Emergency Medicine International

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Editorial

Traumatic Brain Injuries: Comprehensive Management of Complex Clinical Scenarios

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The number of traumatic brain injuries (TBI) is on the rise worldwide, representing 30–40% of injury-related deaths in many countries [1, 2]. TBI is effectively a public health epidemic; this justifies the 6-fold increase in the number of studies published over the last decade [3]. As such, the impact of TBI on the global burden of disease (GBD) is substantial, according to the investigators of the GBD study who annually quantify health loss from all types of diseases and injuries with the aim of improving health systems all over the world, and in the long term helps in reducing/eliminating disparities [1, 2, 4].

Due to groundbreaking mechanistic studies and randomized clinical trials (RCT) published in recent years (accounting for more than 380 new PubMed-indexed RCT on TBI since 2019), the approach to neurotrauma patients has remarkably evolved with an increase in the overall quality of acute care. One of the reasons for this improvement is certainly the care provided by a broad spectrum of multidisciplinary team (MDT) specialists, including prehospital and emergency department (ED) doctors and nurses, neuroradiologists, neurosurgeons, anesthetists, and intensive care physicians. Conceived and addressed to those professionals, this Special Issue has gathered insightful quantitative and qualitative studies on various aspects of the basic sciences, ethics and clinical practice of TBI, contributing to the existing body of literature, reinforcing data from recent trials and covering existing knowledge gaps. This editorial is meant to summarize the main findings from this collection and its overall achievements.

First of all, the greatest measure of this Special Issue's success can be measured by the outreach on authors from both high-income countries (HIC) and low- and middle-income countries (LMIC). In fact, the major contributors to this collection were authors from the United Kingdom and Turkey, heavily involved into academic research in the field of global neurotrauma, and authors from sub-Saharan African countries, such as Cameroon and Ethiopia, who shared their practical experience on the management of adult and pediatric patients with TBI in remote geographical locations. The number of contributions from LMIC, where the epidemiological distribution of TBI is the highest, represents indeed a particularly relevant factor because we know that mechanisms of injury, referral pathways, and access to tertiary centers are vastly different among continents, and the challenges faced for TBI management in LMIC are quite different from those of HIC [5]. Among the reasons for limited resources available in LMIC, and sources of concern for the global neurotrauma community, is the paucity of neurosurgical workforce requiring a remarkable task shifting and sharing practices [6]. This aspect has obviously an impact on hospitals preparedness, as recently shown in a collaborative study published by the NIHR Global Health Unit on Global Surgery [7]. Hence, the first-hand experience from LMIC contributors was obviously deemed extremely valuable and welcomed by our Editorial Board in the context of this Special Issue.

Above all, one aspect that was underscored in this collection reflects the organizational heterogeneity across

centers dealing with high volumes of trauma referrals. This emerged quite well in the observational cross-sectional study from Bedry and Tadele [8], which provided data on the clinical profile and outcome of childhood TBI at a tertiary hospital in Southern Ethiopia where head injuries contribute to 7.4% of pediatric visits in the local EDs. Of note, their clinical series indicated that road traffic accidents (RTA) and falls represent the most common causes of TBI in LMIC, as recently confirmed by Dewan et al. who estimated that the proportion of TBIs resulting from RTA in Africa and Southeast Asia is up to 56% of the total cases of head injuries registered in those continents [9]. Besides the organizational challenges, both articles explored critical aspects allowing clinicians to prognosticate outcome: both concluded that prolonged hospital stay and poor outcome correlate with comorbid illness, loss of consciousness at presentation, increased ICP sign, severity of head injury, presence of seizures, hypotension, and hyperglycemia on presentation.

While early hyperglycemia mentioned in their list of risk factors is a known predictor of mortality and correlates with mechanisms of secondary injury, as previously shown by European studies conducted in the acute phase by Prisco et al. [10] and in the subacute phase by TRACK-TBI investigators [11], other serum, plasma, and cerebrospinal fluid (CSF) markers of inflammatory reaction have also emerged in recent times [12–15]. Some useful biomarkers were extensively discussed in this Special Issue: for instance, the narrative review from Erenler and Baydin [16] indicates that IL-33 has emerged, among multiple plasma biomarkers, as the one mostly implicated in cellular crosstalk and responsible for multiorgans impairment. IL-33 is in fact a powerful endogenous alarm signal (alarmin) meant to alert various types of immune cells to trauma, and the study from Erenler and Baydin allowed revisiting data from experimental preclinical models of TBI [17, 18] and case-control studies [19, 20] on TBI patients, concluding the great potential role of IL-33 as an early indicator of secondary injury.

Together with contributions exploring prognostic factors and the role of biomarkers, this Special Issue includes more studies attempting to answer the demand for new pharmacological treatments. This was the case in the article written by Nguembu et al. [21] who explored the implication of paroxysmal sympathetic hyperactivity triggered by TBI, which could be effectively tackled by innovative neuroprotective strategies based on well-known, conventional drugs such as beta-blockers. Their scoping review suggests that beta-blockers diminish the effect of circulating catecholamines and attenuate the resting metabolism rate, which is markedly increased in patients with severe acute brain injury [22–29]. As such, their conclusions were that propranolol and labetalol should have a greater role in the acute management of TBI [30, 31]. Speaking of pharmacological strategies, another long-term retrospective study from Acar et al. [32] investigated the use of tranexamic acid (TXA) in blunt and penetrating TBI in the context of polytraumas. Their study design represented a pragmatic approach to the use of antifibrinolytic drugs in the treatment and prevention of major bleeding. Conducted between 2012 and 2020, the work from Acar et al. reached a conclusion about the safety of TXA in TBI (none of the 51 patients included had thrombotic complications nor died due to head injury), which is in keeping with the main findings from the CRASH 2 and the more recent CRASH 3 trials [33, 34]. Additionally, the article from Acar et al. offers a much needed confirmation in a civilian ED environment of the findings from the battlefield reported by Dixon et al. [35] and the results obtained within the constraints of the abovementioned RCT.

In terms of surgical strategies for TBI, with a specific focus for those developed in LMIC, Kanmounye [36] focused his attention to the rise of inflow cisternostomy, a more modern alternative to the 1940 ideas of outflow cisternostomy in the form of either ventriculocisternostomy and cystocisternostomy [37, 38]. Starting from the first description of such a surgical technique for the management of severe TBI, which dates back to the 2012 article by Dr. Cherian from Nepal [39], Kanmounye, who is also the founding President of the Association of Future African Neurosurgeons, provided an historical vignette of the evolution of such a technique in limited resource settings and offered a detailed argumentation for its rationale, limitations, and future challenges. That article highlighted that the use of cisternostomy in the surgical management of severe TBI certainly represents a revolutionary step, and we definitely agreed with the statement that the disruptive theory of CSF shift edema behind its conception has already contributed lessons to the entire neurotrauma community [40].

As mentioned in this Special Issue's call for papers new imaging tools, validated surgical strategies and optimized protocols for clinical follow-up, the early resuscitation, and management of difficult cases still represent a clinical, surgical, and ethical challenge most of the time. This is possibly the reason why one of the articles, which received most attention, earning double digits citations (the highest so far for this collection), was the contribution from Hasan et al. [41] revolving on public engagement as a tool to validate research questions and protocols in the management of TBI patients. Their qualitative study, consisting in a survey submitted to severe TBI survivors and their next of kin, helped identifying ways to direct future research into more accurate prognostic models and therapeutic options in the acute and subacute phases of TBI management. Furthermore, they explored the complex ethical aspects of dealing with sensitive issues revolving around TBI and the challenges faced in the aftermath of major trauma, not only by patients but also by clinicians and scientists.

Given the quality of the submissions received, it is no surprise that at time of writing this editorial, our Special Issue has gathered a cumulative number of 15,789 visualizations and a total of 8,111 downloads. Those results not only testify the valuable insights from both a scientific and teaching perspective offered by the authors who joined this endeavor but also the fulfillment of our initial goal of reaching out to and hopefully go beyond the vast scientific community of Emergency Medicine International.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this Special Issue.

Mario Ganau
Antonio Belli
Timothy P. Lawrence
Chris Uff

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Review Article

Paroxysmal Sympathetic Hyperactivity in Moderate-to-Severe Traumatic Brain Injury and the Role of Beta-Blockers: A Scoping Review

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Introduction. Most cases of paroxysmal sympathetic hyperactivity (PSH) result from traumatic brain injury (TBI). Little is known about its pathophysiology and treatment, and several neuroprotective drugs are used including beta-blockers. The aim of our study is to collate existing evidence of the role of beta-blockers in the treatment of PSH. *Methods*. We searched MEDLINE, ResearchGate, and Google Scholar, for keywords related to PSH and the role of beta-blockers in moderate-to-severe TBI on September 23, 2020. Two authors blindly screened the articles found with Rayyan. Both resolved their conflicts by mutual consent. If no solution was found, a third author was consulted. Simple descriptive data analysis was performed and the results were presented both in a narrative and tabular form. *Results*. Of the 19 items found, 10 met the criteria for inclusion. 50% were systematic reviews without meta-analysis, 40% were observational studies, and 10% were experimental studies. Propranolol was the main beta-blocker found in 80% of the studies and was the only molecule used in the treatment of paroxysmal sympathetic hyperactivity in 40% of the included studies. Only two studies evaluated and showed a significant association between beta-blockers and mortality rate (5.1% vs. 10.8%; $P = 0.03$), (3% vs. 15%; $P = 0.002$), respectively. *Conclusion*. Propranolol is the beta-blocker that has been shown to be effective in reducing the length of stay and mortality rate in moderate-severe traumatic brain injury patients with PSH. However, further studies are needed to precisely define the terms and conditions of its use.

1. Introduction

In 1929, Wilder Penfield described a syndrome combining lacrimation, hypertension, diaphoresis, and agitation. He named this syndrome a diencephalic seizure [1]. Electrophysiological investigations of this phenomenon did not show electroencephalographic activity. Many names were attributed to this syndrome: dysautonomia, sympathetic storming, brainstem attack, autonomic dysregulation, and paroxysmal autonomic instability with dystonia [2–5]. In 2014, the International Brain Injury Association convened a consensus workgroup to clarify its nomenclature and diagnostic criteria. The proposed term from this consensus group was "paroxysmal sympathetic hyperactivity (PSH)" [6].

PSH traditionally occurs in severe acquired injuries such as traumatic brain injury (TBI), stroke, anoxic brain injury, tumors, infections, spinal injuries, and serotonin syndrome. The prevalence of PSH is 8–33% [7] and 79.4% of PSH is due to TBI [8]. 80% of PSH patients have moderate-to-severe TBI and 15–33% of severe TBI patients have PSH [7].

The pathophysiology of PSH is poorly understood and the dominant theory suggests the failure of the central autonomic network (insular cortex, amygdala, hypothalamus, medulla, periaqueductal gray matter, parabrachial complex, and nucleus of the tractus solitarius) [9, 10].

PSH has several symptoms variably present: they are well resumed by the consensus position, which defines PSH as a "syndrome of simultaneous, paroxysmal transient increased in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity" [6].

Many pharmacological agents have been used alone or in combination to treat PSH. They include opiates, dopamine agonists, benzodiazepines, baclofen, gabapentin, and beta-blockers [9]. Beta-blockers have a cardioprotective effect: reducing the heart rate, perfusion volume, and mean arterial pressure. This effect limits myocardial oxygen consumption, thus preventing myocardial infarction. Also, beta-blockers have a neuroprotective effect by reducing cerebral blood flow, which reduces the cerebral consumption of oxygen and glucose as metabolism is reduced. Nonselective beta receptor antagonists have a lipophilic property that allows them to cross the blood-brain barrier. As a result, beta-blockers diminish the effect of circulating catecholamines and attenuate the resting metabolism rate, which is markedly increased in patients with severe acute brain injury [11–18]. Propranolol is commonly used to treat PSH and labetalol has shown some effect against PSH [19, 20].

The aim of our review is to collate existing evidence of the role of beta-blockers in the treatment of PSH.

2. Method

2.1. Literature Search Strategy. The first author (SN) developed a comprehensive search strategy which was tested and adjusted by means of a pilot search. The authors searched PubMed and Google Scholar databases for keywords related to PSH and the role of beta-blockers in moderate-to-severe TBI on September 23, 2020. The search strategy included title, abstract, text word, and controlled vocabulary terms for PSH and beta-blockers. All databases were searched from their inception without language and date restrictions. Two authors (SN and USK) performed supplemental hand searches to identify additional publications. The complete research strategies and research terms are available in Appendix 1.

2.2. Data Extraction and Selection Criteria. Results were exported to a free online screening system, Rayyan QCRI (Doha, Qatar). Records were deduplicated and independently reviewed by four authors (MM, EG, DO, and HD). Included articles had to meet the following criteria:

(1) Studies describing PSH secondary to TBI

(2) Studies describing the treatment of PSH with beta-blockers alone or in combination

Conflicts were resolved through discussion and consensus between the two author reviewers and when this was not possible, a fifth reviewer (USK) was consulted.

Authors, study subject, study design, publication date, TBI severity, beta-blockers used and dosage, length of stay, and mortality were extracted from included studies. The data extracted were input into a Microsoft Excel spreadsheet (Microsoft, WA, USA), and the results were presented in a Table 1.

3. Results

The search returned 19 articles: 14 (73.7%) through the systematic search of databases and 5 (26.3%) through the supplementary hand search. A duplicated article was excluded and the titles and abstracts of the 18 (94.7%) remaining articles were screened. Four (21.1%) did not match the inclusion criteria. Full-text review of the 14 (73.7%) remaining articles was done. Four (21.1%) articles were excluded because they did not involve moderate-to-severe TBI. Ten (52.6%) articles were included in the final data extraction and quantitative analysis (Figure 1).

Among the ten articles included in this review, five (50.0%) were reviews, 4 (40.0%) were observational studies, and one (10.0%) was an experimental study. Among the observational studies, 3 were case reports and 1 was a case-control study. The experimental study was a randomized, double-blinded, placebo-controlled trial.

Five (50.0%) studies had severe TBI patients, propranolol was used in 80.0% of the studies, and it was administered either intravenously (between 6 and 85 mg per 24 hours) or orally (20–60 mg every 4–6 hours). Other beta-blockers included labetalol (20.0%, $n = 2$ studies), atenolol (10.0%, $n = 1$ study), and metoprolol (10.0%, $n = 1$ study). These drugs were used in combination with propranolol and labetalol.

Beta-blockers were used in combination with non-beta-blocker drugs in five studies (50.0%.) The non-beta-blocker drugs included α2-agonists, gabapentin, baclofen, bromocriptine, long-acting benzodiazepines, dantrolene, morphine, and fentanyl.

Only two studies (20.0%) established the efficacy of beta-blockers on moderate-to-severe TBI patients with PSH (Table 1).

van der Jagt and Miranda [25] found that the mortality of PSH following moderate-to-severe TBI treated with beta-blockers was lower than for patients who did not receive beta-blockers (5.1% vs. 10.8% $P = 0.03$).

Of note, Schroeppel et al. [24] found that patients who received beta-blockers had a longer hospital stay and higher mortality than patients who did not receive beta-blockers (29 days vs. 10 days and 13% vs. 6%, respectively, $P = 0.001$). Among the patients who received beta-blockers, those who received propranolol had a longer stay, but mortality was significantly low. (44 days vs. 29; $P = 0.001$) days, mortality was significantly lower (3% vs. 15%; $P = 0.002$).

Table 1: Summary of findings.

