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Review

Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: A systematic review and meta-analysis

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ABSTRACT

Background and objectives: Acute traumatic coagulopathy (ATC) has been reported in the setting of isolated traumatic brain injury (iTBI) and associated with high mortality and poor outcomes. The aim of this systematic review was to examine the incidence and outcome of patients with ATC in the setting of iTBI.

Methods: We conducted a search of the MEDLINE database and Cochrane library, focused on subject headings and keywords involving coagulopathy and TBI. Design and results of each study were described. Studies were assessed for heterogeneity and the pooled incidence of ATC in the setting of iTBI determined. Reported outcomes were described.

Results: There were 22 studies selected for analysis. A statistically significant heterogeneity among the studies was observed ($p < 0.01$). Using the random effects model the pooled proportion of patients with ATC in the setting of iTBI was 35.2% (95% CI: 29.0–41.4). Mortality of patients with ATC and iTBI ranged between 17% and 86%. Higher blood transfusion rates, longer hospital stays, longer ICU stays, decreased ventilator free days, higher rates of single and multiple organ failure and higher incidence of delayed injury and disability at discharge were reported among patients with ATC.

Conclusions: ATC is commonly associated with iTBI and almost uniformly associated with worse outcomes. Any disorder of coagulation above the normal range appears to be associated with worse outcomes and therefore a clinically important target for management. Earlier identification of patients with ATC and iTBI, for recruitment into prospective trials, presents avenues for further research.

Contents

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Introduction

Acquired disorders of coagulation have been previously associated with traumatic brain injury [1–4]. The primary mechanisms of such disorders in the setting of trauma are acute traumatic coagulopathy (ATC, also termed early trauma induced coagulopathy, early coagulopathy of trauma and acute coagulopathy of trauma-shock) and delayed coagulopathy secondary to haemodilution [1–5]. Conventionally, the mechanism of ATC has been simplistically proposed as a result of depletion, dilution and dysfunction of procoagulant factors. It is now understood that the pathophysiology is much more complex than this.

A complex dynamic equilibrium exists between anti and procoagulant factors, platelets, endothelium function and fibrinolysis, with ATC a result of an imbalance in this complex system following tissue damage and hypoperfusion in trauma [6,7]. Hypothermia, continued blood loss and acidaemia are also known contributors to coagulopathy that lead to a global derangement in haemostasis and exacerbation of ATC [2,8,9]. The activation of protein C leading to inhibition of co-factors Va and VIIa appears to hold a key position in the development of ATC, and is triggered by hypoperfusion and endothelium damage. This leads to an overall disruption in coagulation via the decreased conversion of fibrinogen to fibrin. Over-activation of protein C occurs when hypoperfusion and endothelium damage releases thrombomodulin, a protein that combines with thrombin to form a complex which leads to the activation of protein C. The uptake of thrombin to form this complex also leaves less available to cleave fibrinogen [8].

The mechanism of platelet dysfunction in the setting of ATC is relatively unknown, but present in severely injured patients [10]. Platelet activation and fibrin generation are mutually dependent processes. Platelet thrombinase assembly creates a thrombin burst that propagates clot formation. Massive transfusion also can result in dilutional thrombocytopenia, this may be confused with true platelet dysfunction [8]. Other physiological factors contribute to global potentiating of coagulopathy in a non-causative relationship. In the context of shock and hypoperfusion, endothelium releases thrombomodulin which complexes with thrombin, which leaves less thrombin able to cleave fibrinogen whilst also helping activation of protein C, further inhibiting the extrinsic pathway and antifibrinolytic factors [5]. Shock is associated with a three-fold increase in the development of ATC [11]. Shock may also contribute to acidaemia caused by tissue hypoperfusion leading to anaerobic build-up of lactic acid. This change in pH alters protease function and increases risk of coagulopathy [11]. Hypothermia also plays a role in both generally impairing the coagulation pathways and hampering platelet function and adhesion [12]. This combination of hypoperfusion, hypothermia and acidaemia are common in the trauma patient and contribute to the exacerbation of ATC [2,6,8], leading to the 'triad of death' [13].

