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Research Article

The Feasibility of Early Chemical Thromboprophylaxis in Traumatic Brain Injury Patients Admitted to a Trauma ICU

S Mathibela[1], MS Moeng[1,2*], IM Joubert[1], M Nel[2]

[1]Department of Trauma, University of Witwatersrand, Johannesburg, South Africa

[2]Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[*]**Corresponding author:** Maeyane Moeng, Department of Surgery, University of the Witwatersrand, Johannesburg, South Africa

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Abstract

Object: Traumatic Brain Injury (TBI) increases the risk of coagulopathy and thromboembolism, and its presence is a poor prognostic factor. There is no clear evidence to support recommendations regarding the preferred drug, dose or the timing of chemical thromboprophylaxis. This study aims to determine the feasibility of initiating early chemical prophylaxis in our clinical setting, given the existing controversies. It further aims to identify the subgroups of TBI patients which may benefit from early chemical thromboprophylaxis based on CT findings.

Methodology: This is a retrospective study from 01 January 2017 to 31 December 2018 of TBI cases 18 years and older admitted to a Trauma ICU unit which required a repeat CTB during their stay. Demographic data, mechanisms of injury, timing of chemical Thromboembolic prophylaxis and complication were included. A comparison between those receiving prophylaxis early (24-hrs), intermediate (48hrs) and late (72hrs) was made. Statistical descriptive analysis was done using the STATA Statistics/Data Analysis version 16.0 to summarise our data. A p-value of <0.05 was considered statistically significant. Ethics approval from the Human Research Ethics Committee (HREC) (medical) of the University of the Witwatersrand, clearance number: M200345.

Findings: One hundred and thirty-two patients were eligible for the study. Most patients had a repeat CTB before the initiation of chemical thromboprophylaxis. Only 18/132 (13,64%) showed clinical or radiological deterioration of their head injury. There was no difference in the ED physiological characteristics, ISS and need for transfusion between those who deteriorated and those who did not deteriorate. However, the mortality was higher among those who deteriorated. Our mortality at 28-days was 4.55% (n=6). The patients in our study had an overall higher ISS, which the literature associated with a worse outcome (6). In our study, however, even with a high ISS, other related injuries were not associated with a poor outcome or even increased 28-day mortality. Comparing the available literature, a repeat CTB scan seems to be the only parameter we can use to guide the initiation of chemical thromboprophylaxis in our study.

Conclusion: The study results do not show any statistically significant difference in the rate of worsening of intracranial bleeding if chemical thromboprophylaxis is initiated at 24 hours, 48-hours vs 72-hours. The deterioration of the bleeds was not further exacerbated by early chemical prophylaxis.

Keywords: Computer tomography; Thromboprophylaxis; Traumatic brain injury

Introduction

Traumatic brain injury (TBI) characterises a major source of trauma-related mortality and is a leading cause of permanent disability in the young population [1,2]. TBI commonly occurs in the background of polytrauma and remains a major obstacle in improving trauma outcomes. Mortality is directly attributable to TBI in up to one-third of patients who die after multiple injuries [3]. The incidence of coagulopathy is higher in patients with TBI than in the general trauma population, especially in those with penetrating injuries. Patients with TBI are at an even further increased risk of developing Pulmonary Embolism (PE) [4-7]. The incidence of Venous Thromboembolism (VTE) ranges between 20 and 32%, with some studies reporting Figure as high as 54% [8-10]. These patients are usually admitted to Intensive Care Units (ICU) [8]. Studies have shown that in addition to trauma-related coagulopathy, TBI increases the risk of coagulopathy, and its presence is a poor prognostic factor [10,11]. Despite using these mechanisms, there is an increased risk of coagulopathy and worsening intracranial haemorrhage [12]. In addition to compression stockings, chemical prophylaxis may be started if the TBI is stable and the benefits outweigh the risk of intracranial haemorrhage [12,13]. There is no clear evidence to support recommendations regarding the preferred drug, dose or the timing of chemical thromboprophylaxis [14]. Most centres around the world, including South Africa, start chemical thromboprophylaxis early (within 72-hours) as compared to late (after 72-hours) once a repeat computer tomography of the brain (CTB) [14,15]. Mesa Galan et al. (2016) suggested that initiating pharmacologic prophylaxis within 72-hours after trauma may provide greater effectiveness in VTE prevention after TBI when there is no haemorrhage progression at 24 hours after admission following a repeat CTB scan.