Articles	Study design	Participants mean or median age	TBI severity	Type of beta-blockers used	Dosage of beta-blockers	Beta-blockers were used	Non-beta-blockers drugs	Length of stay	Mortality rate
Choi et al. [8]	Narrative review	26	Moderate, severe	Propranolol	N/A	In combination	Morphine, baclofen, gabapentin, benzodiazepines, bromocriptine	N/A	N/A
Diamond et al. [21]	Case report	35.5	Severe	Labetalol	10 mg	In combination	Morphine	N/A	N/A
Feng et al. [22]	Narrative review	18.1	Severe	Propranolol	40 mg q12 h IV	In combination	Morphine, baclofen, gabapentin, benzodiazepine, bromocriptine, clonidine, dexmedetomidine, dantrolene	N/A	N/A
Godoy et al. [23]	Letter to the editor	28	Moderate, severe	Propranolol	20 mg q12 h to 20 mg q8 h IV	In combination	Morphine, fentanyl	N/A	N/A
Schroeppel et al. 2014 [24]	Case-control	42	Severe	Propranolol	85 mg IV	Alone	N/A	44	3
Van der jagt and miranda. [25]	Review	55	Moderate, severe	Atenolol	10 mg q6 h IV followed 100 mg q24 h orally	Alone	N/A	N/A	5.1
Garg et al. [26]	Case report	26	Severe	Propranolol	10 mg q12 h to 10 mg q8 h IV	Alone	N/A	N/A	N/A
Monteiro et al. [27]	Case report	27	Severe	Propranolol	10 mg q8 h	Alone	N/A	N/A	N/A
Zheng et al. [9]	Narrative review	30	Moderate, severe	Propranolol, labetalol, metoprolol	20–60 mg q4-6 hr orally	In combination	α2-Agonists, gabapentin, baclofen, bromocriptine, and long-acting benzodiazepines	N/A	N/A
Ammar and Hussein [11]	Randomized, double-blinded, placebo-controlled trial	55	Moderate	Propranolol	1 mg q6 hr IV	Alone	N/A	N/A	N/A

4. Discussion

4.1. Summary of Evidence. The role of beta-blockers in the management of PSH following moderate-to-severe TBI is a fairly recent concept. Before 2010, there was a single study [21], but nine studies have since been published [7, 9, 11, 22–27]. The studies were mostly systematic reviews without meta-analysis (40%) [7, 9, 22, 25] and case reports (30%) [21, 26, 27]. Only two studies evaluated the impact of beta-blockers on post-TBI PSH-related mortality, showing that beta-blocker therapy improved mortality [25]. One study showed a shortened length of stay [27]. However, the randomized controlled trial did not confirm the causal link between beta-blocker therapy and reduced mortality or length of stay [11]. Of note, beta-blockers were often used in combination with other drugs to manage post-TBI PSH (Table 1) [7, 9, 21–23].

Schroeppel et al. [24] performed a case-control study evaluating the use of beta-blockers in severe TBI, comparing propranolol to other beta-blockers. They found that the

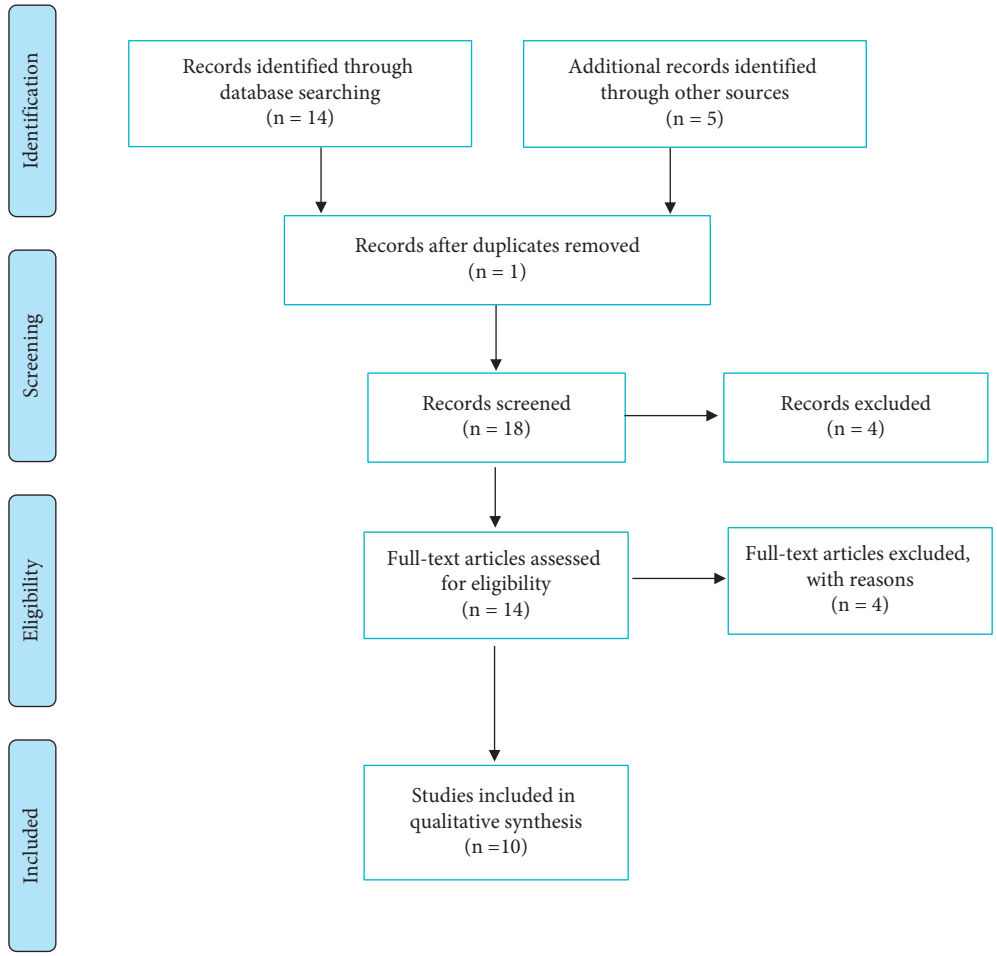

Figure 1: PRISMA flow diagram.

intervention group (i.e., propanol) had significantly longer lengths of stay ($P = 0.001$) but significantly lower mortality rates ($P = 0.002$). However, we note that the intervention group in this study was significantly younger. It can be argued that this group suffered from true PSH. PSH can be diagnosed early clinically [28–31] in the presence of > one episode of four or more of the following features: (1) fever (body temperature >38.3°C), (2) tachycardia (heart rate >120 beats per min in the absence of beta-blocker therapy or >100 beats per min during beta-blocker therapy), (3) hypertension, (systolic blood pressure >160 mmHg in the absence of beta-blocker therapy or >140 mmHg during beta-blocker therapy), (4) tachypnea (respiratory rate >25 breaths per min), (5) diaphoresis, (6) change in or presence of posturing, and (7) spasticity or rigidity. PSH is suspected if these symptoms cannot be explained by alternative causes including airway obstruction, sepsis, drug (e.g., neuroleptic malignant syndrome or serotonin syndrome), pulmonary embolism, withdrawal symptoms, or new or worsening structural brain injury.

PSH can be a devastating condition. PSH patients have higher mortality rates (OR = 0.08; 95% CI = 0.01–0.52) and tend to be older than other TBI patients (OR = 1.08; 95% CI = 1.00–1.16) [32]. In a retrospective study, Cotton et al. [25] reported lower mortality rates with beta-blocker therapy despite older age, higher injury severity scores, and lower estimated probability of survival (5.1% vs. 10.8%, $P = 0.03$). Patients who received beta-blockers equally had more infectious complications, respiratory failure, and longer lengths of stay. In PSH patients, these complications are compounded by an increased likelihood of metabolic disorders, dehydration, and malnutrition [33]. Each of these comorbidities can adversely affect the mortality rate in patients with moderate-to-severe TBI. Therefore, these patients should be monitored closely [34–37].

We did not find consensus data on the time frame of administration, dose, criteria for withdrawal, and the long-term effects (e.g., quality of life measures) of beta-blocker therapy in moderate-to-severe TBI patients with PSH. These gaps in the existing literature warrant further studies.

4.2. Limitations. The limitations of our study are intrinsic to its typology (scoping review): its choice was dictated by the elements of heterogeneity of each article in the final data extraction (combination with several beta-blockers, different dosage, and withdrawal of beta-blockers, lack of data concerning length of stay and mortality rate), resulting in an

inability to perform a meta-analysis review. Notwithstanding these limitations, this review identified research and outcomes of beta-blocker in PSH patients post-TBI. As such, it offers valuable insight into the understanding and management of TBI [41].

5. Conclusion

In this scoping review, we identified studies that explored the role of beta-blockers in the management of post-TBI PSH. Propranolol was the drug of choice and was shown to reduce the length of stay and mortality rate in moderate-to-severe TBI patients with PSH. No other beta-blockers in single administration were able to demonstrate the similar efficacy, probably owing to their pharmacodynamics (i.e., propranolol has lipophilic properties that allow penetration of the blood-brain barrier). More prospective studies are needed to ascertain the ideal time, dose, withdrawal, and long-term effects of beta-blocker therapy.

Appendix

A.1. Search Terms

(i) Paroxysmal sympathetic storm, paroxysmal sympathetic surge, diencephalic seizure, diencephalic storm, paroxysmal autonomic instability with dystonia, acute hypothalamic instability, dysautonomia, sympathetic storming, brainstem attacks, and autonomic dysregulation

(ii) Beta-adrenergic blockers, adrenergic beta antagonists, β-adrenergic blockers, and β-blockers

(iii) Traumatic brain injury, head injury, and craniocerebral trauma

A.2. Search Strings

A.2.1. PubMed. ("Autonomic Nervous System Diseases"[MeSH Terms] OR "Paroxysmal sympathetic storm"[Text Word] OR "diencephalic seizure"[Text Word] OR "paroxysmal autonomic instability with dystonia"[Text Word] OR "acute hypothalamic instability"[Text Word]) AND ("adrenergic beta antagonists"[MeSH Terms] OR "beta-adrenergic blockers"[Text Word] OR "adrenergic beta antagonist"[Text Word] OR "beta-adrenergic blockers"[Text Word] OR "beta-blockers"[Text Word]) AND ("craniocerebral trauma"[MeSH Terms] OR ("craniocerebral"[All Fields] AND "trauma"[All Fields]) OR "craniocerebral trauma"[All Fields] OR ("head"[All Fields] AND "injury"[All Fields]) OR "head injury"[All Fields]).

Disclosure

The authors developed and submitted a review protocol on https://www.scienceopen.com/hosted-document?doi=10.14293/S2199-1006.1.SOR-.PPEBGAR.v1 presented as a preprint.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Clinical Significance of Isolated Third Cranial Nerve Palsy in Traumatic Brain Injury: A Detailed Description of Four Different Mechanisms of Injury through the Analysis of Our Case Series and Review of the Literature

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Third cranial nerve palsy (3cnP) following traumatic brain injury (TBI) is a worrying neurological sign and is often associated with an expanding mass lesion, such as extradural or acute subdural haematomas. Isolated 3cnP can be found in the absence of posttraumatic space-occupying mass lesion, yet it is often considered as a devastating prognostic factor in the context of diffuse axonal injury (DAI). Through the analysis of five exemplificative cases and a thorough review of the literature, we identified four possible mechanisms leading to 3cnP: (1) a partial rootlet avulsion at the site of exit from the midbrain, representing a direct shearing injury to the nerve; (2) a direct traction injury due to the nerve stretching against the posterior petroclinoid ligament at the base of the oculomotor triangle secondary to the downward displacement of the brainstem at the time of impact; (3) a direct vascular compression as a result of internal carotid artery (ICA) dissection or pseudoaneurysm; (4) an indirect injury caused by impaired blood supply to the third nerve in addition to the detrimental biochemical effects of the underlying brain injury itself. Understanding the exact mechanism underlying the onset of 3cnP is key to provide an informed clinical decision-making to the patients and ensure their best chances of recovery. Our experience corroborates data from the literature showing that, even in Grade III DAI, prompt recognition of isolated 3cnP can guide adequate treatment. Nonetheless, even when an overall good neurological outcome is achieved, recovery of isolated 3cnP is dismal, and only rarely the visual deficit completely resolves.

1. Introduction

Third cranial nerve (oculomotor) palsy (3cnP) is seen in all grades of traumatic brain injury (TBI), either immediately after the traumatic event or evolving hours to days after it [1]. 3cnP represents a worrying neurological sign because it is often associated with an expanding mass lesion, such as extradural or subdural haematomas [2, 3]. Isolated 3cnP can be found in the absence of posttraumatic space-occupying mass lesion, yet it is often considered as a devastating prognostic factor in the context of diffuse axonal injury (DAI).

Isolated 3cnP is very rare; its incidence ranges from 8 to 16%, depending on the clinical series [4–9]. In terms of clinical presentation, it can be found in combination with other cranial nerve deficits (particularly VI, V, and VI), can be unilateral or bilateral, and can be transient or permanent [9].

Unfortunately, the pathological basis of isolated 3cnP has been poorly described in previous reports. An oculomotor injury can be the consequence of lesions located anywhere from the oculomotor nucleus in the midbrain to the termination of the third cranial nerve in the extraocular muscles within the orbit. The size of the pupil and its

reaction to light can indicate where the lesion is most likely to be located [4, 10]. In the early stages of central herniation, there is a diffuse bilateral hemisphere dysfunction due to decreased blood flow from increased intracranial pressure (ICP) and diencephalic dysfunction due to downward displacement. In this stage, pupils are normally small (1–3 mm) and reactive to light. In later stages, when the midbrain is affected, pupils are moderately dilated (3–5 mm) and fixed. This stage is also seen in uncal herniations. During the terminal stage of herniation, where the medulla is affected, the diffuse hypoxia continues to sustain mydriasis; therefore, the damage becomes irreversible. Fixed dilated pupils have thus historically been associated with a very poor prognosis in TBI [11–15].

Imaging alone can be ambiguous in defining the management. CT scans are prone to artifacts and poor resolution in proximity to the brainstem, whereas very early MRI may not show DAI or may definitely underestimate the evolving cascade of secondary damage. Furthermore, even when medical and surgical treatments are timely undertaken, 3cnP may not recover; in fact, fewer than 5% of cases eventually show a complete recovery [4–10].

To elucidate the mechanism of injury underlying 3cnP, we present five exemplificative cases of isolated 3cnP in patients suffering severe closed TBI with documented Grade III DAI [16]. Together with a literature review, these cases will help to outline four possible mechanisms of injury in mild to severe TBI and better explain the anatomical basis of 3cnP.

2. Case Presentations

Case 1. A 50-year-old lady female cyclist fell over the handlebars of her bicycle at moderate speed and landed 8 ft away. Her Glasgow Coma Score (GCS) was 3 at the scene with fixed dilated pupils bilaterally (8 mm). Her GCS rapidly improved to 9, but the pupils remained fixed and dilated. A CT scan of her brain on arrival to our A&E department showed traumatic subarachnoid haemorrhage in the left superior cerebellar cistern, left perimesencephalic, and quadrigeminal plate cistern; it raised suspicion of possible DAI. There were no other significant injuries except for a right internal carotid artery (ICA) dissection at the cervical segment, for which she was started on aspirin. She was tubed and her initial ICP was 14 mmHg; hence, she received only medical treatment with deep sedation and optimisation of blood pressure to ensure adequate cerebral blood flow (CBF). On sedation hold, at 48 hours from the event, she showed improvement in her level of consciousness (GCS 10T) and was extubated after one day. However, her pupils remained unreactive and dilated at 8 mm bilaterally. Visual acuity was recorded as perception of hand movements only. She had a divergent gaze and was unable to move her gaze up or down, in keeping with bilateral oculomotor nerve dysfunction. MRI of her head (see Figure 1) showed Grade III DAI involving the tectum of the midbrain bilaterally, the inferior colliculi, and the superior cerebellar peduncles bilaterally. Although her visual acuity subsequently improved, there was very limited recovery in ocular movements. Although she had prolonged posttraumatic amnesia and short-term memory problems, she eventually made a good recovery and was discharged to rehab with a GCS of 14.

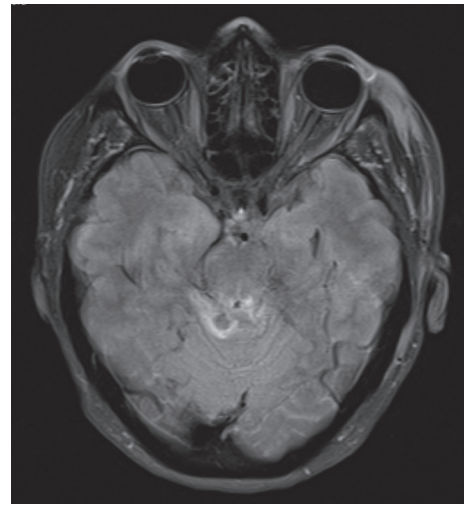

Figure 1: Axial FLAIR MRI showing Grade III DAI with hyperintense lesions at the level of the tectum of the midbrain, in the superior cerebellar parenchyma and the superior cerebellar peduncle.