Coagulation disorders in the setting of traumatic brain injury have been associated with poor outcomes with in-hospital mortality up to 50% [14–18]. The true incidence of ATC in the setting of isolated traumatic brain injury (iTBI) is relatively unknown and has been estimated to be between 10% and 98% [14]. This very wide range has been attributed to inconsistent definitions of coagulopathy and criteria for iTBI [14]. Other factors included differences in times at which patients were tested for coagulopathy and sensitivity of tests. Defining the true incidence may help clarify the rationale for empiric management directed at ATC and subsequent development of appropriate guidelines.

The primary aim of this study was to determine the incidence of ATC in the setting of iTBI. Secondary aims were to investigate appropriate definitions of ATC and associated outcomes.

Methods

A systematic review and meta analysis were performed. The Prisma guidelines were followed in the development of this review. These guidelines [19] were developed to improve the quality and reporting of systematic reviews and meta-analysis. These guidelines were followed in the development of the methodology of this review.

Information sources

The authors searched for English language articles in MEDLINE (1990 – 20 February 2013), PubMed, Embase (1990 – 20 February 2013) and the Cochrane library (to Issue 1, 2013) using a combination of the following subject headings and keywords: "coagulopathy," "blood coagulation," "traumatic brain injury," "craniocerebral trauma," "brain injuries", "traumatic coagulopathy" and "isolated head trauma". Reference lists of relevant articles were scanned for further studies. Results were truncated to clinical trials, clinical studies, guidelines, and meta-analyses.

Study selection

Studies were included if they reported the incidence of acute isolated traumatic brain injury and coagulopathy as an outcome variable among adult patients (>16 years of age). Specific exclusion criteria were studies primarily involving patients with pre-existing coagulation disorders, patients on anticoagulants, studies primarily involving paediatric patients, non-traumatic brain injury, non-isolated traumatic brain injury, case reports and letters.

Eligibility was assessed by two reviewers scanning abstracts for suitability and reviewing the full text where necessary; disagreements were resolved by consensus.

Data collection

We extracted data about study size, number of patients, inclusion criteria, definitions of ATC, the proportion of patients that developed ATC and reported outcomes.

Analysis

The primary outcome was coagulopathy; the secondary outcome was mortality at a timeframe defined in the individual studies. Heterogeneity between studies was assessed using the Q test and I^2 statistic. In the case of significant heterogeneity, a random effects model was used to derive the pooled proportion with 95% confidence intervals. Statistical analyses were conducted using Stata v 12.0 (Statacorp, TX).

Results

Study identification and exclusions

Fig. 1 shows the search and selection procedures. We found 44 studies that fulfilled eligibility criteria and reported outcomes of interest. Of these, 22 studies were excluded. We included the report by Franschman et al. who collected data on 218 patients who were part of The Prospective Observational Cohort Neurotrauma (POCON) multicenter study in the Netherlands between June 2008 and May 2009 [20]. A later report by Franschman et al. on patients from the same centre using the same inclusion criteria was excluded due to duplication of patients and missing outcomes of interest [21]. Similarly, a report by Lustenberger et al. using patients from the USC medical centre surgical intensive care unit (SICU) between June 2005 and December 2007 was used [15], but a paper based on duplicate population also excluded [22]. There were 12 papers that were excluded because their definitions of ATC or iTBI were not clearly defined. Five papers studied paediatric populations and three did not report outcomes of interest. Description of studies and included patient population are presented in Table 1.