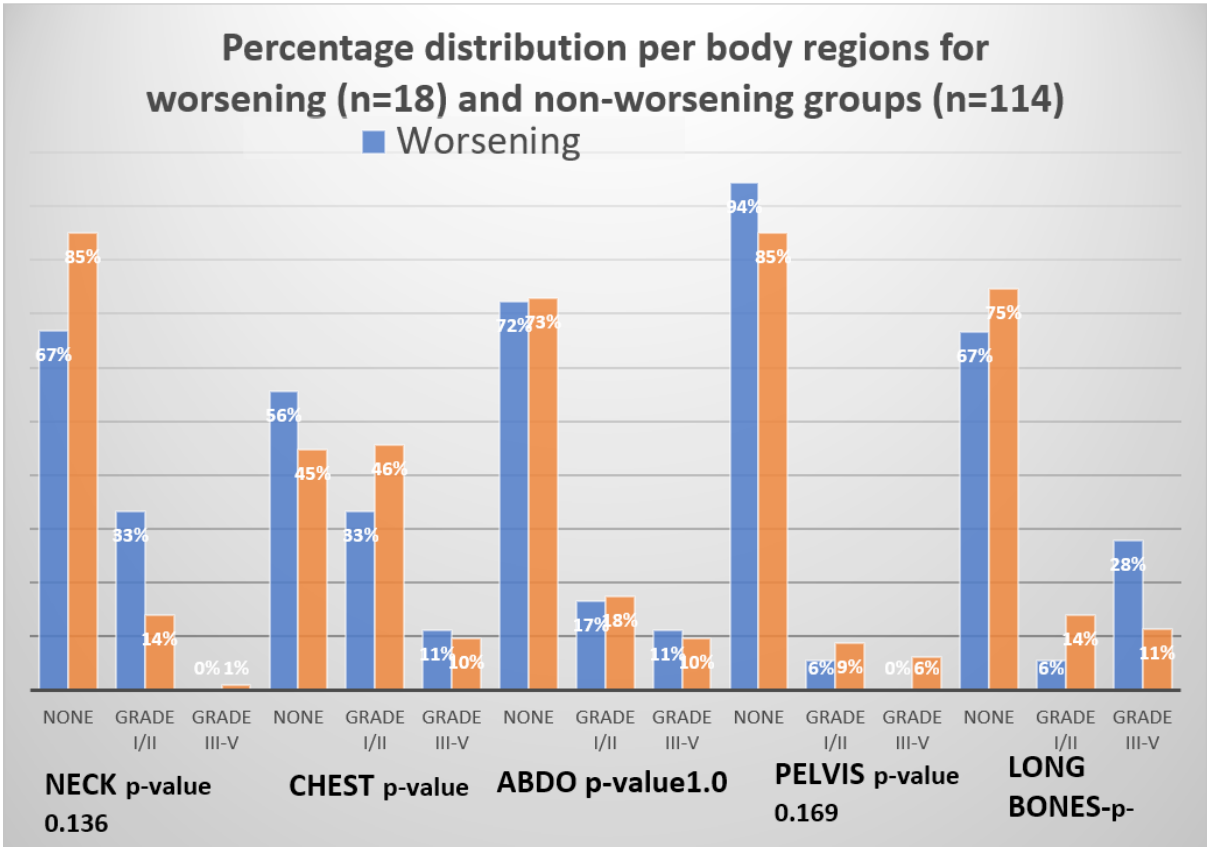

Figure 1: Percentage distribution of different body regions between the Worsening and non-worsening group, with P values per segment.

The Trauma Brain Foundation Guidelines (2016) for the management of TBI cites level 3 evidence for using low molecular weight heparin (LMWH) or low dose unfractionated heparin in combination with mechanical prophylaxis. The guidelines, however, do not provide a recommendation concerning which subgroups of TBI patients might benefit from early chemical thrombo-prophylaxis and the

preferred agent, timing of administration and dose. The practice at our Trauma ICU is to initiate chemical thromboprophylaxis after obtaining a repeat CT in those with intracranial bleeding, a stable or improvement of the brain injury compared with the index CT. All ICU admissions are started on pneumatic compression devices on admission to the unit. Therefore, this study aims to determine the feasibility of initiating early chemical prophylaxis in our clinical setting, given the existing controversies. It further aims to identify the subgroups of TBI patients which may benefit from early chemical thromboprophylaxis based on CT findings.

Method

This is a retrospective study from 01 January 2017 to 31 December 2018 of head injury cases of 18 years and older admitted to a Trauma ICU unit who required a repeat CTB during their stay. Those with delayed admission of more than 24hrs or significant clinical missing data were excluded. , with data collection from the Trauma Unit data sheet and clinical records, Picture archiving and communication system (PACS) records of the radiology department, National Health Laboratory Service results (NHLS), and clinical records of TBI patients admitted to the Trauma ICU at our Trauma unit in South Africa.