Case 2. A 36-year-old female pedestrian was hit by a car. On scene, her GCS was 8 with a right-sided fixed and dilated pupil. She was noted to be moving all limbs. An initial CT head showed subarachnoid blood in the right sylvian fissure and overlying the right cerebral convexity and interpeduncular fossa. Extracranial injuries included a right tibial/fibular fracture and a pelvic fracture. She was extubated 2 days after admission; however, she continued to have a right 3cnP. She was mobilised and started early physiotherapy in the neurosurgical ward. Her MRI (see Figure 2) showed a Grade III DAI with involvement of the left side of the midbrain and pons in addition to the right mesial temporal lobe. Overall, she made a good recovery allowing a direct discharge home; nonetheless, her 3cnP had improved only slightly upon discharge.

Case 3. A 54-year-old female sustained a head injury upon falling from a horse. Her GCS was 15 on scene and she was moving all limbs but had a right fixed and dilated pupil with accompanying ptosis. Her eye was in the classic "down and out" position. An initial CT head showed subarachnoid haemorrhage in the anterior cingulate and right frontal sulci and interpeduncular fossa. She had no other injuries. A CT angiography indicated a dissected right petrous ICA with possible extension of the dissection flap through the right cavernous ICA into the supraclinoid ICA. There was also a small pseudoaneurysm arising from the right cavernous ICA. However, an MRI showed a small haemorrhagic contusion along the lateral aspect of the left side of the midbrain and a very localised hyperintense signal change in the medial aspect of the right cerebral peduncle close to the root entry zone of the right third cranial nerve (see Figure 3). This was interpreted as the cause for the 3cnP, and an MRA

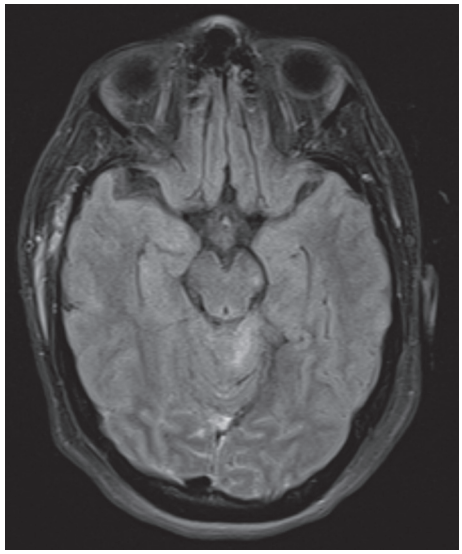

Figure 2: Axial FLAIR MRI, showing Grade III DAI with hyperintense lesions evident in the left midbrain and pons.

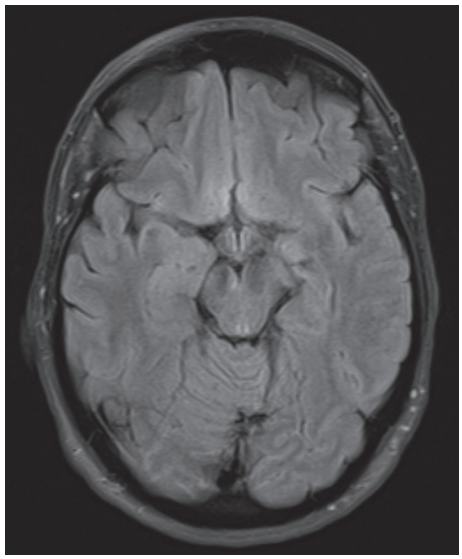

Figure 3: Axial FLAIR MRI showing injury in the medial aspect of the right cerebral peduncle close to the root entry zone of the right third nerve.

became necessary to rule out the possibility of a cavernous ICA dissection.

Case 4. A 6-year-old boy was found by ambulance crew on GCS of 4 with fixed and dilated pupils following a head injury in which a concrete table fell on his head. Initial CT head imaging showed extensive bilateral calvarial, skull base, and facial fractures, bilateral subdural haematomas with minimal mass effect, multiple tiny intraparenchymal contusions within the frontal lobes and brainstem, and a small amount of intraventricular blood. Bilateral orbital subperiosteal haematomas were noted, but the globes and optic nerves were intact. He had an ICP bolt inserted, with opening pressures of 4 mmHg. A follow-on MRI (see Figure 4) showed a haemorrhagic shear injury affecting the tegmentum, tectum, and periaqueductal parenchyma of the midbrain, right cerebral peduncle, right side of the pons, right middle cerebellar peduncle, and superior aspect of the right cerebellar hemisphere. Management included prolonged intensive care unit stay (23 days) while he was kept deeply sedated and ventilated; during the admission, the left pupil regained a slight response to light, although the right one remained fixed and dilated. Following a long but sustained neurological recovery, he was back to full-time education without residual neurological deficits.

Case 5. A 37-year-old cyclist was hit by a car. He was confused with pupils equal and reactive on the scene; however, he rapidly decreased his level of consciousness during transfer to the A&E where he was in GCS of 5 with a right dilated and unreactive pupil. His CT showed extensive traumatic subarachnoid haemorrhage and contusions through both cerebral hemispheres. He had an ICP inserted, with opening pressures of 29 mmHg; this was managed with insertion of external ventricular drain. The MRI (see Figure 5) showed multiple haemorrhagic lesions involving the corpus callosum and brainstem consistent with DAI, a contusion in the left internal capsule and in the left frontal lobe. He eventually recovered to a GCS of 15, although he continued to have minimal cognitive impairment and decreased visual acuity in his right eye.

3. Discussion

The intracranial course of the oculomotor nerve runs from the anterior surface of the mesencephalon and advances between the superior cerebellar artery and the posterior cerebral artery. The third cranial nerve runs parallel, lateral, and below the posterior communicating artery (PCA), with the medial portion of the uncus lateral to it and enters the lateral wall of the cavernous sinus. It divides into its superior and inferior branches at the level of the superior orbital fissure. Along this course, fascicules are labelled as the subarachnoid segment, cavernous segment, orbital apex segment, and intraorbital segment [1, 4, 10, 17]. Once it reaches the orbit, it innervates the extraocular muscles of the eye: superior rectus, inferior rectus, medial rectus, inferior oblique, levator palpebrae superioris, the ciliary muscles, and the constrictor pupillae muscles of the iris. An oculomotor nerve palsy thus presents with a dilated pupil, ptosis, and infraducted and abducted eyeball (the classic down and out sign).

TBI are responsible for most 3cnP [1, 4–10, 17–23]; however, the incidence of isolated 3cnP not caused by space-occupying lesions such as posttraumatic subdural or extradural haematomas is rare. Multiple cranial nerve injuries tend to occur in the context of TBI, regardless of its severity. Our exemplificative cases provide a wide range of different presentations, showing that a 3cnP can be found at the scene or later on after admission to the hospital; it can be unilateral or bilateral and can be associated with other cranial nerve deficits.

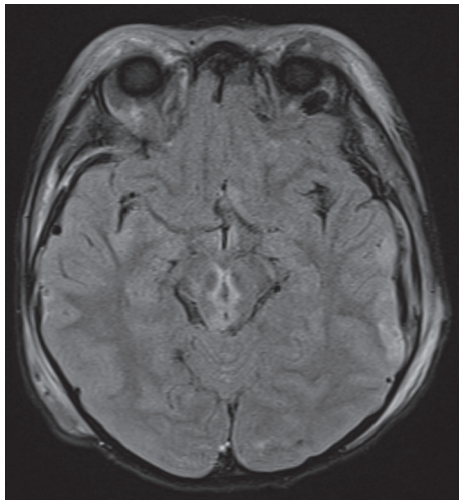

Figure 4: Axial FLAIR MRI showing multiple injuries in the tegmentum, tectum, and periaqueductal parenchyma of the midbrain, with involvement of the right cerebral peduncle, the right side of the pons, and the right middle cerebellar peduncle.

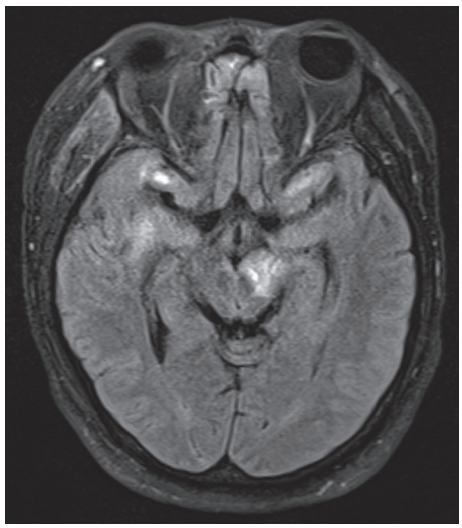

Figure 5: Axial FLAIR and sagittal T1WI MRI showing a significant injury to the left midbrain and multiple intraparenchymal contusions in the frontal, temporal, and parietal lobes.

The pathological mechanisms leading to isolated 3cnP can be direct or indirect. In patients with no obvious significant findings on CT, direct injury may result from extreme distraction of the nerve during the brain movement upon impact, rootlet avulsion, or distal fascicular damage. Direct injury can also occur as a result of compression, displacement, or deformity of the nerve by space-occupying lesions other than an obvious uncal herniation, such as a traumatic pseudoaneurysm [10, 23]. On the other hand, indirect injury can occur as a result of defective blood supply, caused by either the primary injury or its secondary metabolic cascade. Below we systematically explore four mechanisms of injury and subclassify them as either direct or indirect.

3.1. Mechanism 1: Shearing Injury (Direct Injury). Balcer et al. [4] proposed proximal or distal fascicular damage with partial rootlet avulsion as common mechanisms of injury in traumatic 3cnP. This basically involves shearing injury to the nerve at his origin from the mesencephalon, which can be seen on MRI like a haemorrhage at the midbrain exit site of the oculomotor nerve. Gradient echo T2-weighted sequences are the most sensitive to detect haemorrhagic changes associated with shearing injury [4]. This mechanism of injury is generally seen in severe trauma and may be unilateral or bilateral as seen in Case 1.

3.2. Mechanism 2: Traction Injury (Direct Injury). A possible second mechanism of 3cnP is nerve avulsion against the posterior petroclinoid ligament, where the nerve is stretched because of the downward brainstem displacement at the time of impact or herniation in the aftermath of TBI [8]. As such, this mechanism can explain a posttraumatic 3cnP from the outset or its late appearance in the subsequent hours such as in Cases 2 and 5.

The oculomotor nerve pierces the dura of the cavernous sinus through the oculomotor triangle. This triangle is bound by the anterior and posterior clinoid processes and the petrous apex. The medial margin of this triangle is formed by the interclinoid ligament, which extends from the anterior to the posterior clinoid process. The lateral margin is formed by the anterior petroclinoid ligament, which extends from the anterior clinoid process to the petrous apex, whereas the posterior margin is formed by the posterior petroclinoid ligament, which extends from the posterior clinoid process to the petrous apex. The oculomotor nerve runs over the posterior petroclinoid ligament. Direct injury to the pupillomotor fibres on the ventromedial surface of the nerve may occur when the nerve is stretched against this tough ligament as the brainstem moves downward at the time of impact. The nerve then becomes swollen, and ischemia could result from dural constriction at the point where the nerve pierces the dura of the cavernous sinus [21, 22].

3.3. Mechanism 3: Vascular Compression (Direct Injury). Vascular compression was only briefly mentioned as a possible cause of oculomotor nerve damage in previous reports [10, 23]. The oculomotor nerve has an intimate relationship with the PCA and ICA, making the fibres, especially the pupillomotor ones, vulnerable to compression arising from a vascular anomaly. A painful oculomotor palsy is a well-established symptom and sign of an enlarging PCA aneurysm, and a traumatic pseudoaneurysm in this area may also cause neural compression (an oculomotor palsy). However, many patients suffering TBI are unconscious and so unable to report ocular pain. Case 3 is a typical example of this rare scenario, which should always be kept into account as a fourth possible mechanism of injury whenever isolated palsies are noticed without involvement of the IV or VI nerves.

3.4. Mechanism 4: Defective Blood Supply (Indirect Injury). Muthu and Pritty suggested that the III cranial nerves may suffer from disturbances in their blood supply or detrimental biochemical effects arising from the head injury [20]. The frontal, zygomatic, and maxillary bones (the facial "crumple zone") frequently absorb the initial impact and are fractured in trauma. The III, IV, and VI cranial nerves and their supplying arteries are in close relationship to these bones, especially at the anterior portion of the cavernous sinus. The blunt movement and distortion of these bony structures may disrupt the vessels that provide the fragile pial blood supply to the nerves (1). To this regard, it is important to consider the blood supply to the oculomotor nerve: its proximal, extracavernous portion is supplied by perforators arising from the PCA, whereas its middle portion has no specific extraneural supply and its distal, intracavernous portion is supplied by perforators from the cavernous ICA. Therefore, any maxillofacial trauma such as in Case 4, any medial orbital fracture, and any dissection of the cavernous ICA can compromise the vascular supply of the distal nerve, causing a 3cnP.

3.5. Management and Prognosis. The prognosis of patients presenting with unilateral or bilateral fixed and dilated pupils in the setting of TBI without a mass lesion is generally devastating [24]. Decision-making in TBI should always be in adherence to internationally agreed management protocols relying on clinical history, neurological examination, neuroradiological investigations, and continuous multimodality monitoring [14, 16]. While the goal should be to maintain a good ICP and CBF, prognostic factors are to be kept into account [15, 24]. An isolated 3cnP has been for a long time considered as an end-stage sign in the pathological evolution of TBI. However, this sign may not always be a marker of irreversible diffuse brain injury and has the potential to confound early management and prognostication. Our exemplificative cases demonstrate that despite the long clinical course, recovery to a good neurological outcome is not impossible in both adult and paediatric patients.

A methodological approach to 3cnP is of paramount importance to ensure satisfactory outcomes. A baseline ophthalmology assessment should always be requested and initial clinical findings monitored over time until additional investigations could be carried out.

From a neuroradiology perspective, CT and MRI (particularly gradient echo and FLAIR sequences) should always be considered in patients with isolated 3cnP. Vascular imaging in the form of either CTA, MRI, or diagnostic digital selective angiography (DSA) should be requested whenever a vascular dissection is suspected. Interventional radiologists should be involved in the management of posttraumatic pseudoaneurysms, which might cause direct vascular compression [10, 23, 24].

4. Conclusion

Although isolated traumatic 3cnP is relatively uncommon in TBI, it may not represent a prognostic sign of devastating or unsurvivable injury. In all circumstances, it is important to correlate these signs with adequate imaging and additional investigations. Only a comprehensive assessment can enable clinicians and neurosurgeons to timely identify the underlying aetiology/mechanism of injury and provide their patients with adequate solutions.

Data Availability

Data are available upon request to our Institutional Review Board.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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Review Article

The Rise of Inflow Cisternostomy in Resource-Limited Settings: Rationale, Limitations, and Future Challenges

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Low- and middle-income countries (LMICs) bear most of the global burden of traumatic brain injury (TBI), but they lack the resources to address this public health crisis. For TBI guidelines and innovations to be effective, they must consider the context in LMICs; keeping this in mind, this article will focus on the history, pathophysiology, practice, evidence, and implications of cisternostomy. In this narrative review, the author discusses the history, pathophysiology, practice, evidence, and implications of cisternostomy. Cisternostomy for the management of TBI is an innovation developed in LMICs, primarily for LMICs. Its practice is based on the cerebrospinal fluid shift edema theory that attributes injury to increased pressure within the subarachnoid space due to subarachnoid hemorrhage and subsequent dysfunction of glymphatic drainage. Early reports of the technique report significant improvements in the Glasgow Outcome Scale, lower mortality rates, and shorter intensive care unit durations. Most reports are single-center studies with small sample sizes, and the technique requires experience and skill. These limitations have led to criticisms and slow adoption of the technique. Further research is needed to establish the effect of cisternostomy on TBI outcomes.

1. Introduction

The burden of traumatic brain injury (TBI) is enormous and disproportionate. TBI causes 111 years of life lived with disability per 100 000, and 80% of its burden occurs in low- and middle-income countries (LMICs) [1]. In LMICs, the burden of TBI, and those classified as severe, is aggravated by lack of resources for efficient prevention and management [2].

Moreover, there is a disparity in TBI research and innovation. Most TBI research, guidelines, and innovations are developed in high-income countries (HICs), where TBI management's epidemiology and resources are more favorable [3–5]. Consequently, international TBI guidelines are either inconsistently implemented or not implemented in most LMICs [6–9]. To curtail TBI's burden in LMICs, stakeholders must develop and implement holistic health systems strengthening policies, and evidence-based TBI guidelines should equally be mindful of the local context [10].

Cisternostomy is one of the few innovations in the field of neurotraumatology developed in LMICs for use in resource-limited settings. Keeping this in mind, this article will describe the history, rationale, technique, indications, and efficacy of cisternostomy for severe TBI.