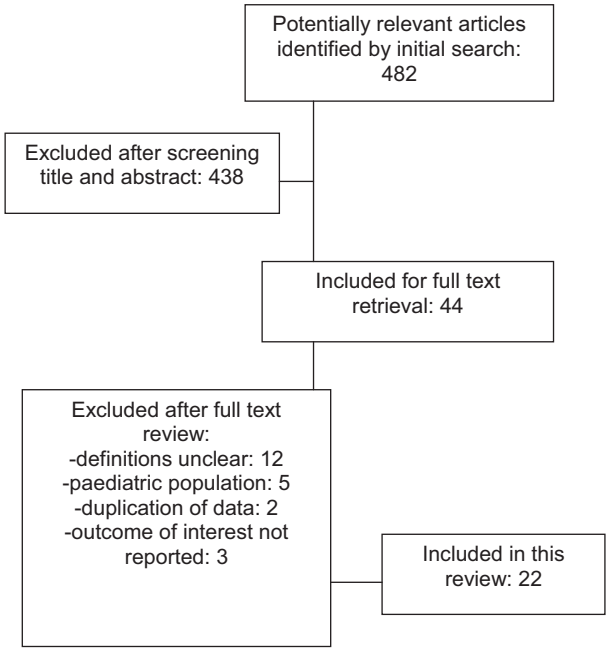

Fig. 1. Search and selection procedures.

Definitions of iTBI

The definition of isolated traumatic brain injury was consistent in the more recent papers – defined as head AIS ≥ 3, with other injuries <3 [15–17,23–25]. However, a substantial variation in the definition used was observed, particularly among older studies with 16 different criteria within the 22 studies. Zahtabchi et al. used AIS ≥ 3 but also the presence of brain haematoma, while two groups of authors have used a head AIS score of >3 to select their population. The presenting GCS has been variably used, but mainly among older studies and varying between GCS ≤ 8 and GCS ≤ 13.

Table 1
Study characteristics included in systematic review.

Author (year)	Methodology	Number of iTBI patients	Male %	Age years (mean with range)	Mechanism of injury (proportion %)
Carrick (2005) [43]	Retrospective analysis of patients presenting to trauma centre	184	–	–	Blunt (100)
Chang (2006) [44]	Retrospective analysis of observational database	113	75	45	Blunt (100)
Chhabra (2010) [33]	Prospective pilot study level 1 trauma centre	100	100	21.8	Unspecified
Cohen (2007) [45]	Prospective cohort study in admission to trauma centre	39	85	48 (18–89)	Blunt (88) penetrating (12)
Franschman (2012) [20]	Prospective observational cohort study to level 1 trauma centre	218	52	48 (21)[a]	Unspecified
Genet (2013) [24]	Prospective observational study	23	–	–	Unspecified
Greuters (2011) [35]	Retrospective analysis of patients presenting to emergency department	107	74	48 (20)[a]	Blunt (92) penetrating (8)
Hulka (1996) [26]	Retrospective observational study based on medical records	91	–	–	Unspecified
Kearney (1992) [34]	Prospective cohort study admitted TBI to ED	36	–	–	Blunt (72) penetrating (28)
Kuo (2004) [27]	Prospective observational study TBI admitted to ED	61	74	41.9 (19.8)[a]	Blunt (100)
Kushimoto (2001) [28]	Case–control study based on good/bad disability outcome	47	–	–	Unspecified
Lustenberger (2010) [15]	Retrospective cohort study those presenting to SICU	132	83	35 (1.6)[a]	Blunt (83) penetrating (17)
Piek (1992) [18]	Retrospective analysis of database	613	77	24 (1–93)	Unspecified
Schochl (2011) [25]	Retrospective analysis of database, patients presenting to level-1 trauma centre	88	76	47 (13–87)	Unspecified
Selladurai (1997) [29]	Prospective observational study patients admitted to neurosurgical service	204	–	21–30	Unspecified
Stein (2008) [46]	Retrospective database analysis	681	85	39	Blunt (95) penetrating (5)
Stein (1992) [32]	Retrospective analysis of CT images	253	–	3–74	Unspecified
Sun (2011) [30]	Prospective observational multicentre study	242	75	45 (17.9)[a]	Unspecified
Takahasi (2000) [31]	Prospective cohort study patients admitted to neurosurgery	70	–	–	Unspecified
Talving (2009) [16]	Prospective analysis of patients admitted to ICU	397	78	37 (20)[a]	Blunt (89) penetrating (11)
Wafaisade (2010) [17]	Retrospective analysis of multicentre trauma database	3114	69	50 (22)[a]	Blunt (100)
Zehtabchi (2008) [47]	Prospective observational study urban level-1 trauma centre	224	79	35 (25–52)[b]	Blunt (88) penetrating (12)

[a] Standard deviation.
[b] Interquartile.
TBI, Traumatic brain injury; ED, emergency department; SICU, surgical intensive care unit; CT, computerised tomography; ICU, intensive care unit.