Types of data collected

Demographic data, mechanism of injury, brain injuries sustained, and other injuries were collected. Physiological data included blood pressure, pulse and temperature in the emergency department. The Injury Severity Score (ISS), pH, and Base deficit (BE)were also recorded. CTB findings on arrival and repeat CT scans were documented, and comments on the deterioration or improvement of these findings were noted. Those with radiological or neurological deterioration were contrasted with those who did not show deterioration. Platelet levels and coagulation status on time for chemical prophylaxis were noted. Outcomes included 28-day in-hospital mortality, bleeding on initiating chemical prophylaxis, and clinical evidence of deep venous thrombosis or pulmonary embolism. Further classification of the study group into three groups based on chemical prophylaxis: the 24-hour group received prophylaxis within 24-28hrs of admission, 48-hours received prophylaxis from 29-48hrs and the 72-hour group from 49hrs to 72hrs. These three groups were further analysed to compare differences in outcomes. Data was gathered from the Trauma Unit data sheet and clinical records, Picture archiving and communication system (PACS) records of the radiology department, and National Health Laboratory Service results (NHLS). The radiologist on call independently reviewed all Ct scans.

Statistical Analysis

The STATA Statistics/Data Analysis version 16.0 was used to summarise our data using descriptive statistics. Statistical difference between comparable groups was calculated using Pearson's Chi-square test for categorical variables as appropriate. Fisher's exact test was used for continuous variables, such as repeat CTB, initiation of chemical thromboprophylaxis, etc. A p-value < 0.05 was statistically significant.

Ethics Approval and Study Permission

Ethics approval from the Human Research Ethics Committee (HREC) (medical) of the University of the Witwatersrand, clearance number: M200345. Permission to access hospital records was obtained from the office of the CEO and Trauma Surgery Unit.

Results

One hundred and thirty-two patients were eligible for the study. The majority were males with a median age of 33.77. Only 18/132 (13,64%) showed clinical or radiological deterioration of their head injury. There was no difference in the ED physiological characteristics, ISS and need for transfusion between those who deteriorated and those who did not (See Table 1). However, the mortality was higher for those who deteriorated. One patient was from the group that received chemical thromboprophylaxis within 24-hours of admission, two patients were from those that received chemical thromboprophylaxis in 48-hours, and three patients were from the group that received chemical thromboprophylaxis at least 72-hours after admission (P=0.565).

Demographic parameters		Total N=132	Non-worsening features N=114	Worsening features N=18	P-value
Age(years)		33.77 (±9.17)	33.73 (±9.37)	34.06 (±7.99)	0.696
Sex	Male	116 (87.88%)	99 (85.34%)	17 (14.66)	0.696
	Female	16 (12.12%)	15 (93.75%)	1 (6.25%)	0.696
GCS	Mild	7	6	1	
	Moderate	32	30	2	
	Severe	93	78	15	
Blood Pressure	Systolic	137.39 (±31.59)	136.96 (±31.44)	140.17 (±33.34)	0.889
	Diastolic	86.55 (±27.74)	86.24 (±27.89)	88.56 (±27.44)	0.827
Pulse		95.70 (+/-22.81)	95.14 (+/-22.10)	99.28 (+/-23.74)	0.551
Platelets	Initial	214.65 (±83.40)	215.15 (±84.51)	211 (±78.20)	0.876
	48hours	162.11 (±64.82)	164.81 (±66.65)	145.17 (±50.08)	0.369
pH	-	7.310 (±0.105)	7.314 (±0.11)	7.284 (±0.09)	0.118
Lactate	-	4.05 (±2.61)	3.94 (±2.57)	4.79 (±2.86)	0.212
BE/D	-	-5.68 (±5.27)	-5.53 (±5.34)	-6.61 (±4.83)	0.255
Need for transfusion	Blood/ products	26(19.70%)	21(80.77%)	5(19.27%)	0.350
ISS	-	19.59 (±7.80)	19.25 (±7.67)	21.72 (±8.46)	0.303
Mortality	28day	6(4.54%)	2(33.33%)	4(66.67%)	0.003

BP-blood pressure in mmHg, Plt-platelets. GCS=Glasgow coma scale, BE/D=base excess/deficit, ISS-injury severity score.

Table 1: Patient characteristics and physiology.