2. History

Cisternostomy in the context of severe TBI aims at opening the basal cisterns to atmospheric pressure and tackle the vicious process leading to posttraumatic brain swelling [11]. There are two types of cisternostomy based on the mechanism of action: outflow (ventriculocisternostomy and cystocisternostomy) and inflow (cisternostomy proper) [12]. Outflow cisternostomies were the first to be described in modern neurosurgery. Arne Torkildsen performed the first successful ventriculocisternostomy in 1937 for cerebrospinal fluid (CSF) diversion, and the intervention was the preferred treatment of noncommunicating hydrocephalus after World War II [13, 14]. The idea of inflow cisternostomy was

developed in the context of vascular neurosurgery and still represents a valuable microsurgical step routinely carried out during clipping of anterior circulation aneurysms [15]. The first mention of inflow cisternostomy for the management of severe TBI was in 2012 by Dr. Cherian from Nepal [16].

3. Rationale

The idea of offering cisternostomy to TBI patients is intertwined with the discovery of the glymphatic system. The glymphatic system is a network of perivascular channels that promote entry and exit of substances within the CNS [17]. The fluid in the glymphatic system is made from CSF produced by the choroid plexus and circulates within the subarachnoid space into perivascular (Virchow–Robin) spaces. The interstitial fluid collected within perivenous spaces is then drained to the cervical lymphatic circulation [18]. TBI affects the flow and composition of extracellular fluids within the central nervous system (CNS). It damages the glymphatic system and causes biomarkers' liberation (glial fibrillary acidic protein, neuron-specific enolase, and S100 calcium-binding protein B) and waste CNS products [19]. Acute TBI causes the translocation of type 4 aquaporin channels away from astrocytes' endfeet, thereby altering the flow of extracellular CNS fluid (glymphatic and interstitial) and causing reactive astrogliosis [20].

Based on these facts, the concept of CSF shift edema started to emerge, as it was suggested that, following posttraumatic subarachnoid bleeding which impairs the normal CSF flow and resorption, the interstitial and intracellular fluid could increase as a result of the shift from the rising pressure of the basal cisterns into the brain parenchyma [11]. A similar concept has been described in acute ischemic stroke edema. Mestre et al. [21] tracked CSF flow in mice after middle cerebral artery stroke and found evidence of CSF shift edema in the ipsilateral hemisphere. Therefore, the rationale of cisternostomy is to open and rinse the basal cisterns allowing a removal of blood products and addressing the altered gradient pressure between subarachnoid space and the brain parenchyma [11].

Numerous authors have studied the association between subarachnoid CSF flow and TBI. For example, the role of cisternotomy on glymphatic flow and TBI was studied in mice models by Plog et al. [22] who used horizontal cisternotomy to drain CSF from mice that had acute TBI continually. Of note, they found no evidence in favor of cisternostomy preventing the secondary cascade of TBI. The reason is that CSF drainage by the cisterna magna cisternotomy reduces the hydraulic pressure that drives fluid exchange between CSF and interstitial fluid [17]. As a result, it inhibits glymphatic efflux, which alters TBI biomarkers' clearance and waste products. Unlike cisterna magna cisternotomy, cisternostomy exposes more cerebral cisterns (interoptic, optico-carotid, lateral carotid, interpeduncular, and prepontine) to atmospheric pressure and removes blood products from the subarachnoid space. Traumatic subarachnoid hemorrhage occurs in 11–60% of TBI cases due to injury to subarachnoid vessels [23, 24]. This might explain the efficacy of cisternostomy in some TBI cases. Another important consideration is the timing of TBI-related glymphatic dysfunction. Glymphatic disruption occurs between days 3 and 28 in mice models, although in a small number of cases, it occurs as early as day 1 [19]. Therefore, if cisternostomy could in the future prove its effectiveness in all TBI cases, some of its effects could not be simply explained by the CSF shift edema theory alone and should perhaps be attributable to the reduced intracranial pressure and the overall optimization of the CSF flow as seen following decompressive craniectomy [25].

4. Practice of Cisternostomy for TBI Management

Cisternostomy is always performed in conjunction with DC, and such approach represents the last resource in the treatment of medically refractory severe TBI [3, 26, 27].

In the seminal report on the advantages of cisternostomy, Cherian et al. [28] reported lower mortality (15.6% in the cisternostomy group vs. 26.4% in the DC and cisternostomy group vs. 34.8% in the DC group), shorter mechanical ventilation times (2.4 days in the cisternostomy group vs. 3.2 days in the DC and cisternostomy group vs. 6.3 days in the DC group), and better Glasgow outcome scales at 6 weeks (3.9 in the cisternostomy group vs. 3.7 in the DC and cisternostomy group vs. 2.8 in DC group) [28]. Unsurprisingly, the adoption of cisternostomy has increased significantly in the past 8 years in several LMICs, diffusing from its birthplace, Nepal, to neurosurgical units in Brazil, China, Egypt, India, Iran, and Iraq [28–35].

Shorter mechanical ventilation and intensive care unit times are most needed in resource-limited settings where most TBI cases tend to happen [30, 36]. Cisternostomy poses a lesser risk and cost than DC because DC must be followed by a second intervention, a cranioplasty, which carries its own risk and cost [30, 37]. However, we note that economic comparisons have been limited to direct expenses, and no study has compared the cost-effectiveness of cisternostomy and DC. A cost-effectiveness analysis will factor in TBI's societal cost and benefit (mortality and morbidity averted by both interventions) and ascertain the economic superiority of one intervention over the other [38–43]. Another consideration is technicality and resource availability. Cisternostomy is a complex microsurgical procedure, and few LMIC neurosurgeons have the experience and equipment to perform cisternostomy safely [32, 33, 44, 45]. The expansion of cisternostomy in LMICs will require capacity building and increased access to microscopes in the form of fellowships and the development of low-cost microscopes [38–43].

5. Quality of Evidence

Most published cisternostomy studies are either observational (retrospective and nonrandomized), run in single centers, or have small sample sizes [29–35]. This diminishes the quality of evidence generated and has precluded their inclusion in TBI meta-analyses and guidelines [3, 4]. Further studies are needed for cisternostomy to be accepted as an option for TBI

management. Future cisternostomy must be robust, i.e., ideally, they must be randomized multicentric studies with low risk of bias in randomization and concealment and a large sample size (i.e., ≥100 patients) [46]. Although randomized control trials are the preferred study design for quality evidence, they are not always feasible. Randomized control trials can be impractical, costly, and lengthy [47]. For these reasons, a significant proportion of evidence in neurosurgery spawns from cohort, case-control, and quasi-experimental studies [47]. The evidence from these studies can be valuable if they are designed to minimize bias [47–50].

6. Implications and Future Direction

Cisternostomy is the epitome of TBI innovation for LMICs and by LMICs. The inventor of this technique is an LMIC neurosurgeon, and most publications on the topic are from LMICs. This experience lays the ground for LMIC research collaborations in the form of large multicentric (randomized, cohort, case-control, or quasi-experimental) studies. The evidence generated from robust studies will facilitate a more widely and consistent adoption of cisternostomy and will eventually improve the technique by generating new research questions, such as the usefulness of relying on intraoperative ultrasound to visualize the cisterns in a swollen brain. [51].

7. Conclusions

The management of TBI is complex, even more so in resource-limited settings. To solve the public health and clinical problem posed by TBI, LMIC researchers must be ready to innovate. The use of cisternostomy in the surgical management of severe TBI represents a revolutionary step, and disruptive theory of CSF shift edema has already contributed lessons to the entire neurotrauma community. LMIC TBI researchers and innovators can build on the cisternostomy experience to develop context-specific and evidence-based solutions.

Data Availability

No data were used to support this study.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Early and Ultraearly Administration of Tranexamic Acid in Traumatic Brain Injury: Our 8-Year-Long Clinical Experience

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Introduction. The most important result of head trauma, which can develop with a blunt or penetrating mechanism, is traumatic brain injury. Tranexamic acid (TXA) can be used safely in multiple trauma. Recent studies showed that TXA can be useful in management of intracerebral hemorrhage, especially in reducing the amount of bleeding. The TXA given in the first 3 hours has been shown to reduce mortality. The aim of our study was to evaluate the effectiveness of tranexamic acid used in patients with traumatic brain injury. *Method*. Patients with trauma in the emergency room between January 2012 and January 2020 were screened in this retrospective study. The inclusion criteria were being over the age of 18 years, tranexamic acid administration in the emergency department, and traumatic brain injury on brain computerized tomography (CT) and control CT imaging after 6 hours. *Results*. The number of study patients was 51. The median score of GCS was 12.00 (8.00–15.00). Subdural hemorrhage and subarachnoid hemorrhage were the most common findings on brain CT scans. In the group TXA treatment for less than 1 hour, the arrival MAP was low and the pulse was high ($p = 0.022$ and $p = 0.030$, respectively). All the patients were admitted with multiple trauma. None of the 51 patients had thrombotic complications and died due to head injury. *Conclusion*. TXA appears to be a safe drug with few side effects in the short term in head injuries. According to our experience, it comes to mind earlier in multiple trauma, especially in head trauma with pelvic trauma.

1. Introduction

The most important result of head trauma that can occur with blunt or penetrating mechanism is traumatic brain injury (TBI). It has been reported in the literature that there are an average of 1.1 million head trauma applications to emergency departments (ED) each year. It was stated that 21% of these cases required hospitalization and 4% were exitus [1].

In studies conducted, the risk of bleeding due to head trauma was found to be approximately 3-4 times higher in patients over 50 years of age than in those under 30 years old. It has been reported that 15.7% of mild head injuries require hospitalization and 35% of these hospitalizations included patients of65 years and older [2]. Even mild head traumas have been reported to cause mortality and serious morbidity in patients using antiaggregants or anticoagulants [3, 4]. Secondary brain injury from intracranial bleeding, cerebral edema, and increased intracranial pressure is the cause of morbidity and mortality after TBI [4, 5].

The antifibrinolytic agent tranexamic acid (TXA) is commonly given to patients to reduce the need for blood transfusion. TXA reduces the number of patients receiving a blood transfusion by about one-third, reduces the volume of blood transfused by about one unit, and halves the need for further surgery to control bleeding in elective surgical patients [6]. TXA has been shown to reduce mortality in trauma patients with extracranial bleeding. The CRASH-2 trial showed that the administration of TXA within 8 h of injury significantly reduces deaths due to bleeding compared to placebo, with no apparent increase in vascular occlusive events [7]. Studies have shown that tranexamic acid can be used safely in head trauma and in the management of intracerebral hemorrhages, especially in reducing the amount

of bleeding [8, 9]. The TXA given in the first 3 hours has been shown to reduce mortality, and the regimen of starting treatment and maintaining it in 8 hours is used in the early period [7].

The aim of our study was to evaluate the effectiveness of tranexamic acid used in patients with traumatic brain injury.

2. Materials and Methods

This study was conducted retrospectively in a tertiary university hospital with an average of 100,000 emergency applications per year. Patients who came to the emergency room with trauma between January 2012 and January 2020 were screened. The inclusion criteria of being over the age of 18 years, TXA administration in the emergency department, and traumatic brain injury on computed brain tomography were employed. Patients who underwent computerized tomography 6 hours after formed the study group. Patients who are given TXA in the emergency department are started with 1 gr IV in 10 minutes, and then, a 1 gr maintenance regimen is applied in 8 hours. As it is an observational study, it is arranged according to the STROBE statement.

By evaluating the patient's file information, age, gender, trauma mechanism, mean arterial pressure, pulse, oxygen saturation, drugs used, Glasgow Coma Scale (GCS), pupil reflex, pH, lactate, base deficit, brain computerized tomography (CT) findings, bleeding in other regions tomography, TXA administration time, control brain CT time, and increased bleeding in control brain CT were evaluated. In the files, the increase in bleeding in the radiology reports and related clinical notes is noted. The increase in bleeding was evaluated as an enlargement over 1 mm in BT, increase in shift, and any increase in bleeding volume.

2.1. Statistical Analysis. Continuous data are given as mean ± standard deviation. Categorical data are given as percentage (%). Shapiro–Wilk's test was used to investigate the suitability of the data for normal distribution. In comparison to groups that do not conform to normal distribution, the Mann–Whitney *U* test was used for cases with two groups. Pearson chi-square and Pearson exact chi-square analyzes were used in the analysis of the created cross tables. Logistic regression analysis was used to determine risk factors. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) program was used in the implementation of the analyzes. For statistical significance, $p < 0.05$ value criterion was accepted.

3. Results

The number of patients receiving TXA in the emergency room was determined to be 289. 145 of them were patients with trauma. The number of patients with TBI in the emergency department, TXA given for any reason and control brain CT after hospitalization, was determined as 51 (Figure 1).

The median age of the patients was 44.00 (32.00–66.00). The number of female patients was determined as 13 (25.5%). Trauma mechanisms, vital parameters, and demographic features are given in Table 1. The most common injury was *In-Vehicle Traffic Accident*. When the patients who were at risk of bleeding from the drugs used by the patients were evaluated, the most used drug was found to be acetylsalicylic acid (ASA). Three patients were using clopidogrel in the study group. Other antiaggregant and anticoagulant medication uses were not detected.

Neurological examination evaluations and laboratory findings of the patients are given in Table 2. The median value of GCS was 12.00 (8.00–15.00) in the study group. 41 (80.4%) of the patients had pupil reaction.

The tomography findings of the study group are given in Table 3. In the study group CT, subdural hemorrhage and subrachnoid hemorrhage were the most common on brain CT. It was found that hemothorax and pelvic bleeding were higher in thorax, abdominal, and pelvic CT, where other injuries were evaluated. An increase in the amount of bleeding in control tomography was observed in 8 patients in the study group. The increase in control tomography was evaluated as an enlargement of more than 1 mm and any volume increase.

Since TXA was given in our center within 3 hours, no patient received TXA after 3 hours. 26 (51.0%) of the patients received TXA in the first hour. The characteristics of the patients whose TXA-taking time periods are evaluated are given in Table 4. In patients with low MAP and high pulse, TXA was thought to be preferred earlier ($p = 0.022$ and $p = 0.030$, respectively). When the duration of TXA administration was evaluated with CTs taken, it was observed that TXA treatment was given earlier in patients with pelvic injury ($p = 0.022$). It is thought that physicians act earlier, since bleeding can be detected late in the case of pelvic injury, and there is no mechanism to stop bleeding in this area.

All of the patients were admitted with multiple trauma. None of the 51 patients had thrombotic complications and died due to head injury. In the case of isolated head injury, it should be considered that it can be used safely as in multiple trauma.

4. Discussion

TXA is a safely used agent especially in the management of multitrauma patients. Due to decrease in the amount of bleeding, morbidity, and mortality, as a result of its increasing use in the last decade, bleeding-related deaths (exsanguination) decrease [8, 10]. The use of TXA in combination with performing damage control surgery, proper use of blood products, and thromboelastography has an important role in this reduction. The advantages of TXA are that it has no obvious contraindications, it is inexpensive, it is given only by iv infusion, and its complications are rare [11–13]. In our study, we wanted to evaluate the benefit of TXA for intracranial hemorrhage in patients with multiple trauma, however, with TBI. In the CRASH-3 study published in 2019, the benefits of using TXA in mild head injuries were mentioned [8]. In our study, we found that there were no patients who died due to intracranial hemorrhage in

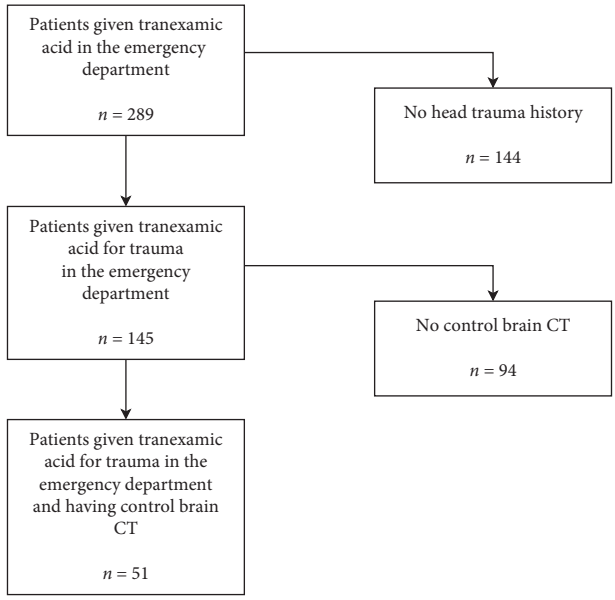

Figure 1: Flow diagram of the study population.

