores).[14]

Patient selection

We included trauma patients ≥ 18 years of age who met the criteria for full trauma team activation, and had an arterial cannula inserted. Exclusion criteria were arrival in the TC > 2 h after injury, > 2000 mL of intravenous fluids administered before hospital arrival, transfer from another hospital, and burns $> 5\%$ total body surface area. Patients were retrospectively excluded if they were taking anticoagulant/antiplatelet medications (except aspirin), had moderate or severe liver disease, or had known bleeding diathesis. Data on demography, clinical and biochemical parameters, transfusion, and 30 day mortality were recorded, and ISS scores were obtained from the Trauma Audit & Research Network (TARN) database or registered locally. No patients received tranexamic acid, adrenaline, or noradrenaline prior to blood sampling.

Definition of coagulopathy

ACoTS was defined as APTT and/or INR above normal reference, that is, > 35 sec or > 1.2 ratio, respectively.[15]

Definition of overt disseminated intravascular coagulation (DIC)

Overt DIC was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria, with the following cutoff values: 1) platelet counts $< 50 \times 10^9$/l (two points), $50–100 \times 10^9$/l (one point); 2) fibrinogen < 1 g/L (one point); 3) d-dimer > 4 mg/L (three points), 0.39–4.00 mg/L (two points); and 4) INR (prothrombin time [PT] is not available at our hospital) > 2.3 (two points), 1.4–2.3 (one point). Overt DIC was diagnosed as a sum of five or more points.

Blood sampling

Blood was sampled at arrival for standard arterial blood gas, routine biochemistry, and research analyses (citrate, heparin, ethylenediaminetetraacetic acid [EDTA] plasma, serum) and routine biochemistry samples were analyzed as previously described.[11,15–18] Plasma samples were kept at 5°C during the first hour, whereas serum samples were kept at room temperature (RT) for 1 h before centrifugation (one [serum] or two [plasma] times 1800 *g* at 5°C for 10 min) and stored at -80°C within 2 h.

Enzyme linked immunosorbent assay (ELISA) measurements

Soluble biomarkers of tissue, endothelial cell and glycocalyx damage, coagulation activation/inhibition and factor consumption, fibrinolysis, and inflammation were measured in serum/plasma in uniplicate by commercially available immunoassays according to the manufacturer's recommendations.

EDTA plasma: angiopoietin-2 (Ang2) (R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN; mean minimum detectable dose [MDD] = 8.29 pg/mL); AnnexinV (American Diagnostica Inc. [ADI], Stamford, CT; lower limit of detection [LLD] not stated, normal reference < 10 ng/mL); soluble thrombomodulin (sTM) (Nordic Biosite, Copenhagen, Denmark; LLD 0.38 ng/mL) and d-dimer (ADI; LLD 2–4 ng/mL).

Citrate plasma: angiopoietin-1 (Ang1) (R&D Systems, Mean MDD = 3.45 pg/mL); protein C (PC) (Helena Laboratories, Beaumont, TX; LLD 5% of reference plasma); activated protein C (APC) (USCNLIFE; LLD 4.2 pg/mL); tissue type plasminogen activator (tPA) (ADI, detects single chain [sc]-tPA, two chain [tc]-tPA and tPA/plasminogen activator inhibitor (PAI-1) complexes; LLD 1 ng/mL); PAI-1 (Assaypro, St. Charles, MO; LLD 0.2 ng/mL); prothrombin fragment 1 + 2 (PF1.2, USCNLIFE; LLD 0.043 nmol/L); thrombin/antithrombin complex (TAT) (USCNLIFE, Wuhan EIAab Science Co, Wuhan, China; LLD 0.215 ng/mL); TF pathway inhibitor (TFPI) (ADI, detects intact TFPI, truncated TFPI, TF/Factor VIIa/TFPI complexes; LLD 0.18 ng/mL); von Willebrand factor antigen (vWF) (Helena Laboratories, LLD 5% of reference plasma); factor XIII (FXIII) (Assaypro; LLD 50 pg/mL); interleukin-6 (IL-6) (Quantikine HS, R&D Systems Europe; LLD 0.039 pg/mL).

Serum: Syndecan-1 (Diaclone SAS, Besancon, France; LLD 2.56 ng/mL).