In Table 2: 8.33% (n=11) participants had a repeat CTB within 24 hours of admission, 40.50% (n=54) had a repeat CTB between 24 and 48 hours of admission, and 50.41% (67) had a repeat CTB between 48 and 72hours of admission. Eighteen (13.64%) had worsening features on repeat CTB (P=0.909). Eighty-six (65.2%) patients had initiation of chemical thromboprophylaxis at least 72 hours after admission; of these, 14% (n=12/86) were those with worsening features on a repeat CTB (P-0.081). Forty-six (34.85%) had chemical thromboprophylaxis between 24 hours (n=18) and 48 hours (n=28), and six (13.04%) of those patients were in the group with worsening features on a repeat CTB (P=0.000). In patients (n=18) with worsening features, 50% (n=9) had new-onset bleeding, and the other 50% (n=9) had progression of the index injuries (P=0.000).

		Total N=132	Non-worsening features n=118	Worsening features n=14	P-value
Mechanism of injury	RTA	69(52.27%)	61 (88.41%)	8(11.59%)	0.695
	Assault	38(28.79%)	35(92.11%)	3(7.89%)	0.695
	FFH	16(12.12%)	13(81.25%)	3(18.75%)	0.695
	GSW	9(6.82%)	9(100%)	0(0.00%)	0.695
CT Findings	SAH	46(34.85%)	40(86.96%)	6(13.04%)	0.909
	EDH	26(19.70%)	23(88.46%)	3(11.54%)	0.909
	SDH	41(31.06%)	34(82.93%)	7(17.07%)	0.909
	ICH	19(14.39%)	17(89.47%)	2(10.53%)	0.909
Repeat CT	24hours	11(8.34%)	9(81.82%)	2(18.18%)	0.081
	48hrs	60(45.45%)	49(81.67%)	11(18.33%)	0.081
	±72hours	61(46.21%)	56(91.80%)	5(8.20%)	0.081
Initiation of Clexane	24hours	18(13.64%)	16(88.89%)	2(11.11%)	0.544
	48hourrs	28(21.21%)	24(85.71%)	4(14.29%)	0.544
	±72hours	86(65.15%)	74(86.04%)	12(13.95%)	0.544
Mechanism of injury	RTA	67(55.83%)	59 (88.06%)	8 (11.94%)	0.695
	Assault	30(25%)	27(90.00%)	3(10.00%)	0.695
	FFH	16(13.33%)	13(81.25%)	3(18.75%)	0.695
	GSW	7(5.30%)	7(100%)	0(0.00%)	0.695

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	±72hours	86(65.15%)	74(86.04%)	12(13.95%)	0.544

SAH-subarachnoid haemorrhage, EDH-extradural haematoma, subdural haematoma. CT- computer tomography. RTA-road traffic accident, FFH-fall from height GSW-Gunshot wounds.

Table 2: Showing the different mechanisms of injury (MOI), CT findings and initiation of Clexane in both the non-worsening and the worsening groups.

Discussion

Upon arrival in the trauma emergency area, all patients received an index CT scan. Getting a repeat CTB varied in intervals from 24 to 72-hours; 49 patients (40%) had their repeat CT at least 48hrs. In some cases, delays in getting a repeat CTB were excessive, mainly due to the limited availability of CT scan machines. This delay is a reality in low-middle-income countries like ours. There are no dedicated trauma surgery scans in our settings. Traditionally we initiate chemical thromboprophylaxis post a repeat CT. At the time of our study, there was no international guideline or consensus on the strict timing for the initiation of chemical thromboprophylaxis. Even centres with easy access to CT scans had not yet developed clear guidelines for initiating chemical thromboprophylaxis [12,16]. Guidelines advocate for an individualised approach to the initiation of prophylactic therapy, patients are evaluated, and appropriate treatment is given to the right patient. All TBI patients are placed on pneumatic mechanical thromboprophylaxis unless factors preclude the placement of such devices [17]. This approach is also practised in our settings.

Some studies posit that it is safe to initiate chemical thromboprophylaxis within 72-hours of sustaining a traumatic brain injury, especially in patients at low risk of progression of intracranial bleeding [12,16]. These patients must have a confirmed stable injury on the repeat CT brain, thus showing that repeat CT brain findings are a major determining factor for initiating chemical thromboprophylaxis in these patients. The study confirms our institutional practice of administering chemical prophylaxis when the CT scan does not reveal the expansion of the bleeding. This practice is in keeping with international standards [12]. Studies showed that chemical thromboprophylaxis was safe in patients with a stable CT at 24 hours of admission; however, it would expose patients with initial TBI progression to a 13-fold higher risk of worsening ICH [18]. Patients who had worsening injuries on repeat CTB (13.64%) were given chemical thromboprophylaxis case-by-case basis, based on their clinical improvement, and a third CTB. In some patients, chemical thromboprophylaxis was initiated at least 168 hours after the injury.