Table 1: Demographic data, trauma mechanisms, and medications of the patients.

Age (years)	44.00 (32.00–66.00)
Sex	
Female (*n* (%))	13 (25.5%)
Vitals	
MAP (mmHg)	83.33 (66.67–93.33)
Pulse (bpm)	88.00 (85.00–110.00)
Saturation (%)	95.00 (91.00–97.00)
Trauma mechanism	
MVA (*n* (%))	17 (33.3%)
Pedestrian trauma (*n* (%))	9 (17.6%)
Motorcycle bike (*n* (%))	5 (9.8%)
Fall from heights (*n* (%))	16 (31.4%)
Assault (*n* (%))	1 (2.0%)
Gunshot injuries (*n* (%))	2 (3.9%)
Stab wounds (*n* (%))	1 (2.0%)
Medications	
ASA (*n* (%))	16 (31.4%)
Clopidogrel (*n* (%))	3 (5.9%)

MAP, mean arterial pressure; MVA, motor vehicle accident; ASA, acetylsalicylic acid.

Table 2: Neurological examination and laboratory findings.

Neurologic exam	
GCS	12.00 (8.00–15.00)
Pupil reaction	41 (80.4%)
Laboratory	
pH	7.364 (7.284–7.398)
Lactate (mmol/L)	3.90 (2.40–4.90)
Base deficit (mmol/L)	−4.20 (−7.10–−2.20)

GCS, Glasgow Coma Scale.

Table 3: CT findings of the study population.

	Study
Brain CT findings	
Contusion (*n* (%))	23 (45.1%)
Subarachnoid hemorrhage (*n* (%))	21 (41.2%)
Subdural hematoma (*n* (%))	22 (43.1%)
Epidural hematoma (*n* (%))	10 (19.6%)
Intraparenchymal (*n* (%))	4 (7.8%)
Other (pneumocephalus) (*n* (%))	2 (3.9%)
Total (*n* (%))	
Other injuries	
Hemothorax (*n* (%))	9 (17.6%)
Liver injury (*n* (%))	5 (9.8%)
Splenic injury (*n* (%))	3 (5.9%)
Kidney injury (*n* (%))	2 (3.9%)
Pelvic bleeding (*n* (%))	11 (21.6%)
External bleeding (*n* (%))	3 (5.9%)
Control CT time (Δ hours)	14.00 (7.00–26.50)
Control CT increased bleeding (*n* (%))	8 (15.7%)

CT, computerized tomography.

the early period, especially after TXA intake. Since our study is retrospective, it should be noted that TXA was not given to patients with isolated TBI before the CRASH-3 study was published.

In our study, the median age was determined to be 44, and a rate similar to the average of 41.7 in the CRASH-3 study was achieved, in which most patients were studied. The fact that trauma especially affected the young population was the most important factor in this regard. In our study, females were more affected than other studies [8, 10]. The CRASH-3 showed the efficacy of the TXA in reducing the mortality rate only on mild and moderate TBI and not on severe TBI. Our sample size was small, and we could not compare the mild or severe TBI differences about TXA.

In our study, the duration of TXA administration was compared between 1 hour and 1–3 hours. Previous studies

Table 4: The factors affecting the time of TXA treatment.

	TXA <1 h	TXA 1–3 h	*p*
Age (years)	45.00 (25.75–66.00)	42.00 (33.00–66.50)	0.970
Female (*n* (%))	6 (23.1%)	7 (28.0%)	0.687*
MAP (mmHg)	73.33 (63.33–90.83)	90.00 (75.00–95.00)	**0.022**
Pulse (bpm)	100.00 (90.00–110.00)	90.00 (79.00–102.50)	**0.030**
Saturation (%)	92.50 (90.00–95.25)	95.00 (91.50–97.50)	0.067
GKS	12.00 (7.00–14.25)	12.00 (8.50–15.00)	0.871
pH	7.356 (7.275–7.391)	7.365 (7.318–7.405)	0.361
Lactate (mmol/L)	3.70 (2.40–4.90)	3.90 (2.25–5.10)	0.977
Base deficit (mmol/L)	−5.10 (−8.13–−2.82)	−3.50 (−6.35–−1.75)	0.184

*Pearson chi-square. $p < 0.05$ is statistically significant.

have shown that with the onset of TXA at the appropriate time, all-cause deaths are reduced and hospital stay is shorter [10, 14]. In the CRASH-2 study, all-cause mortality rates were 14.5% in the group of patients receiving TXA and 17.4% in the MATTERs study. Although we could not compare in our study that there was no control group, all-cause mortality rates were 18%, similar to other studies [8, 10, 15].

In the CRASH-2 study published in 2010, evaluating the use of TEA in 20.211 trauma patients with hemorrhage or hemorrhagic shock, a significant decrease in mortality due to all causes and a decrease in bleeding-related mortality were also detected. Moreover, TXA exhibited these positive effects without causing any vascular occlusion or thrombosis [7]. The MATTERs study, designed similar to the CRASH-2 study and performed in the military field, showed that mortality was reduced in polytrauma patients treated with TXA; such reduction was more pronounced in those undergoing "massive" transfusions of blood products, including packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitates to restore circulating volume and clotting factors [15].

Our study group is small-sized and gunshot wounds were seen in only two patients. But gunshot wounds are known for their devastating consequences in terms of profuse intracranial bleeding; hence, TXA can be useful [16].

TXA research has been performed in many bleeding forms due to the variety of ways of using the drug and still continues [17]. In observational studies in which IVA was performed by applying IV, mortality rates were found lower than in the current literature, but no comparison was made because there was no control group [18, 19].

Although there are articles about the restriction of the use of TXA maintenance therapy in recent years, we found that maintenance therapy did not cause any complications in our study [13, 20].

TXA may increase the risk of thromboembolism: in the MATTERs study, the rates of deep vein thrombosis and pulmonary embolism were greater in the TXA group than in the no-TXA group [15]. There are several studies about thromboembolic complications in neurosurgery [21, 22], and these indicate that the perioperative period of immobility should be tackled with appropriate thromboprophylaxis protocols. It should also be highlighted that strict monitoring of coagulation cascade (platelet count, INR, PT, and PTT) is helpful in the acute phase of their management [23, 24].

5. Conclusion

In light of the above, TXA appears to be a safe drug with few side effects in the early management of TBI. According to our experience, its use is particularly helpful in multiple trauma or whenever TBI is associated to pelvic trauma. Further studies are warranted to establish the role of TXA in the ED management of patients with isolated and non-isolated TBI.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of the article.

Authors' Contributions

NA and MEC conceived the study and designed the trial. NA, MEC, and UB formulized the research question. NA supervised the conduct of the trial and data collection. MEC and UB provided data transfer to the electronic database and performed the literature search. NA, MEC, and UB provided statistical advice on study design and analyzed the data. NA, UB, and MEC drafted the first manuscript. NA and MEC contributed to final editing. All authors contributed substantially to its revision. All authors read and have approved the final version. NA takes responsibility for the paper as a whole.

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Research Article

Pattern and Outcome of Pediatric Traumatic Brain Injury at Hawassa University Comprehensive Specialized Hospital, Southern Ethiopia: Observational Cross-Sectional Study

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Background. Traumatic brain injury (TBI) is the most common cause of death/disability in children. The Glasgow coma scale and other parameters are used for treatment/follow-up of TBI. Childhood TBI data are scarce from sub-Saharan Africa. The study aimed to determine the pattern and predictors of the TBI outcome in Southern Ethiopia. *Methods*. An observational cross-sectional study was conducted from September 2017 to September 2018 at Hawassa University Hospital. Structured questionnaires were used for data collection. Significant associations were declared at a P value of <0.05. *Results*. There were 4,258 emergency room (ER) visits during the study period, and TBI contributed to 317 (7.4%) cases. The mean age of study subjects was 7.66 ± 3.88 years. Boys, predominantly above 5 years of age, comprise 218 (68.8%) of the study subjects with a male to female ratio of 2.2 : 1. Pedestrian road traffic accidents (RTA), 120 (37.9%), and falls, 104 (32.8%), were the commonest causes of TBI. Mild, moderate, and severe TBI were documented in 231 (72.9%), 61 (19.2%), and 25 (7.9%) of cases, respectively. Most of the TBI cases presented within 24 hrs of injury, 258 (81.4%). Recovery with no neurologic deficit, 267 (84.2%); focal neurologic deficit, 30 (9.5%); depressed mentation, 10 (3.2%); and death, 10 (3.2%), were documented. Signs of increased intracranial pressure (ICP) at admission [AOR: 1.415 (95% CI: 1.4058–9.557)], severe TBI [AOR: 2.553 (95% CI: 1.965–4.524)], presence of hyperglycemia [AOR: 2.318 (95% CI: 1.873–7.874)], and presence of contusion, diffuse axonal injury (DAI), or intracranial bleeding on the head computed tomography (CT) scan [AOR: 2.45 (95% CI: 1.811–7.952)] predicted poor TBI outcome. *Conclusion*. TBI contributed to 7.4% of pediatric ER visits. Pedestrian RTA and falls, early presentation (<24 hours of injury), and mild form of TBI among boys were the most common documented patterns. ICP, hyperglycemia, severe TBI, and presence of contusion, DAI, or intracranial bleeding on head CT predicted poor outcome. Strategies to ensure road safety and to prevent falls and animal-related injuries and TBI follow-up for ICP and glycemic controls are recommended.

1. Introduction

Traumatic brain injury (TBI) is a brain injury that occurs following a blow to the head, a fall, a bullet, a high-speed crash, or explosion injuries. TBI could be an open (penetrating) or closed type [1]. Childhood injury requires immediate attention given its contribution to high childhood mortality and long-term disabilities. Injuries contribute to 5.4% (265,000–348,000) of childhood deaths per year worldwide [2]. In 2015, injuries resulted in 25,000 deaths among the Ethiopian children 0–14 years of age [3]. TBI is a single, severe, and the most common form of injury in children [4].

Worldwide, it is estimated that TBI affects 69 million individuals each year. Low- and middle-income countries (LMICS) have three times higher TBI burden than high-income countries. Road traffic-related head injuries were reported to be common in LMICS. Globally, TBI is projected to be the third leading cause of death and injury by the World Health Organization in 2020 [2, 5, 6]. Pediatric TBI is

reported to be the most common cause of injury-related death, and it commonly follows road traffic accidents and falls [7, 8]. TBI accounted for 8.3% of the pediatric emergency department (ED) visits with mild severity according to the Western studies [9, 10]. Several studies from developing countries documented TBI as a very common public health problem with milder severity and most notably following motor vehicle accidents [11–17]. Road traffic accidents (RTA) and falls from height were common reported pediatric TBI causes. Assaults or intentional injuries were reported in the minority of cases [2, 9–11, 18].

Primary brain injury involves initial tear, shear, or hemorrhage. Secondary injuries, which are targets for interventions, usually involve cascades of biologic reactions following primary injury. These changes include cellular, chemical, tissue, or blood vessel changes in the brain resulting in further damage to the brain tissue [19, 20]. Severity of TBI is assessed using the Glasgow coma scale (GCS) and graded into mild (13–15), moderate (9–12), and severe (≤8). The GCS also assists in assessing the outcome of TBI cases [6, 21, 22]. Mild TBI presents with concussion symptoms, affecting physical, cognitive, and emotional (affective) domains. Various degrees of autonomic and neurologic dysfunctions are seen in moderate and severe TBI cases in addition to mild TBI features [23, 24]. Head computed tomography (CT) is recommended for children presenting with drowsiness or decreased mentation, any sign of basal skull fracture, focal neurologic deficit, etc. [25]. Several arguments are forwarded on abandonment of skull X-ray as an investigation means for TBI [26, 27].

Acute management of TBI includes resuscitation and airway management, nutritional support, intubation when GCS ≤ 8, follow-up for ICP and other complications, and neurosurgical intervention [6]. Presence of cerebral edema, GCS ≤ 8, hypoxemia, and hypernatremia were reported as predictors of poor TBI outcome [21, 22, 28]. Poor TBI outcome was documented in resource-limited settings, and neurocritical protocol for prehospital care was recommended [29]. The TBI mortality rate ranged from 8% in Western settings to 21.2% in the developing regions [7, 11, 29]. Lack of prospective studies and injury data registries in most parts of Africa has made the assessment of TBI difficult [15]. Evidences on the epidemiologic profile and outcome of TBI are also scarce from Ethiopia, sub-Saharan Africa. Our study aimed to determine the epidemiologic profile and outcome of childhood TBI at a tertiary hospital in Southern Ethiopia.

2. Methods

2.1. Study Area. The study was conducted at Hawassa University Comprehensive and Specialized Hospital (HUCSH), Hawassa, Ethiopia. Hawassa city is located 270 km south of Addis Ababa, Ethiopia's capital. HUCSH is the first and largest referral and teaching hospital in Southern Ethiopia. It serves a catchment population of over 18 million. The pediatrics department provides inpatient and outpatient services. Neurosurgical interventions are provided by neurosurgeons, and radiologic images like head CT are read by radiologists. These services are available 24 hours a day, and head CT is acquired up on presentation of TBI cases. The hospital had an eight-bedded intensive care unit (ICU) for care of critically ill adults and pediatric patients.

2.2. Study Design and Period. An observational cross-sectional study was carried out among pediatric TBI cases, aged between 2 months and 14 years and that visited HUCSH from September 2017 to September 2018. Consecutively, admitted TBI cases fulfilling the predefined criteria were included in the study after informed consent was obtained from the family or guardians. Cases were excluded from the study when consent was not secured.

2.3. Sample Size. The study was planned for one year with an assumption of getting a minimum sample size of 221 as calculated from a similar study with P, 17.4% [30]. During the one-year study period, 317 TBI cases were observed (95% CI: 314–320) and all were included in the study.

2.4. Variables. The dependent variable was a patient's outcome on discharge, i.e., full recovery, neurologic deficit, or death. Poor outcome was defined as death or neurologic disability and was assessed up on hospital discharge of TBI cases. Independent variables included sociodemographic data (age, sex, and place of residence), intent, mechanism and nature of injury, place of occurrence, severity of injury, associated extracranial injury, investigation and treatment type, and duration of hospital stay.

2.5. Operational Definitions. Traumatic brain injury (TBI) was defined as a brain injury that occurs following a blow to the head, a fall, a bullet, a high-speed crash, or explosion injuries [1]. TBI severity was graded into mild, moderate, and severe when the GCS was 13–15, 9–12, and ≤8, respectively [6]. Outcome was assessed using the GCS during discharge from the hospital [21, 22]. Hypotension and hypertension were considered when blood pressure for age and sex was below the 5^{th} percentile and $\geq 95^{th}$ percentile, respectively [31]. Hypoglycemia and hyperglycemia were considered when the admission random blood sugar was <70 mg/dl and >200 mg/dl, respectively [32, 33].

2.6. Data Collection Tool, Procedure, and Data Quality Assurance. Data were collected at the pediatric emergency room, inpatient ward, and intensive care unit by trained Bachelor of Science graduate nurses and intern doctors. Data were collected using a structured questionnaire, and information consisting of sociodemographic characteristics, characteristics of injury (i.e., intent, mechanism, nature, and place of injury), patient's previous medical history, clinical workup and management, duration of admitted stay, and discharge outcome were collected. All consecutive TBI cases seen at the pediatric emergency department of HUCSH were included after consent was obtained from the family or guardian. Daily collected data were checked for

completeness by the supervisor and resident doctor, and correction was made on the spot and on a daily basis.

2.7. Data Analysis. Data were double-entered into excel spread sheets and analyzed using SPSS version 20 software. Mean and standard deviations were used to present continuous variables. Frequency and percentages were used to present categorical variables. After checking for normality and other parameters, parametric tests were chosen for analysis to assess associations between variables and outcome. Binary logistic regression was used to assess the association between dependent and independent variables. Variables with P value < 0.05 on binary logistic regression analysis were taken into multiple logistic regression models for controlling the possible effect of confounders to ascertain associations. Finally, variables which had an independent association with outcome of TBI were identified on the basis of the adjusted odds ratio (aOR), with 95% CI and P value < 0.05.