Statistical analysis

Data are reported as medians with interquartile ranges (IQR). Statistical analyses were performed using SPSS v. 20 (IBM corporation, Armonk, NY). Data from patients stratified according to isoTBI, sTBI + other and non-TBI were compared by Kruskal–Wallis and Bonferroni adjusted Wilcoxon rank sum post-hoc tests, and χ^2/Fisher's exact tests, as appropriate. The number of patients included in the

Table 1. Demography, Injury Severity, Transfusion, and Mortality in 80 Trauma Patients Stratified According to IsoTBI (AIS-Head/Neck ≥ 3 and AIS-Other < 3), sTBI + Other (AIS-Head/Neck ≥ 3 and AIS-Other ≥ 3), and Non-TBI (AIS-Head < 3, Including All AIS-Other)

n		*isoTBI* 23	*sTBI + other* 15	*non-TBI* 42	p-*value*
Demography, injury severity, shock and mortality					
Age	years	56 (39–73)	45 (27–71)	43 (33–58)	0.168
Male gender	% (*n*)	65% (15)	80% (12)	64% (27)	0.517
ISS	score	25 (15–26)	35 (32–37)	10 (7–22)	**0.000**
Blunt trauma	% (*n*)	91% (21)	93% (14)	83% (35)	0.487
GCS on scene	score	7 (5–12)	3 (3–7)	15 (13–15)	**0.000**[a,b]
AIS-head/neck	score	4 (3–5)	4 (3–5)	0 (0–0)	**0.000**[a,b]
AIS-face	score	0 (0–1)	1 (0–2)	0 (0–0)	**0.004**[c]
AIS-thorax	score	0 (0–0)	3 (1–3)	2 (0–3)	**0.000**[b,c]
AIS-abdomen	score	0 (0–0)	2 (0–3)	0 (0–2)	**0.000**[b,c]
AIS-extremities	score	0 (0–0)	3 (2–4)	2 (0–3)	**0.000**[b,c]
HR on scene	mmHg	75 (61–90)	82 (74–106)	86 (78–99)	0.113
SBP on scene	mmHg	142 (129–155)	135 (107–150)	130 (120–145)	0.141
RR on scene	frequency	15 (13–20)	15 (9–22)	18 (14–20)	0.524
Mortality 30-day	% (*n*)	22% (5)	40% (6)	5% (2)	**0.005**[a]
Transfusions					
Crystalloids (PH)	mL	500 (400–950)	1200 (550–1500)	700 (400–1400)	0.057
RBC 0–24 h	units	0 (0–2)	2 (0–11)	0 (0–3)	0.053
FFP 0–24 h	units	0 (0–0)	0 (0–8)	0 (0–2)	0.116
PLT 0–24 h	units	0 (0–0)	0 (0–4)	0 (0–0)	0.071
MT (> 10 RBC/24h)	% (*n*)	4% (1)	27% (4)	12% (5)	0.125

Data are presented as medians (interquartile range [IQR]) or *n* (%), with *p* values in bold for $p < 0.050$. Groups were compared by Kruskal-Wallis and Bonferroni adjusted Wilcoxon rank sum post- hoc tests, and χ^2/Fisher's exact tests, as appropriate.

[a]sTBI + other vs. non-TBI Bonferroni adjusted $p < 0.05$.

[b]isoTBI vs. non-TBI Bonferroni adjusted $p < 0.05$.

[c]IsoTBI vs. sTBI + other Bonferroni adjusted $p < 0.05$.

ISS, injury severity score; GCS, Glasgow coma scale; AIS, Abbreviated Injury Score; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; PH, pre-hospital; RBC, red blood cells; FFP, fresh frozen plasma; PLT, platelets; MT, multi-transfused.

present study was not based on power calculations but on the number of samples available for analysis by one ELISA kit, as this was a hypothesis-generating study in which we performed a large number of biomarker analyses (19 biomarkers × 80 samples = 1520 analyses). *P*-values < 0.05 were considered significant. Data from these 80 patients have been reported previously in other articles.[11,15–18]

Results

Patients

Twenty-three patients presented with isoTBI, 15 with sTBI + other, and 42 with non-TBI (Table 1); 68% of the patients were males who had sustained blunt trauma, and there was no difference across groups in age or vital parameters regarding the scene of the accident. Patients with sTBI + other had the highest ISS score and lowest Glasgow Coma Scale (GCS) score at the scene of the accident and had higher 30 day mortality followed by patients with isoTBI (Table 1). Patients with non-TBI were less severely injured, with higher GCS scores at the scene of the accident, and survival in this group was highest, despite that they received the same numberof transfusions. Blood was sampled at a median of 68 min (IQR 48–88) post-injury.