Table 2
Study size, ATC definition, reported incidence and outcomes.

Author (year)	Definition of iTBI	Definition of ATC	Proportion of ATC	Mortality among patients with ATC
Carrick (2005)	GCS < 14, extracranial AIS < 3	PT > 14.2 or PTT > 38.4 s	21%	62%
Chang (2006)	Head AIS > 3, non-penetrating, admission CT with IPH, subsequent CT within 72 h.	PT > 13.2 s or PTT > 32 s	18%	–
Chhabra (2010)	GCS < 13	Fibrinogen ≤ 200 mg/dL	7%	–
Cohen (2007)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	PT and PTT**	28%	66%
Franschman (2012) (J Neurotrauma)	GCS ≤ 13, CT confirmed brain injury, extracranial AIS < 3	aPTT > 40 s or INR > 1.2 or platelet count < 120×10^9/L	34%	52%
Genet (2013)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	aPTT > 35 s or INR > 1.2	13%	–
Greuters (2011)	CT confirmed isolated TBI, AIS extracranial < 3	aPTT > 40 s or INR > 1.2	54%	–
Hulka (1996)	CT evidence of brain injury	Disseminated intravascular coagulation score ≥ 5	41%	40%
Kearney (1992)	GCS ≤ 9	Modified DIC score ≥ 5	86.1%	50%
Kuo (2004)	Midline shift on CT and GCS measurement**	Modified coagulopathy score ≥ 1	78.1%	75%
Kushimoto (2001)	"Isolated head injury from blunt trauma"	Alpha-2 plasmin inhibitor deficiency less than 60% normal	83%	86%
Lustenberger (2010) (J Trauma)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	Plt < 100,000 or INR > 1.2 or aPTT > 36 s	36.4%	37%
Piek (1992)	GCS ≤ 8	PLT < 50,000 or PT > 16 s or PTT > 50 s	19%	35%
Schochl (2011)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	PTI > 70% or aPTT > 35 s or fibrinogen < 150 mg/DL or PLT < 100,000	15.8%	–
Selladurai (1997)	GCS ≤ 14 and parenchymal/extra-axial lesions on CT	DIC score ≥ 2	38%	17%
Stein (2008) (J Trauma)	Head AIS > 3, GCS > 8	INR ≥ 1.4	13.9%	–
Stein (1992)	GCS > 13, serial CT scans	PLT count, PT, PTT	55%	41%
Sun (2011)	Head AIS ≥ 2, exclude existing coagulopathy, acidosis, massive transfusions, hypothermia, penetrating.	DIC score ≥ 5 or PT > 13.4 s	36%	21%
Takahasi (2000)	GCS ≤ 14	DIC score > 6	35.7%	–
Talving (2009)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	PLT < 100,000 or INR > 1.1 or aPTT > 36 s	34%	50%
Wafaisade (2010)	Head abbreviated injury score [AIS] ≥ 3 and all other AIS < 3	INR > 1.3 or PLT < 100,000	22.7	50.4%
Zehtabchi (2008)	AIS head > 2, brain haematoma on CT	INR > 1.3 or PTT > 34 s	17%	–

GCS, Glasgow coma scale; PTT, partial thromboplastin time; ICU, intensive care unit; AIS, abbreviated injury scale; aPTT, activated partial thromboplastin time; GOS, Glasgow outcome scale; IPH, intraparenchymal haemorrhage; INR, international normalized ratio; CT, computerised tomography; DIC, disseminated intravascular coagulation; PT, prothrombin time; Plt, platelet.

Definitions of ATC

The definition of ATC, used to select the primary endpoint, varied considerably. Among the selected studies, there were 19 different definitions of coagulopathy. This included combinations of 23 different proposed values of international normalized ratio (INR), platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, disseminated intravascular coagulation (DIC) score, modified coagulopathy score and alpha-2 plasmin inhibitor value. These are listed in Table 2.