3. Results

3.1. Sociodemographic Characteristics. There were 4,258 pediatric emergency room (ER) visits, and TBI contributed to 7.4% (317) of ER visits in a one-year study period. A total of 317 study subjects were included. Among 317 study subjects, 218 (68.8%) were males and 99 (31.2%) females with a male to female ratio of 2.2 : 1. The study subjects were aged from 7 months to 14 years with a mean age of 7.66 ± 3.82 years. School age groups, 5–10 years, and adolescents, 10–14 years, contributed to 36.9% (117) and 36.3% (115) of TBI, respectively. One hundred and eighty three (57.7%) of the study subjects came from Southern Nations, Nationalities, and People's Regional State (SNNPR) while the rest 134 (42.3%) came from the neighboring Oromia and Ethiopian Somali regional states (see Table 1). Boys were predominantly affected, and they accounted for 65.8%, 68.3%, and 71.3% of TBI in under fives, school aged, and adolescent age groups, respectively. The majority of our study subjects' parents were farmers or small-scale businesses owners, 313 (98.7%).

3.2. Pattern and Mechanism of Traumatic Brain Injury. The main cause of TBI was RTA (road traffic accidents), 144 (45.4%) cases. From RTA, the majority were pedestrians, 120 (83.3%), while 24 (16.7%) were occupants in vehicles. The other TBI causes were falls, 104 (32.8%); fighting/violence, 40 (12.6%); animal bite or kick injury, 28 (8.8%); and one case of assault (child maltreatment). Most preschool falls occurred at home 29 (60.7%), while 94.1% (32) of school aged and 97.6% (41) of adolescent falls happened outdoor. Eighty three (79.8%) of falls and 84 (58.3%) of road traffic accidents occurred in boys.

Concerning the timing of presentation, most of the study subjects presented within 24 hours of injury, 258 (81.4%). Thirty one (9.8%) and 28 (8.8%) of TBI cases presented between 24 hours and 72 hours and after 72 hours of injury (see Table 2).

The majority of TBI followed unintentional injuries, 87.4% (277). Almost all of the intentional injuries, 38 (97.5%), were due to fighting with only one case of child maltreatment. Eighty nine (28%) of TBI cases had lost consciousness at the time of presentation. Among the study subjects, 26 (8.2%) exhibited seizure, 40 (12.6%) had abnormal pupillary signs, and 60 (18.9%) showed signs of increased ICP. Hypertension and depressed mentation were the most common manifestations of increased ICP, each accounting for 22 (6.9%) raised ICP cases. Vomiting 16 (5%) was the other commonly raised ICP feature (see Table 2).

Majority of our study subjects were conscious at the time of presentation, and 195 (61.5%) had a GCS of 15/15. The least GCS was 3 in 4 cases, and mean GCS at admission was 13.4 ± 2.7. Concerning TBI severity, mild, moderate, and severe form accounted for 231 (72.9%), 61 (19.2%), and 25 (7.9%) of study subjects, respectively. Mild TBI was caused by all mechanisms of injury, while moderate and severe TBI were mainly caused by RTA. On presentation, hypotension and hyperglycemia were documented in 9 (2.8%) and 20 (6.3%) of TBI cases (see Table 2).

Skull X-ray was done in 177 (55.8%) of study subjects, and skull fractures were reported in 100 (31.5%) TBI cases: linear skull fractures, 27 (8.5%); depressed skull fractures, 72 (22.7%); and basal skull fracture, 1 (0.3%). Head CT scan was done in 70.7% (224) of the study subjects, and intracranial hematomas were documented in 4.4% (14) of the study subjects: 3 epidural, 6 subdural, 4 intracerebral, and 1 subarachnoid hemorrhage. Additional head CT findings included cerebral contusion and diffuse axonal injury, simple skull fractures without intracranial bleeding, and depressed skull fractures with contusion or intracranial bleeding in 30 (9.4%), 94 (29.7%), and 36 (11.4%) of the study subjects, respectively. Normal head CT scan was documented in 50 cases (15.8%) of TBI. Extensive intracerebral hemorrhages, 4 (40%), and diffuse axonal injury (DAI), 4 (40%), were the head CT findings in fatal cases. Head CT was not done in the other two fatal cases (see Table 2).

Associated extracranial injuries were reported in 256 (80.7%) cases of TBI. From these, soft tissue injury was the most common form, 179 (56.5%), followed by extremity bone fracture, 70 (22.1%); chest or abdominal injury, 6 (1.9%); and one case of vertebral bone injury (see Table 3).

3.3. Management and Outcome. One hundred twenty nine (72.2%) TBI cases were managed conservatively, while 88 (27.8%) underwent various surgical interventions within the first (01) week of presentation. Most of the operated cases were aged 5 to 10 years, 48/88 (55%). No death was documented among the operated patients. The common surgical indications were the evacuation of epidural and subdural hematoma, 4 (4.5%); wound debridement for compound skull fracture, 19 (21.3%); and depressed skull fracture elevation, 66 (74.2%) (see Table 3). Elevation of depressed skull fracture was done for 66 cases with mild (53), moderate (12), and severe (1) TBI categories. Burr hole and evacuation was done for four mild TBI cases. Irrigation and

Table 1: Sociodemographic characteristics of pediatric traumatic brain injury at HUCSH from September 2017 to September 2018.

Variable	Category	Number (*n*)	Percentage (%)
Age (years)	<5	85	26.8
	5–10	117	36.9
	10–14	115	36.3
Gender	Male	218	68.8
	Female	99	31.2
Parental occupation	Employee	75	23.7
	Merchant	65	20.5
	Farmer	173	54.6
	Driver	2	0.6
	Other	2	0.6
Place of residence	Hawassa city	112	35.3
	Oromia	133	42
	Other SNNPR	71	22.4
	Somali	1	0.3
Chronic illness	No	313	98.7
	Severe acute malnutrition	2	0.6
	Epilepsy	1	0.3
	Other	1	0.3

debridement were done for mild (16) and moderate TBI (1) cases.

Concerning the hospital stay, majority of the TBI cases stayed from 4 to 7 days, 34% (108), while 78 (24.6%) were discharged within 24 hours of arrival. Prolonged hospitalization (≥1 month) was documented in 2 patients with severe TBI and extremity fracture with extensive soft tissue injury. The average length of hospitalization days among those who died was 4.5 days (median 2 days), and 5/10 (50%) of deaths occurred within the first 3 days of admission (see Table 3).

Concerning the outcome at discharge, 303 (95.6%) study subjects recovered from the injury. Good recovery without neurologic deficit, focal neurologic deficit, and depressed mentation were documented in 267 (84.2%), 30 (9.5%), and 10 (3.2%) of study subjects, respectively. Ten (3.2%) deaths were documented, and 2 cases were referred to another hospital and 2 left against medical advice (see Table 3).

3.4. Factors Affecting Outcome. On bivariate analysis, factors significantly associated with a poor outcome of pediatric TBI with 95% CI and P value < 0.05 were comorbid illness, loss of consciousness and convulsion at presentation, increased ICP sign, severity of head injury, presence of hypotension, hyperglycemia on presentation, and head CT scan findings.

On multivariable logistic regression, presence of increased ICP at admission was associated with 1.4 times the odds of death or neurologic disability [AOR: 1.415 (95% CI: 1.458–9.557)]. Severe TBI was associated with doubled odds of death or disability compared with moderate and mild TBI [AOR: 2.553 (95% CI: 1.965–4.524)]. Presence of hyperglycemia [AOR: 2.318 (95% CI: 1.873–7.874)] and contusion, DAI, or intracranial bleeding on head CT [AOR: 2.45 (95% CI: 1.811–7.952)] were also found to be significantly associated with death or neurologic disability among pediatric TBI (see Table 4).

4. Discussion

In our study, boys and children above 5 years of age were predominantly affected by TBI. This finding is in agreement with Nigerian, South African, and Tunisian studies. This could be related to boy's risk-prone behavior resulting in high energy transfer and their outdoor engagement [14, 30, 34–37]. Concerning mechanisms of injury, unintentional pedestrian RTA and falls were the most common causes followed by intentional fights/violence injuries. This is in line with most of the studies done in developing countries [2, 8, 18, 22, 30, 34, 37–39].

Most of our study subjects presented within 24 hours of injury and had a mild form of TBI. This is in harmony with reports from Nigeria and Tunisia [30, 34, 38, 40]. However, severe TBI was the most common form in other Nigerian and Tunisian studies. The possible reason for the noted difference could be the exclusion of mild TBI cases not meeting the admission criteria in the Nigerian study as well as all studied subjects in the Tunisian study were ICU (intensive care unit) admitted patients with severe TBI or severity feature [30, 39]. Our study subjects had hypotension, lost consciousness, convulsion, and increased intracranial pressure sign at presentation. Comparable reports were documented in other studies [30, 37].

In this study, subjects were evaluated with random blood sugar, skull X-ray, and head CT scan at presentation. Most of the subjects had normal glucose levels with hyperglycemia documented in 6.3% of TBI cases. Head CT scan was ordered in 70.7% of study subjects and showed various types of skull bone fractures, brain contusion, intracranial bleeding, and diffuse axonal injury. These findings are in agreement with studies done in India, Tunisia, and Nigeria, and head CT scan requests conform to the recommended neurosurgical practice [22, 25, 30, 37, 39].

In our study, associated extracranial injuries were documented in 80% of the study subjects with soft tissue

Table 2: Pattern and mechanism of pediatric traumatic brain injury at HUCSH from September 2017 to September 2018.

Characteristics of traumatic brain injury	Subclassification	*N* (%)
Mechanism of injury	Road traffic accident	144 (45.4)
	Falls	104 (32.8)
	Fighting	40 (12.6)
	Animal kick or bite	28 (8.8)
	Assault/child abuse	1 (0.3)
Time of arrival after injury	<24 hours	258 (81.4)
	1–3 day	31 (9.8)
	>3 day	28 (8.8)
Place of occurrence	Home	29 (9.1)
	Outdoor	144 (45.4)
	Occupant in vehicle	24 (7.6)
	Pedestrian	120 (37.9)
Loss of consciousness at presentation	No	228 (71.9)
	Yes	89 (28.1)
Convulsion at presentation	No	291 (91.8)
	Yes	26 (8.2)
Signs of increased ICP*	No	257 (81.1)
	Yes	60 (18.9)
Sign and symptom of increased ICP	Vomiting	16 (5.1)
	Hypertension	22 (6.9)
	Decreased mentation	22 (6.9)
Pupillary sign	Unilaterally fixed	22 (6.9)
	Symmetrically fixed	3 (0.9)
	Midsized and reactive	277 (87.4)
	Bilaterally dilated	15 (4.8)
Severity of TBI**	Mild TBI	231 (72.9)
	Moderate TBI	61 (19.2)
	Severe TBI	25 (7.9)
Head CT and scan finding	Normal	50 (15.8)
	Skull fracture	94 (29.7)
	DSF*** with contusion, DAI+, intracranial bleeding	36 (11.4)
	Contusion/DAI	30 (9.5)
	Intracranial bleeding	14 (4.4)
	Not done	93 (29.3)
Skull X-ray finding	Normal	77 (24.3)
	Linear skull fracture	27 (8.5)
	Depressed skull fracture	72 (22.7)
	Not done	141 (44.5)
Hypotension on admission	No	308 (97.2)
	Yes	9 (2.8)
Hyperglycemia on admission	No	297 (93.7)
	Yes	20 (6.3)

*Intracranial pressure. **Traumatic brain injury. ***Depressed skull fracture, +diffuse axonal injury. CT: computed tomography

injury being the most common followed by extremity bone fracture. Reports from Nigeria and Nepal documented similar findings [18, 40]. Most of the subjects in our study were managed conservatively (72.2%), while neurosurgical interventions like depressed skull elevation, irrigation and debridement, and hematoma evacuation were common procedures. Studies from India, South Africa, Nigeria, and Tunisia had documented similar findings [37–39, 41]. Concerning the length of hospital stay, majority of our study subjects stayed from 4 to 7 days while nearly a quarter (24.6%) were discharged in the first 24 hours of admission. Shorter hospital stays could be due to the higher percentage of milder forms of TBI in our study. These findings are comparable to similar studies done in Africa and China [22, 29, 41, 42]. Moreover, a detailed review and discussion on the challenges in the surgical and medical management of severe and penetrating TBI suggested a more conservative approach envisioning for better options and outcomes in the future [43].

In this study, good functional outcome (recovery without any neurologic deficit) was documented in 84.2% (95% CI, 80.2–88.1) of study subjects. This is higher than the Indian and Chinese studies [37, 42]. It is lower than the Nigerian and South African studies [34, 39, 41]. Ten (3.2%, 95% CI: 1.5–5.7%) of our study subjects died. This is comparable with the South African report [41], but it is

Table 3: Management and outcome of pediatric traumatic brain injury at HUCSH from September 2017 to September 2018.

Head injury characteristics	Subclassification	*N* (%)
Associated extracranial injury	No injury	61 (19.2)
	Soft tissue injury	179 (56.5)
	Extremity bone fracture	70 (22.1)
	Chest/abdominal injury	6 (1.9)
	Vertebral bone fracture	1 (0.3)
Management type	Surgical	88 (27.8)
	Conservative	229 (72.2)
Type of surgical intervention	Burr hole	2 (0.6)
	Elevation for depressed skull fracture	66 (20.8)
	Craniotomy and evacuation	2 (0.6)
	Irrigation and debridement	19 (6.0)
Condition on discharge	Survived/recovered	303 (95.6)
	Died	10 (3.2)
	Referred	2 (0.6)
	Left against medical advice	2 (0.6)
Neurologic outcome at discharge	No deficit	267 (84.2)
	Focal deficit	30 (9.5)
	Depressed mentation	10 (3.2)
Duration of hospital stay	≤24 hours	78 (24.6)
	1–3 days	64 (20.2)
	4–7 days	108 (34.1)
	8 days–01 month	65 (20.5)
	≥1 month	2 (0.6)

Table 4: Multivariable logistic regression analysis of factors associated with pediatric traumatic brain injury outcome at HUCSH ($n = 317$).

Variables	Categories	No. (%)	COR* (95% CI)	AOR** (95% CI)	*P* value
Hyperglycemia at presentation	No	297 (93.7)	1	1	$P = 0.003$
	Yes	20 (6.3)	4.461 (1.855–10.728)	2.318 (1.873–7.874)	
Increased ICP^{+} sign	No	257 (81.1)	1	1	$P = 0.002$
	Yes	60 (18.9)	2.757 (1.951–3.895)	1.415 (1.4058–9.557)	
Severity of TBI$^{\#}$ at presentation	Mild TBI	231 (72.9)	1	1	$P = 0.029$
	Moderate	61 (19.2)	1.904 (1.547–2.343)	2.553 (1.965–4.524)	
	Severe	25 (7.9)			
CT% scan finding	Normal or skull fracture	134 (45.5)	1	1	$P = 0.005$
	Contusion, DAI, or ICH$^{\$}$	80 (25.3)	2.061 (1.635–2.599)	2.45 (1.811–7.952)	
Loss of consciousness at presentation	No	228 (71.9)	1	1	$P = 0.168$
	Yes	89 (28.1)	1.844 (1.523–2.246)	1.271 (0.874–2.116)	
Hypotension at presentation	No	308 (97.2)	1	1	$P = 0.259$
	Yes	9 (2.8)	2.591 (1.027–6.534)	1.629 (0.301–5.101)	
Convulsion at presentation	No	291 (91.8)	1	1	$P = 0.816$
	Yes	26 (8.2)	3.344 (1.773–6.307)	1.244 (0.296–0.902)	
Comorbid illness	No	313 (98.7)	1	1	$P = 0.873$
	Yes	4 (1.3)	1.706 (1.64–4.551)	1.325 (0.157–2.124)	

COR*, crude odd ratio; AOR**, adjusted odds ratio; ICP^{+}, intracranial pressure; TBI$^{\#}$, traumatic brain injury; CT%, computed tomography; DAI, diffuse axonal injury; ICH$^{\$}$, intracranial hemorrhage.

lower than the Chinese and Nigerian studies [34, 37, 38, 40, 42]. Differences in outcome could be explained by the health facilities capacities, severity and mode of head injury, and age of inclusion as the above Nigerian study included children up to 18 years of age. Additionally, the majority of our study subjects had a milder form of TBI.