Sympathoadrenal activation, shock, hemostasis, tissue and endothelial damage, inflammation, and vasculogenesis

ACoTS on admission was found in 47% of the patients with sTBI + other compared with 13% of isoTBI and 5% of non-TBI patients, respectively. STBI + other patients had significantly higher plasma levels of adrenaline, noradrenaline, and glucose, and lower pH, which were associated with a higher degree of activation/consumption of the natural anticoagulants and markers of fibrinolysis: low PC, antithrombin (AT), fibrinogen, and FXIII, and higher d-dimer levels (table 2). Also, in sTBI + other patients, white blood cells (WBC), including neutrophils and plasma levels of IL-6, were higher, and patients had more extensive damage to the endothelium (higher sTM) and glycocalyx (higher syndecan-1) (Table 2) than the isoTBI and non-TBI groups. Importantly, isoTBI and non-TBI patients presented with similar levels of biomarkers, except for borderline higher levels of APC in isoTBI ($p = 0.054$). No difference in vasculogenesis (ang-1 and ang-2) was found among the three groups, and none of the patients had overt DIC.

To investigate if patients in the non-TBI group with brain injuries equivalent to AIS-head/neck = 1 ($n = 3$) and 2 ($n = 5$) were capable of making the results misleading, we performed a new subgroup analysis of patients with AIS-head/neck = 1–2 excluded from the non-TBI group. PC, APC, PAI-1 and tPA (related to the protein-C system) were not affected after excluding patients with head/neck injuries from the non-TBI group. The only significant difference between isoTBI ($n = 23$) and AIS-head/neck = 0 ($n = 34$) patients was higher ISS and lower GCS in isoTBI. Further, we found no difference in the incidence of ACoTS between isoTBI and AIS-head/neck = 0 patients. sTBI + other patients still presented with increased mortality and biomarkers reflecting a higher degree of coagulation and sympathoadrenal activation, as described previously.

Table 2. Hemostasis, Hematology, Tissue Perfusion, Sympathoadrenal Activation, Immunology, Endothelial Damage, Glycocalyx Degradation, and Vasculogenesis in 80 Adult Trauma Patients Stratified According to IsoTBI (AIS-Head/Neck ≥ 3 and AIS-Other < 3), sTBI + Other (AIS-Head/Neck ≥ 3 and AIS-Other ≥ 3), and Non-TBI (AIS-Head/Neck < 3, Including All AIS-Other)