Incidence of ATC

Beginning with the fixed effect model, the pooled proportion of patents with ATC in the setting of iTBI was 24.6% (95% CI: 23.6–25.6). But there was marked heterogeneity ($p < 0.01$) with an I^2 statistic (variation in incidence attributable to heterogeneity) of 96.9%, indicating that the use of the fixed effects model was unsuitable. Using the more appropriate random effects model, the pooled proportion (95% CI) was 35.2% (95% CI: 29.0–41.4). Mortality at hospital discharge or 28 days was reported in 14 included studies. The finding of ATC was associated with increased mortality [15,26,27], with reported odds ratios between 3.0 (CI (95): 2.3–3.8; $p < 0.001$) and 9.6 (4.1–25.0); $p < 0.001$) [16,17]. The incidence of mortality ranged between 17% and 86% [28,29].

Increased transfusion rates of 41% [20], longer hospital stays [16,30], longer ICU stays [16,17,20], decreased ventilator free days [17,23], higher rates of single and multiple organ failure [17,31] and higher incidence of delayed injury and disability at discharge [17,32] were observed among the population of patients with ATC in iTBI.

Discussion

The pooled incidence of ATC among patients presenting with iTBI was 35.2% (95% CI: 29.0–41.4). This incidence varied according to the definitions used between 7% and 86.1% [33,34]. The need to use a random effects model because of marked heterogeneity led to a marked increase in the pooled ATC incidence compared to the fixed effects model (35.2% versus 24.6%). This is because the very large study by Wafasaide et al. [17], where the incidence of ATC was 22.7%, dominated the fixed effects analysis, but had far less weight in the random effects model.

The development of ATC was associated with higher mortality ranging from 17% to 86% [28,29]. Poorer outcomes were associated with acute coagulopathy on presentation or where coagulopathy developed in the first 24 h post trauma [35]. Additional factors associated with unfavourable outcomes post iTBI were reported to be increasing age, male gender, pupillary reflex abnormalities, head injury severity and hypo-perfusion [20,35].

A systematic review on this topic 5 years ago included studies from 1966 to 2007 and had highlighted the variability among study designs and definitions contributing to the wide variance in the incidence of ATC among patients with iTBI [14]. For the definition of iTBI, authors used a combination of the AIS, CT findings and GCS. The AIS alone was the most commonly used definition (12 studies);

CT findings were evaluated for inclusion in 7 studies, while 10 studies included the GCS in combination with AIS or CT findings. A large proportion of included studies were retrospective reviews of data from clinical registries and the use of the AIS dictionary to describe injuries is probably limited to clinical registries. It is rarely employed for clinical and therapeutic purposes or in data collection for clinical trials because a trained coder is needed to code the injuries and also because the description and classifications of injuries is more detailed than required for clinical purposes. A further limitation of AIS codes is that injuries are based on their anatomical features rather than physiology and while documented as an ordinal scale, do not always correspond to prognosis, e.g. a smaller haematoma of the posterior fossa may have a poorer prognosis than a similar sized frontal haematoma. However, AIS coding is performed at discharge or death and incorporates unexpected progression of pathophysiology.

Classifications based on clinical and CT findings may be more generalisable to a clinician. The Marshall and Rotterdam classifications of structural brain damage are based on CT findings of TBI patients [36,37]. Imaging based classifications provide the opportunity to identify TBI patients at risk of developing intracranial hypertension. However, they ignore brain stem and cerebellar injuries that are present in the AIS dictionary. Additionally, the CT based scoring systems are focused on closed head injuries only. The GCS is the simplest and most often used measure of brain injury severity. However, in the setting of major trauma, many factors hamper its utility – pre-existing comorbidities, analgesia and sedation, intoxication, shock and hypoxaemia.

The ideal criteria to identify patients with iTBI in prospective studies are therefore likely to be multifactorial, using a combination of clinical and scoring systems. In retrospective analyses, classification will be limited by data availability. Retrospectively assigning clinical scores may be possible, but they are complex, require assessment of CTs by experts and make some assumptions [38]. We would recommend trauma clinical registries record data on clinical signs at presentation and CT findings to better classify patients with TBI.