In the current study, severe TBI was associated with doubled odds of death/neurologic disability, when compared with mild and moderate head injuries. This finding is in harmony with the Nigerian and Indian studies [39, 40, 44]. Severe TBI is associated with primary is are flexia and secondary brain edema, which predict the outcome of the patient [45]. Head CT scan findings of contusion, diffuse axonal injury, and intracranial bleedings were associated with 2.45 times higher chances of death or neurologic disability when compared with normal head CT cases. This is in agreement with the Tunisian and Nigerian studies [22, 30, 39]. Diffuse

axonal injury that occurs in TBI is reported to be secondary to axonal swelling, calcium-mediated irreversible blockade of axonal transport, swollen endoplasmic reticulum, etc. Intracerebral, brainstem, intraventricular and corpus callosum hemorrhages, and bleeding near the third ventricle on head CT are reported evidences for DAI. It is reported that these findings predict poor outcomes among TBI cases with the highest accuracy [46–48].

Our study documented 1.42 times higher chances of death and neurologic disability among TBI cases who presented with ICP signs when compared with those without ICP signs. This is in line with the Tunisian and Argentinian studies [22, 30, 49]. Glial swelling with narrowed lumina of the microvasculature due to podocytic process swelling results in increased ICP. Diffuse cerebral ischemia also results in calcium hemostatic imbalance and activation of anaerobic metabolism. Increased ICP clinically presents as hypoxemia, seizure, mental level deterioration, and neurologic deficits [50, 51].

In this study, admission hyperglycemia was associated with 2.32 times higher chances of death and neurologic disability. Similar findings were reported in studies conducted in Turkey and Singapore [32, 52, 53]. Impaired cerebral mitochondrial dysfunction following TBI is thought to result in hyperglycemia [54, 55], though detailed mechanisms are yet to be studied [56]. We did not measure increased intracranial pressure by invasive methods as devices and facilities were not readily available, and this is the major limitation of our study, as the practice of these and related neuromonitoring methods for TBI are currently recommended [57, 58]. Secondly, long-term follow-up on neurological outcomes was not determined as the outcome was assessed on hospital discharge.

5. Conclusion

In our study, boys and children above 5 years of age were highly affected by TBI. Pedestrian RTA, falls, fights, and animal-related injuries with milder form and early presentation were the most common mechanisms of injuries. Various forms of skull vault fractures, hemorrhage, contusion, and axonal injuries were documented on the head CT scan. The majority of our study subjects were managed conservatively and recovered without neurologic deficits. Death was documented in 10 (3.2%) of the study subjects. Increased ICP, hyperglycemia, severe TBI, and contusion, diffuse axonal injury, or intracranial bleeding on head CT were predictors for death or neurological disability among pediatric cases of TBI. Strategies to ensure road safety and to prevent falls and animal-related injuries, closer follow-up of TBI cases for ICP, and proper glycemic controls are recommended.

Data Availability

The datasets analyzed during this study are available from the corresponding author on reasonable request.

Ethical Approval

Ethical approval for the study was obtained from the institutional review board of Hawassa University.

Consent

Purpose of the study was explained to participants, and consent was obtained from the parent or legal guardian of the child and assent was secured from adolescents.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Interleukin-33 (IL-33) as a Diagnostic and Prognostic Factor in Traumatic Brain Injury

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Interleukin-33 (IL-33) is a cytokine involved in interleukin-1 family. Role of IL-33 in immune system activation is well described in the literature. IL-33 has been identified as an endogenous alarm signal (alarmin) to alert various types of immune cells to trauma. In this narrative review, we aimed to underline the diagnostic and prognostic importance of IL-33 in trauma, particularly in brain trauma.

1. Introduction

IL-33 is known to be released from damaged cells following trauma. It is also known as an "alarmin" which means an endogenous signal of tissue injury [1]. It is a nuclear-associated cytokine belonging to IL-1 family and well known with the inducer role in type-2 allergic immunity [2]. In central nervous system (CNS), IL-33 activates microglias and macrophages in order to limit glial scarring [3, 4]. Here, we sought the utility of IL-33 in traumatic brain injury (TBI).

2. Materials and Methods

This narrative review was conducted by entering keywords "interleukin-33" or "IL-33" and "trauma" into MEDLINE/PubMed, EMBASE, and CINAHL scientific databases. During the database search, we excluded studies which did not relate with the objective by reading the title and abstract. Studies that were not published in English, studies without explanatory abstracts, and studies that do not focus on brain injury were excluded. Two reviewers conducted independent screening and data extraction. First, the reviewers independently screened titles and abstracts of the returned articles to decide if they met the inclusion criteria. Original articles and reviews published in the last 5 years were preferred. If there were studies from the same source, the more recent or more informative study was selected. A total of 23 articles out of 71 studies were included into study.

3. Structure and Function of IL-33

Alarmins, including IL-33, are released when a trauma occurs, and their role is to activate immune system against damage [5]. IL-33 is a member of the IL-1 cytokine family along with IL-1α, IL-1β, and IL-18 and expressed in structural and lining cells exposed to the environment including fibroblasts, endothelial, and epithelial cells of skin, gastrointestinal tract, and lungs [6, 7].

IL-33 shows its effects by activating signaling pathways depending on gene 88 (MyD88) of immune cells which is the primary response gene on the myeloid differentiation expressing the cytokine receptor IL-1 receptor-like 1 (ST2) molecule and signals through a heterodimeric receptor complex comprising an IL-33-specific ST2 coupled with the coreceptor IL-1 receptor accessory protein (IL-1 RAcP), which belongs to other members of the IL-1 cytokine family [8–10]. Following proteolytic cleavage of its precursor pIL-33 (full-length IL-33), IL-33 is considered to be released to the extracellular space. When exogenous pathogen-associated molecular patterns (PAMPs) are triggered, IL-33 is

actively released; however, there is lack of evidence that it is secreted from dendritic cells or mast cells. Unlike other members of the IL-1 family, active IL-33 secretion is independent of caspase-1 and caspase-8 (required for cleavage of pIL-1β and/or pIL-18) or calpain (required for cleavage of pIL-1α). In vitro, recombinant pIL-33 is cleaved by recombinant caspase-1; however, role of caspase-1 in the cleavage of pIL-33 is not clear [11].

IL-33 serves as an inhibitor of autophagy, and to our knowledge, it is expressed in various organ tissues in the human body, such as endothelial, bronchial, and intestinal epithelial cells [12, 13]. It is also known that IL-33 is mainly secreted from macroglia, including grey-matter astrocytes and oligodendrocytes [2].

4. IL-33 and Traumatic Brain Injury

It is well documented in the literature that TBI is a major cause of morbidity and mortality worldwide. The damage mechanism of TBI is a complex process that may mainly be divided into two categories as primary and secondary brain injury. Primary brain injury is a type of injury directly caused by external force, and the secondary brain injury is a sort of indirect injury containing a complex process in which inflammation plays an essential role [14].

Following an injury or an organ damage and regardless of its type (physical, chemical, or metabolic assault), cells die by necrosis. Following necrosis, rupture and disintegration in a sterile environment occur. This type of traumatic cell death also results in the accumulation of inflammatory cells to the injury site, and a massive immune response triggered by recognition of such danger or alarm signals emerges [15]. Biomarkers such as IL-33 have been considered in the early hours after TBI, and it has been suggested that they could guide clinicians in planning the next stages of patient management [16–19] on a more general perspective, and it should be noted that in some instances, biomarkers already hold the potential for prognostication of mid- and long-term outcomes [20, 21]. The importance of biomarkers is also meant to grow because of innovation in biomedical engineering and point of care detection, with the ultimate goal of coupling them with neuroradiological patterns to define robust biosignatures for TBI patients [22].

Proinflammatory cytokines of the IL-1 family (IL-1α, IL-1β, IL-18, IL-33, and IL-36) play essential role on inflammatory and immune processes. These cytokines are released during the early stages of inflammation and, as mentioned before, have been named "alarmins" because they alert the host to induce an inflammatory reaction [12].

In a report, it was stated that the combination of markers including IL-33 improved the prognostic performance and might be used as a useful tool for risk determination in trauma patients [23].

A study with mice showed that IL-33 appeared to downregulate the autophagic activation of apoptosis and the inflammatory response. This downregulation results in protection of mice against injury from collagenase-induced intracerebral hemorrhage. Also, inhibitor role of IL-33 in autophagic activity and apoptosis in neonatal rats was reported. Thus, neurons were not affected from recurrent seizures [12].

In an animal study by Heuvel et al., a weight-drop TBI model was performed to mice, and inflammatory cytokines were measured. In the study, the serum levels of IL-33, IL-1β, IL-38, TNF-α, IFN-α, and IL-19 in the hippocampus were found to be elevated at 3-hour time point [24].

The relationship between trauma and IL-33 was reported in a study with 472 patients. It was found that plasma IL-33 levels elevated on admission and over time in a positive correlation with other cytokines IL-4, IL-5, and IL-13 in patients with blunt trauma [25].

In another study, it was shown that mortality in hospital following blunt trauma was associated with increased plasma sST2 concentrations and suppressed IL-33 levels. Additionally, sST2 levels were found to correlate with injury severity, organ dysfunction, and altered inflammatory response. According to these results, it was concluded that the ST2/IL-33 axis played an important role in the human response to trauma. It was also concluded that sST2 might be a useful biomarker in trauma severity prediction [26].

Elevated serum IL-33 levels after multiple injuries indicate that IL-33 can be referred as an alarmin in human response to polytrauma. It may also be an indicator of the amount of damaged structural cells by mechanical effects of trauma [27]. Damage to central nervous system (CNS) results in IL-33 release, particularly from oligodendrocytes and astrocytes [28].

Foster et al. hypothesized that secretion of IL-33 in response to CNS trauma might initiate a protective feedback loop on neurons involving T cells, glial cells, and monocytes [1]. It was also reported that meningeal ILC2s were activated in an IL-33-dependent manner after CNS injury [29].

In a study using human TBI microdialysate, tissue sections from human TBI, and mouse models of CNS injury, it was revealed that expression of IL-33 in the brain was elevated reaching a maximum after 72 hours in both human samples and mouse models. It was also reported that IL-33 was mainly produced by astrocytes and oligodendrocytes. When brains of mice were deficient in ST2, IL-33 receptor, number of microglia, and macrophages were decreased, and in response damage, their cytokine and chemokine status was altered. These results indicated the essential role of IL-33 in neuroinflammation following TBI. Moreover, IL-33 targets microglia and macrophages in response to damage [30]. Similarly, spinal cord injuries (SCIs) also result in increased IL-33 levels. In the subchronic SCI stage, IL-33 remains elevated particularly in astrocytes' nuclei. Pomeshchik et al. demonstrated that when recombinant IL-33 was given after contusion, SCI results in improved and long-lasting motor recovery, and secondary tissue damage reduces. Even following the initial dose of IL-33, the expression of cytotoxic TNF-α in the injured spinal cord reduced [4]. Literature involved in this review on usefulness of IL-33 in TBI is summarized in Table 1.

Table 1: Comparison of studies on IL-33 in traumatic brain injury involved in the review.

Study type	Study design	Conclusion	Reference
Original article	A blunt, weight-drop approach to model TBI in mice.	It was shown that TBI causes the elevation of IL-33, IL-1β, IL-38, TNF-α, IFN-α, and IL-19 in the hippocampus at 3 h time point, and concomitant EI results in the dose-dependent downregulation of IL-33, IL-1β, IL-38, TNF-α, IFN-α, and IL-19.	[24]
Original article	Spinal cord of mice was damaged, and recombinant IL-33 was injected.	Addition of wild-type lung-derived ILC2s into the meningeal space of IL-33r-/- animals partially improves recovery after spinal cord injury. IL-33 released after CNS injury not only initiates a local response but also a meningeal one through actions of ILC2s.	[29]
Comment	Comment on "The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury" by Gadani SP, Walsh, J. T., Smirnov, I., Zheng, J. and Kipnis, J. published in neuron in 2015.	Administration of recombinant IL-33 might be beneficial for treating TBI.	[1]
Original article	Transient focal ischemia was induced by intraluminal occlusion of the left middle cerebral artery for 1 h with silicone-coated sutures in mice.	IL-33/ST2 signaling was described as a potential immune regulatory mechanism that enhances the expression of IL-10 in M2 microglia and reduces acute ischemic brain injury after stroke.	[28]
Original article	Serum ST2 concentrations in 106 healthy controls and 106 severe TBI patients were measured.	Serum ST2 concentrations are significantly related to inflammation. In TBI, it may be a potential diagnostic marker.	[14]
Original article	Samples from human TBI microdialysate, tissue sections from human TBI, and mouse models of CNS injury were used.	IL-33 plays a role in neuroinflammation, and microglia/macrophages are cellular targets for this IL following TBI.	[30]

5. Conclusion

ST2/IL-33 cytokine signaling system has emerged as an intercellular signaling system that participates in processes of the immune response, homeostasis, and tissue injury/repair. IL-33 is released by endothelial cells, immune cells, and epithelial cells as a result of cell injury or death. There are many extracellular actions of IL-33 including type-2 cytokine production, epithelial repair, and regeneration through amphiregulin, activation of ST2-positive Tregs, and polymorphonuclear neutrophil recruitment and activation [26]. It may be concluded that IL-33 levels tend to increase following TBI. Thus, in combination with other cytokines that take part in tissue damage, it may be used as a diagnostic and prognostic indicator of TBI severity. However, as an inflammatory marker, it must be kept in mind that IL-33 may elevate in various conditions, and diagnosis of TBI must not be based solely on serum IL-33 level.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Neurosurgical Care of Nonpowder Firearm Injuries: A Narrative Review of the Literature

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Background. Nonpowder firearms discharge a projectile using compressed gases. Unlike traditional firearms, there is a perception that nonpowder guns do not cause serious injury. However, intracranial injury disproportionally affects children and can cause significant neurological disabilities and mortality. Management of nonpowder firearm injuries has received little attention in the literature and presents unique surgical challenges. *Materials and Methods*. We conducted a narrative review of the literature of the management of nonpowder firearm injuries with particular emphasis on intracranial injury. *Results*. Modern nonpowder firearms have muzzle velocities which are capable of penetrating the skin, eyes, and bone. Direct intracranial injury commonly results from entrance of projectile through thinner portions of the skull. Operative intervention is needed to debride and safely explore the trajectory to remove fragments which can easily cause neurovascular injury. *Conclusions*. Neurosurgeons play a crucial role in managing serious nonpowder firearm injuries. A multidisciplinary team is needed to manage the direct results of penetrating injury and long-term sequalae.

1. Introduction

Unlike traditional firearms which use gunpowder, nonpowder firearms are designed to discharge a projectile using kinetic energy derived from compressed air and carbon dioxide or using a spring mechanism. These projectiles can be made of a variety of materials such as aluminium, lead, and plastic, and in a variety of shapes and sizes including spherical ball bearings (BB guns) and pellets.

Management of high-kinetic gunshot wounds to the cranium has been extensively reviewed. They are frequently fatal in 66–90% of cases with 71% of patients dying at the scene [1–3]. Low-kinetic cranial injuries associated with nonpowder firearms present with different aetiologies, causing different mechanisms of injury, and have been less extensively studied [4]. In the USA, nonpowder firearm injuries have long been recognised as a public health concern, particularly in children [5]. In the UK, nonpowder firearms have also been increasingly recognised as a potential cause of serious injury and death [6]. We present a review of the literature on the aetiology and neurosurgical management of nonpowder firearm cranial injuries.

2. Epidemiology

The incidence of nonpowder gun injuries is associated with the prevalence of nonpowder guns within the population under study. It has been estimated that by the mid-1990s in the USA, 3.2 million nonpowder firearms were sold per year causing up to 32,000 injuries per year [7, 8]. Cultural factors relating to gun use and their perception as toys may also contribute to the sale of nonpowder guns in the USA [7]. Compared to traditional firearm injuries, there are certain differences in the aetiology and populations affected. Single-centre studies from the USA have shown that nonpowder firearm injuries were more likely to be unintentional and to affect a greater proportion of Caucasian patients compared to traditional firearm injuries [9, 10]. Patients were also more frequently male and young with a mean age of 10-11 years rather than adolescents [9].

Throughout the 90s, the incidence of nonpowder gun-related injuries appears to have declined from 24.0/100,000 people in 1988 to 8.8/100,000 people in 1999 [5]. This decline may coincide with increased public awareness of the risks associated with these weapons and the increased legislation

preventing their sale to minors [5]. Yet the danger from these weapons does not seem to have abated over time. In 2013, 16,259 BB or pellet gun injuries were recorded in the National Electronic Injury Surveillance System with 1237 of them estimated to occur in the head [11]. A retrospective study sampling of paediatric populations (<16 years) from three midwestern trauma centres in the USA found that nonpowder gun injuries to the head were associated with significant morbidity with 71% of patients requiring operative management and 43% of patients being left with permanent neurological deficits [11].