n		*isoTBI* 23	*sTBI + other* 15	*non-TBI* 42	p-*value*
Hemostasis, shock, sympathoadrenal activation, and biochemistry					
APTT	sec	25 (24–26)	27 (23–34)	25 (24–28)	0.698
INR		1.1 (1.0–1.1)	1.2 (1.1–1.3)	1.1 (1.1–1.1)	0.084
ACoTS	% (*n*)	13% (3)	47% (7)	5% (2)	**0.000**[a]
Overt DIC	% (*n*)	0% (0)	0% (0)	0% (0)	NA
Hemoglobin	mmol/L	8.3 (7.4–8.7)	7.9 (6.6–8.5)	8.3 (7.6–8.9)	0.288
Platelet count	10^9/L	185 (166–253)	189 (173–251)	211 (187–261)	0.506
Fibrinogen	g/L	2.3 (1.8–2.7)	2.0 (1.3–2.4)	2.6 (2.2–2.9)	**0.042**[a]
FXIII	μg/mL	29 (24–33)	24 (18–30)	33 (25–41)	**0.003**[a]
Lactate	mmol/L	1.7 (1.0–2.5)	2.0 (1.3–2.7)	1.7 (1.3–2.7)	0.876
BE	mmol/L	−1.8 (−2.6–0.3)	−3.9 (−6.2–1.4)	−1.8 (−3.5–0.0)	0.147
pH		7.4 (7.3–7.4)	7.3 (7.2–7.3)	7.4 (7.3–7.4)	**0.036**[a,b]
Adrenalin	pg/mL	274 (103–935)	1104 (798–3145)	295 (137–1107)	**0.003**[a,b]
Noradrenalin	pg/mL	644 (212–990)	1379 (822–1706)	489 (258–1247))	**0.009**[b]
Glucose	mmol/L	8.7 (6.8–10)	13 (8.1–15)	7.4 (6.2–8.7)	**0.000**[a,b]
Natural anticoagulants					
PC	%	109 (93–129)	83 (71–103)	116 (99–128)	**0.009**[a,b]
APC	ng/mL	11 (10–13)	10 (9–13)	9 (7–11)	0.054[(c)]
TFPI	ng/mL	66 (44–81)	68 (48–103)	57 (47–70)	0.528
AT	10^3 U/L	0.9 (0.8–1.0)	0.9 (0.7–0.9)	1.0 (0.8–1.0)	**0.048**[a]
Fibrinolysis					
d-dimer	ng/ml	170 (133–174)	173 (171–176)	145 (61–171)	**0.003**[a]
tPA	ng/ml	5.7 (3.4–8.8)	7.1 (4.8–13)	8.5 (3.7–14)	0.479
PAI-1	ng/ml	21 (9–32)	36 (18–54)	22 (15–38)	0.382
Platelet activation and thrombin generation					
PF 1 + 2	nmol/L	6.5 (2.0–35.0)	6.8 (2.4–16)	4.9 (1.6–16)	0.575
TAT	ng/mL	42 (35–45)	36 (31–39)	36 (30–40)	0.064
vWF%	%	159 (124–225)	198 (142–215)	201 (133–226)	0.801
AnnexinV	ng/mL	24 (21–29)	43 (28–49)	28 (20–37)	**0.015**[b]
Immunology					
WBC	10^9/L	12 (9.7–14)	19 (14–23)	12 (8.9–20)	**0.021**[b]
IL-6	pg/mL	60 (26–87)	123 (102–128)	38 (11–117)	**0.000**[a,b]
Neutrophils	10^9/L	7.7 (6.5–10)	15 (9.8–17)	8.2 (5.1–15)	**0.012**[b]
Endothelial damage, glycocalyx degradation, vasculogenesis, and tissue damage					
Syndecan-1	ng/mL	33 (16–43)	59 (31–88)	31 (18–49)	**0.018**[b]
sTM	ng/mL	1.4 (1.0–2.5)	3.7 (2.0–4.6)	1.3 (0.9–3.4)	**0.018**[b]
Ang1	pg/mL	24 (19–37)	26 (18–35)	28 (21–38)	0.909
Ang2	pg/mL	2405 (1993–2718)	2499 (2247–4085)	2473 (1974–3335)	0.523

Data are presented as medians (interquartile range [IQR]) or *n* (%), with *p* values in bold for $p < 0.050$. Groups were compared by Kruskal-Wallis and Bonferroni adjusted Wilcoxon rank sum post- hoc tests, and χ^2/Fisher's exact tests, as appropriate.

[a]sTBI + other vs. non-TBI Bonferroni adjusted $p < 0.05$.

[b]IsoTBI vs. sTBI + other Bonferroni adjusted $p < 0.05$.

[c]IsoTBI vs. non-TBI Bonferroni adjusted $p < 0.05$.

APTT, activated partial thromboplastin time; INR, international normalized ratio; ACoTS, acute coagulopathy of trauma shock; DIC, disseminated intravascular coagulation; BE, base excess; PC, protein C; APC, activated protein C; TFPI, tissue factor pathway inhibitor; AT, antithrombin; tPA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor-1; PF, prothrombin fragment 1 and 2; TAT, thrombin antithrombin; vWF, von willebrand factor; FXIII, coagulation factor XIII; WBC, white blood count; IL-6, interleukin-6; sTM, soluble thrombomodulin; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2.

Discussion

The main finding of the present study was that the severity of extracranial injuries rather than head/neck injuries in trauma patients determined the hemostatic and biomarker response to the injury. The findings here of an association between ISS and coagulopathy are in accordance with previous findings.[3,6,19–21] Patients with sTBI + other were more severely injured, and had the highest incidence of ACoTS, transfusion requirements, and mortality. Patients with isoTBI and non-TBI had fewer injuries and a lower incidence of shock, evidenced here by lower sympathoadrenal activation (circulating catecholamines) and higher pH.