The definition of ATC was varied and consistent with previous reports. A lack of consensus regarding the exact mechanism of ATC in the setting of iTBI may be responsible. Current hypotheses point to hypocoagulability from a combination of platelet dysfunction, fibrinolysis, consumptive coagulopathy and inhibitors of coagulation [4]. The PT, aPTT and INR can measure derangements in individual pathways but are obviously inadequate to capture the combination of multiple complex pathways. Literature is evolving around the use of thromboelastography (TEG) and thromboelastometry (TEM) in the trauma setting, showing they can accurately diagnose ATC. As thromboelastometry is a measure of clot strength (the end product of all hypo- and hyper-coagulability mechanisms at work, it does not rely on the biochemical pathways affecting coagulation. In the acute setting, continuous use of TEG or TEM may be used to influence transfusion practice and as they become more commonly used, may provide newer definitions of ATC [8,25,39].

Regardless of varied definitions, our study demonstrated high mortality in the setting of ATC and iTBI. Where the definition limits of ATC were set at any abnormal level of PT, aPTT or INR, mortality was lower than when limits were set at higher values of PT, aPTT or INR. Assuming normal coagulation profiles prior to injury, this finding suggests that outcomes are worse when ATC is unrecognised or poorly treated. This generates the hypothesis that outcomes post iTBI may be improved by early management of ATC.

The early, prospective selection of patients with iTBI and ATC to trial agents against coagulopathy, remains challenging. While initial GCS is currently being used for prospective trials, the sample selected is likely to include only a small proportion of patients with ATC [40]. Anatomical or physiological scoring systems to predict coagulopathy are directed towards patients with massive haemorrhage while scores predicting massive transfusion were not designed for coagulopathy and perform poorly when applied to the ATC [41]. Point-of-care tests have not been validated in the trauma setting and early results demonstrate poor performance [42].

For the clinician, guidelines to treat ATC in iTBI based on robust evidence are unlikely in the short term. In their absence, best evidence gleaned from observational studies and expert opinion currently recommend the array of procoagulant agents – FFP, platelets, cryoprecipitate (if fibrinogen count < 1.0 g/L) and consideration of tranexamic acid, calcium activated recombinant factor VIIa, together with supportive measures to maintain cerebral perfusion pressure. The end-point of such management is equally arbitrary, but our recommendation would be towards normalisation of measured tests for coagulation as early as possible.

Strengths of this review stem from the comprehensive literature search; evidence review by blinded pairs of reviewers and exploration of heterogeneity. Adding to the previous review on the topic [14], this study and meta-analysis has synthesised the evidence and outlined the incidence and outcomes of patients with ATC and iTBI. No studies were found that contributed towards level I evidence on the topic. In examining the association between ATC and mortality or the secondary outcomes reported at hospital discharge, this study did not adjust for possible confounders such as age, severity of injury, or GCS. It is possible that any reported associations demonstrated between ATC and mortality, and between ATC and the secondary outcomes (i.e. transfusion rates, length of stay, length of ICU stay, number of ventilator-free days, organ failure rates, disability on discharge) may not have been sustained had the analysis adjusted for the afore-mentioned potential confounders. Similarly, an ideal target for coagulation and the effect of early management of ATC towards any improvement in outcome remain targets for further research. Due to the retrospective nature of most included studies, one of the limitations of this review is the likely publication and reporting biases. It is also quite plausible that studies with negative findings were conducted and remained unpublished, which would lead to exaggeration of estimates presented in this review. Accurately assessing magnitudes of publication bias was not feasible; statistical tests based on funnel plot asymmetry, regression, or other methods are unreliable when the number of included studies is low and heterogeneous, as was the case in this analysis and not used.

Conclusions

This systematic review of the incidence of ATC in iTBI demonstrated marked heterogeneity among definitions of iTBI and ATC. Despite this heterogeneity, an estimated 35% of patients with iTBI present to hospital in a coagulopathic state. This coagulopathy is almost universally associated with worse outcomes. Specific agents for the early management of ATC exist and prior to intervention trials, consensus on the best approach to early prediction and detection of ATC is required.

Conflict of interest statement

No authors have any financial or institutional interest in the content of this review.

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