Our mortality at 28 days was 4.55% (n=6). The low mortality rate may be influenced by patients' good physiology reserves, an objective trauma system, which involves an excellent pre-hospital system and prompt in-hospital resuscitation and ICU care [17,19]. The in-patient mortality was higher in the worsening group; this was also observed by Matsushima K et al. 2021 [20]. The patients in our study had an overall higher ISS, which the literature associated with a worse outcome [6]. In our study, however, even with a high

ISS, other related injuries were not associated with a poor outcome or even increased 28-day mortality. This is because related injuries are managed with damage control surgery, with precise and early haemorrhage control. They are mentioned as factors contributing to morbidity and, in certain studies, as factors affecting mortality [21]. Crawford AM et al. (2019) suggested that most severe chest traumas are associated with significant concomitant injuries, such as TBI and are prone to developing PE. Males had higher death rates than females, especially in the 24–54 age group [22]. All the patients who died in our study were males, in keeping with the available literature that the male gender is associated with worse injuries and outcomes [18]. Appropriately, our study's endeavour to identify patients who may benefit from early chemical thromboprophylaxis didn't find any differing results from those reported internationally. However, our patient population included different types (SAH, SDH, EDH, etc.) and grades of injuries (mild, moderate & severe). Some studies investigated patients with moderate to severe TBI. The heterogeneity of our patient population makes it challenging to interpret outcomes and extrapolate clear practice guidelines [18,23,24]. Brandi et al. 2020, reported that various risk profiles were included in their patient population, and interpretation of these findings remains difficult. Specifically, patients with moderate and severe TBI have more extended periods of immobilization than those with mild TBI.

Comparing the available literature, a repeat CTB scan seems to be the only parameter to guide the initiation of chemical thromboprophylaxis. In our unit, investigations for VTE are carried out based on clinical suspicion only. The mode of investigation, whether doppler or CTPA, was ordered depending on the suspected site of the VTE [10,24]. Therefore the perceived number of patients with VTE is lower for us to even include as a variable, like that reported in the literature. In other studies, the trauma patients diagnosed with VTE were not necessarily those with severe TBI or severe associated injuries [23,24]. Our results highlight that there may be an overestimation of the risk of TBI progression in our clinical practice; in the process, we may underestimate the development of VTE and delay the initiation of chemical thromboprophylaxis. Furthermore, with a small percentage of TBI progression, from all three TBI groups, we cannot draw a conclusion on the clinical settings in which the deterioration occurs. This is in keeping with findings from the available literature. Progression of the injuries cannot be attributed to the initiation of chemical thromboprophylaxis. A third CTB was only ordered on a case-by-case basis, based on the patient's clinical condition [18,23]. A plausible explanation for our observed variation in the rate of ICH progression could be an unidentified selection bias.

As evident above, the question of when to start chemical thromboprophylaxis in TBI patients depends mainly on the findings of a repeat CT scan and the need for a surgical procedure, as noted in the literature [18]. In future, active surveillance for VTE, homogeneity of the study population, the variables and study design would help answer some of the pertinent questions raised in this study. There should be a concerted effort to do studies on specific TBI subpopulations to create recommendations that apply to the entire spectrum of injuries seen in clinical practice. Part of such work will be investigating the natural development of the brain injuries in each subgroup so that the earliest time for the safe initiation of chemical thromboprophylaxis can be identified [18,23,24]. This further study will help categorize patients based on the risk of TBI progression and VTE rates, thereby helping with developing clinical guidelines [25-31].

Limitations

This was a single-centre retrospective study, prone to selection bias. The limited resources in our low-to-middle-income country may have impacted the findings in our study compared to the clinical pathways observed in other centres. Resource limitations encourage us only to investigate the clinically suspected VTE, which may have contributed to missing some clinically insignificant VTE. Though this study is on old data, it remains relevant in our current situation. It leaves a message of hope for managing head injuries with limited resources while observing the basic standards of care.

Conclusion

The study's results do not show any statistically significant difference in the rate of worsening intracranial bleeding if chemical thromboprophylaxis is initiated at 24-hours vs 72-hours. It was, therefore, feasible to initiate early chemical prophylaxis for head injury cases at our institution. No specific bleed identified on CTB was noted to be unique in prohibiting the initiation of early chemical thromboprophylaxis. However, the data is promising, and there is a need for active surveillance of PE/DVTs in TBI patients. A prospective, multicentre study with higher study numbers is required to establish local practice guidelines on this subject. A multicentred prospective study in low-to middle income countries would clarify our observations even further and offer more straightforward guidelines for the VTE prevention strategy in TBI.

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