Another key finding of the present study was that isoTBI and non-TBI patients did not differ significantly in any of the investigated parameters, except for a borderline higher APC level in isoTBI patients. This borderline difference was, however, not evident when excluding patients with AIS-head/neck = 1–2 from the non-TBI group. Low levels of unactivated protein C, which

precedes APC, has previously been reported in patients with TBI and concurrent hypoperfusion, which is consistent with the findings in hypoperfused trauma patients in general.[8,22]

Recently, Laroche et al. proposed that coagulopathy secondary to TBI may be caused by extensive TF release, an overactive fibrinolytic system, decreased platelet count/function, activation of the protein C system, and elevated sTM.[23] We found no evidence of increased coagulation activation as evaluated by PF 1 + 2 and TAT in isoTBI patients as compared with non-TBI patients, which was still evident when excluding patients with AIS-head/neck = 1–2 from the non-TBI group. Similarly, we did not find any evidence for an overactive fibrinolytic system as evidenced by tPA and PAI-1 levels among the groups, which argues against the hypothesis of an overactivation of the fibrinolytic system. Also, no difference in platelet count was found. However, because of the limited number of patients included in the present study, this finding should be reproduced in a larger cohort of patients, as ACoTS tended to be more common in isoTBI patients (13% vs. 5% for non-TBI patients).

We have previously reported in trauma patients that sympathoadrenal activation is an important driver of coagulopathy and endothelial/glycocalyx damage,[6,20] and in alignment with this, sTBI + other patients demonstrated the highest levels of circulating catecholamines, sTM, and syndecan-1 together with the highest incidence of ACoTS. Furthermore, and in alignment with our previous findings in this cohort, no patients presented with overt DIC, whether they had isoTBI or not.[15]

Importantly, isoTBI and non-TBI patients demonstrated similar levels of circulating catecholamines, biomarkers of endothelial/glycocalyx damage, and ACoTS, which was still evident when excluding patients with AIS-head/neck = 1–2 from the non-TBI group. IsoTBI patients, however, had significantly higher mortality (22%), emphasizing the poor prognosis of these patients related to the head/neck injury itself, which is in accordance with the mortality in isoTBI patients found by Talving and colleagues.[21] In alignment with Brohi et al.,[10,24] we found decreased levels of protein C and increased levels of sTM in patients with sTBI + other, indicating activation of the protein C system and damage to the endothelium. In alignment with the findings of the present study, Brohi et al. did not find any difference between patients with exclusively isolated brain injuries (AIS-head ≥ 3 and AIS-other < 3) and polytraumatized patients, including some with sTBI.[8,22]

Ang-2 has recently been reported to be elevated in trauma patients on admission, and has currently been given much attention in the literature because of its angiogenic properties.[25–27] Nag et al. has previously reported that ang-2 is associated with endothelial apoptosis and blood–brain barrier breakdown following TBI in a rat model.[28] Regarding a difference between isoTBI and non-TBI patients, Ganter et al. found that the presence of brain injury did not influence ang-2 levels, indicating no difference in the pathophysiological mechanism between isoTBI and non-TBI patients.[27] Data from the present study confirms this finding, which was still evident when excluding patients with AIS-head/neck = 1–2 from the non-TBI group.

Limitations

The results presented here are subject to the limitations inherent to observational studies, and, thereby, do not allow independent evaluation of the cause-and-effect relationship suggested. Further, the presents study presents data from a limited number of patients on the investigated biomarkers investigating TIC following TBI, and is also limited by general concerns about the use of the AIS-system.[29]

Conclusion

We found no significant difference in TIC pathophysiology whether patients had isoTBI or non-TBI, even when excluding patients with AIS-head/neck = 1–2 from the non-TBI group. On the basis of these findings, we propose that the hemostatic, vascular, and endothelial responses may be the same in isoTBI and non-TBI patients, and because of downstream effects from the sympathoadrenal response, mainly determined by the extracranial injuries.

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Author Disclosure Statement

No competing financial interests exist.

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