In the UK, there is an estimated 4 million air-powered weapons in households [12]. The Home Accident Surveillance Survey has found that there was an annual average of 1961 injuries attributable to airguns between 1989 and 1993 [12]. However, ballistics injuries may be increasing in the UK along with an increase in violent crime [13]. In one study, a large proportion (41%) of gunshot injuries to one urban trauma centre in the UK was attributable to air rifles [13]. Over time, there has been a decrease in the incidence of firearm offences along with air-weapon offences. By April 2017 and March 2018, there were 2898 air-weapon offences (30.8% of all firearm offences) recorded compared to 13822 in the period between April 2002 and March 2003 (50.7% of all firearm offences) [14]. This coincides with an increase in the bladed-weapon offences and may reflect changing trends in violent crime.

However, crime statistics do not reflect the most common method of injury which is accidental injury, particularly in children [6]. One study found in one urban UK hospital over a five-year period 73 injuries caused by air-weapons between January 1996 and June 2001. 81% of the patients were male with a median age of 15 years [6]. In cases of reported fatalities from the UK, the predominant mechanism of death is intracranial injury [6, 15, 16]. The high operative burden of managing nonpowder weapon injuries and their comparatively uncommon nature mean individual experience may be limited. Therefore, it is important for surgeons to gain a broad understanding of their management.

3. Medico-Legal Considerations

In the USA, regulation of nonpowder guns is applied at the state level. Federal law prevents states from prohibiting the sale of nonpowder guns but allows states to prohibit their sale to minors. Only 24 states have some form of regulation regarding the possession of nonpowder guns with only 13 states regulating the sale of nonpowder to minors. The definitions used in these laws tend to be variable with states defining minors from under 18 years to under 12 years. In addition, states vary in their definition of which nonpowder guns are firearms with some states such as New Jersey and Rhode Island classifying all nonpowder guns as firearms. The aim of this is keeping all nonpowder guns out of the hands of minors and individuals with criminal records. Other states define nonpowder guns as firearms when they exceed a certain calibre or muzzle velocity. For example, in Illinois, nonpowder guns with calibre less than 0.18 and muzzle velocity less than 700 feet/second are excluded from the definition of firearms.

The UK has some of the most stringent regulations governing airguns in the world. Apart from Northern Ireland, firearms are defined as any air pistol with a muzzle velocity of greater than 6 foot/pound or any air rifle with a muzzle velocity greater than 12 foot/pound. In Northern Ireland, nonpowder guns with a muzzle velocity greater than 0.737 foot/pound are defined as firearms [17]. Possession of these weapons requires an adult to apply for a firearm license from the police. For weapons with muzzle velocity less than these limits, the regulations vary depending on the constituent country in the UK. In Scotland, any individual over the age of 14 must apply for an Air Weapons Certificate if they use or possess an airgun from January 2017. In England and Wales, any air weapon is considered "specially dangerous" if it exceeds the limits described above and is thus regulated by firearm law.

Licenses are granted by the police to individuals who are deemed to not pose a threat to public safety and also have good reason to own a firearm. The assessment of whether an individual is fit to own forearms is the responsibility of local police forces. They may visit individual homes, check references, and request medical records from a person's primary care physician.

4. Mechanics of Nonpowder Weapons

All airguns propel a projectile using kinetic energy derived from compressed air or carbon dioxide. Projectiles can be made of several materials including plastic, brass, or steel and have different calibres including 0.177 (4.5 mm), 0.20 (5 mm), and 0.22 (5.5 mm) [18]. Factors which affect the degree of tissue damage include muzzle velocity, mass of the projectile, and range at which injury occurs [18].

Tissue damage caused by projectiles results from temporary cavitation or crush damage [11]. In general, the damage caused by small pellets is caused by crush of tissue in the path of the penetration. This crush is caused by shear forces generated as projectiles do not always follow a perfectly straight line to the target [19]. The ability to penetrate tissue is proportional to the kinetic energy and inversely proportional to the cross-sectional area of the projectile. Kinetic energy is proportional to the mass of the projectile and the square of the velocity of the projectile [11, 20]. Therefore, large-calibre heavier pellets are able transfer greater amounts of kinetic energy to tissue when at closer range compared to smaller lighter pellets. However, smaller projectiles can also be lethal at a close range. Forensic ballistics studies on subcalibre (0.173) steel BB pellets suggest that up to 36 mm of penetration can occur in solid bone [21]. Children are at high risk for nonpowder gun injuries not just due to the perception of airguns as toys and lack of licensing but also because paediatric patients have thinner skulls and soft tissue compared to adults [11].

Muzzle velocity is a crucial measure of the force of projectile on tissue. The primary determinants of muzzle velocity include projectile calibre, mass, propulsion system, and barrel length/width [7]. Muzzle velocities of 245 to 450

feet/sec have been found to be sufficient to cause skin penetration [7, 18]. Ocular penetration occurs at even lower muzzle velocities of 127 feet/second–246 feet/second [22, 23]. The most common calibre of pellet is 0.177 with a weight of 5.1 grains (0.33 grams) to 7.9 grains (0.5 grams) [11]. Based on this calibre and weight, skull penetration can occur in humans at muzzle velocities between 825 feet/second and 1026 feet/second [11]. The US Consumer Product Safety Commission (CPSC) estimates that over 80% of airguns sold have a muzzle velocity of greater than 350 feet/second and 50% of airguns have a muzzle velocity of between 500 and 930 feet/second [7]. Modern technologies involving CO_2 propellant-based airguns and multiple pump action airguns can reach extremely high muzzle velocities between 400 and 450 feet/second and between 700 feet/second and 900 feet/second, respectively [18]. These muzzle velocities compare to those of conventional powder firearms, highlighting the potential lethality of these weapons. For example, the Colt 0.45 can reach a muzzle velocity of 800 feet/second [7].

5. Effects of Direct Intracranial Injury

Early retrospective case series describing nonpowder injuries highlighted common mechanisms of injury as important considerations for neurosurgeons. Lawrence reviewed nine cases of fatalities caused by airguns between 1956 and 1990. He found that in all but one case of cardiac injury, periorbital penetration or penetration into the thinner portions of the skull such as the pterion resulted in severe intracranial injury caused by pellet trajectories crossing the midline [18]. A 11-year review of cases at a single trauma centre in Philadelphia found that the eye, head, and neck were the most common sites of nonpowder firearm injury (41%) followed by the extremities (39%) and thorax (13%) [8]. Despite the severity of the injuries, the entrance wound may be deceptively small and easily missed [24]. The entrance site may have a small rim of abrasion but there will be no powder burns [15]. Therefore, patients with airgun injuries should be carefully evaluated in the emergency room for potential entrance sites. Relatively asymptomatic soft tissue injuries may be potentially dangerous. One case report describes a nine-year-old girl with a BB pellet entering her cheek and resting medial to the internal carotid artery [25]. Headlight with magnification may be helpful to identify the entrance site.

A recent review of nonpowder airgun injuries focusing on intracranial injuries in paediatric patients from three trauma centres found that the majority of patients were male (86%) with a mean age of nine, suffering from accidental injury in 71% of cases [11]. Skull penetration most frequently occurred in the frontal region (57%) followed by the orbital region (21%) [11]. Importantly operative intervention was required in 71% of cases including craniotomy, removal of projectile remnants, and elevation of depressed bone fragment [11]. Furthermore, the incidence of permanent neurological deficits was high including visual problems, cognitive problems, and seizures [11]. A retrospective review of paediatric airgun cases from three trauma centres in the USA found that approximately 10% of patients had intracranial injuries. Importantly, all the mortalities were from patients with intracranial injury [26].

Various case reports show that certain regions of the head are more vulnerable to airgun projectile penetration. Penetration of the thin roof of the orbital cavity is an easy route for the projectile to enter the cranial cavity [27, 28]. The entrance wound may be as smaller than 5 mm in diameter yet this disguises the severity of the intracranial damage with significant distance travelled by a pellet before stopping in the occipital lobe [27]. Along the projectile track, there can be significant damage including subarachnoid haemorrhage, subdural bleeding, and parenchymal haemorrhage [11]. It has been suggested that the passage of the projectile through the skull base can be halted by regions of relatively thicker bone such as the sella [28]. This leaves surrounding neurovascular structures such as those in the cavernous sinus vulnerable [28, 29].

The lack of cavitation damage and relatively straight projectile path means that nonpowder gun pellets are easily able to lodge into soft tissue and cause vascular laceration [30]. Case reports have shown that airgun pellets can embolise in the intracranial internal carotid artery (ICA) and travel distally to occlude the middle cerebral artery (MCA) [30, 31]. In theory, any projectile small enough to lodge into the ICA can cause distal embolization and migration, particularly in the fast-flowing arterial circulation [30]. Patients may present with hemiparesis and aphasia [30]. In an attempt to salvage neurological function, various techniques for projectile retrieval have been attempted including endovascular suction with emergency extracranial-intracranial bypass [30, 32].

These cases highlight the importance of pellet localisation. Following detailed clinical examination, the next step in management of these patients should include radiographic and computerised tomography (CT) imaging to localise projectiles, assess the degree of injury, and plan the surgical approach. There should be a low suspicion of vascular injury, especially if there is any evidence of cranial nerve palsies or entrance of the projectile involving the medial canthus or orbit. These features suggest possible involvement of the medial cranial fossa and cavernous sinus [33]. Some authors suggest that CT angiography is indicated in nearly all cases of airgun injury to the head and neck [28]. In a retrospective series of 120 patients with penetrating neck injury to the neck, CT angiography reduced the rate of negative surgical exploration by 48% [34].

Intracranial injury results in a variety of damage. Kumar et al. found in a retrospective review from three institutions that there was a wide range of overlapping pathologies including subarachnoid haemorrhage (50%), parenchymal contusion (29%), depressed bone fracture (21%), cerebral oedema (21%), intracerebral haemorrhage (21%), subdural haemorrhage (7%), intraventricular haemorrhage (7%), and pseudoaneurysm formation (7%). Amongst these patients, 71% required operative intervention [11]. Operated patients may require neurointensive care admission for neuromonitoring [35, 36]. Prevention of intensive care-related complications such as thromboembolism and delirium is

necessary [37–39]. In stable patients who do not require operative intervention for intracranial pressure control, surgery may still be indicated to debride contaminated wounds and reduce the risk of late infections [28, 40–42]. Furthermore, given the proximity of projectile tracks with the skull base, duroplasty may also be needed to prevent cerebrospinal fluid (CSF) leak [43–45].

6. Secondary Effects of Intracranial Injury

Metallic foreign bodies which are left in situ may act as a nidus for further infections. Compared to powder-gun injuries airgun, projectiles may be more prone to infection due to their lower velocity and temperature [43]. A single-centre retrospective review over 15 years showed that long-term sequala of head and neck airgun injuries included meningitis, CSF leak, brain abscess formation, carotid-cavernous sinus fistula, intracerebral projectile migration, and projectile splitting [46].

The incidence of all infections from penetrating brain injury including soft tissue, osteomyelitis, epidural/subdural empyema, meningitis, ventriculitis, and cerebritis ranges between 5% and 23% [47]. As early as 1947, Gillingham showed that infection rates for penetrating brain injuries decreased from 25% to 5% when the length of time between injury and operative debridement was from 72 hours to 24 hours [48]. Cerebral abscesses have been reported as late as 19 months following airgun injury [16]. However, recent case series of airgun injuries have not reported any similar infections and this may be related to the use of synergistic antibiotic regimens [43]. To avoid multidrug resistance, microbiological advice and samples should always be taken where possible prior to starting treatment to allow drug rationalisation.

In wounds where there has been adequate debridement and successful removal of foreign bodies, a two-week course of antibiotics have been advocated [43]. Cairns showed in 1947 that the infectious organisms associated with penetrating intracranial wounds were related to in-driven bony fragments and from the paranasal sinuses [49]. Skin commensals such as *Staphylococcus epidermidis*, *Staphylococcus aureus*, and Gram-negative bacteria are common causative organisms [47]. Tetanus vaccination is mandatory given the risk of soil/dirt contamination of pellets [50]. Wooden pellets are especially associated with cerebral abscesses due to their porus nature offering easy bacterial culture [33]. In a series of 42 cases, Miller et al. reported that 50% of cases developed cerebral abscesses [51].

The exact incidence of postairgun injury seizures is unknown. Data from traditional powder missile injuries show that the incidence of seizures within the first 14 days is 9% and that by 24 months, the incidence can be as high as 80% [16]. In a series of 14 patients, Kumar et al. report that one patient developed epilepsy 12 years following airgun injury to the right frontal lobe [11]. In the absence of seizures, it would be prudent to follow conventional guidance and treat patients with all intracranial penetrating injuries with seven days of prophylactic antiepileptic medications.

CSF leaks can occur in 9% of patients with penetrating brain injury [47]. The incidence of CSF leaks with nonpowder projectiles entering the cranium is likely to be higher because transorbital entry is frequently associated with low-velocity projectiles [33]. In addition, low-velocity projectiles commonly enter via sinus spaces with dural breach causing communication with the intracranial compartment and acting as a nidus for infection [40]. Primary repair should be considered for any case of CSF leak associated with air-sinuses.

Vascular injury associated with airgun projectiles includes embolization of the intracranial internal carotid artery [31], pellet migration through the MCA [30], pseudoaneurysm of the anterior cerebral artery [11]. carotid-cavernous fistula [52], and possible development of dural arteriovenous fistula [53]. These injuries may be caused by skull-base fractures or shearing of the transmural vessel wall by the projectile [47]. These injuries can occur more than a week from injury, and therefore, a low threshold for angiography at diagnosis is needed [53]. Improvements in endovascular approaches such as the use of stent retrievers may improve the success rate of pellet removal. Second-line treatment requires a multidisciplinary approach given the technical challenges associated with craniotomy and embolectomy [30].

Projectile migration is a potentially serious complication [47, 54]. This may occur in the context of movement within haematoma, CSF, abscesses, and parenchyma caused pellet specific gravity and brain pulsations [54]. Studies of intracranial bullet migration show that the incidence of migration is 4.2% [55]. Copper and lead are major components of BBs, and both have been implicated in projectile migration [11]. Migration can lead to evolving neurological symptoms and can be deadly causing seizures, haemorrhage, and hydrocephalus. Importantly, migration of up to a cm has been reported three years following injury [42].

Due to potential infection and the problems associated with projectile, where possible, early surgery to explore the trajectory and remove the projectile has been recommended [28, 40, 56]. Intraoperative localisation of airgun pellets is potentially challenging. Dandy first reported using a ventriculoscope to remove a bullet from the lateral ventricle [42]. A variety of other approaches have been reported in the literature including ultrasound guidance [57], endoscopy [58], use of stereotaxis [59], intraoperative dual-plane radiography [60], and open surgery [42]. Optimal surgical strategy should be chosen balancing the risks of migration and proximity to vascular structures with the potential for iatrogenic damage.

Retained pellets may be associated with long-term complications due to the material the projectile is made from. Airgun pellets are generally made of lead (95%), tin (2.5%), and antimony (2.5%) [61]. Lead toxicity caused by retained bullets has been described [41]. Toxicity can result from levels as low as 80 μg/L in children and can cause effects in multiple body systems including anaemia, renal toxicity, and encephalopathy [62].

Although lead is not ferromagnetic, some airgun pellets are made from ferromagnetic materials or coated with ferromagnetic materials such as steel [11]. Another long-term sequalae of these injuries is that future MRI scanning in

Table 1: Summary of important considerations when managing airgun injuries.

Initial assessment
Entry wound may be inconspicuous. Assessment especially of the orbital region is needed.
Prophylactic antibiotic therapy should be instigated for all penetrating wounds.
Investigations
Low threshold for CT angiography/digital subtraction angiography.
Management
Debridement and exploration of projectile track to remove fragments where safely possible.

these patients with retained projectiles is contraindicated as these projectiles can move in a three-tesla scanner [63]. Neurosurgeons must counsel patients and parents about this prior to discharge.

Table 1 outlines the key areas neurosurgeons must be aware of when managing patients with nonpowder gun injuries.

7. Conclusions

Nonpowder gun injuries are an important and under-recognised problem for surgeons. The perception of non-powder guns as harmless recreational instruments leads to widespread societal misconceptions about their potential harms. Intracranial injuries can result in significant long-term neurological deficits and mortality. A significant proportion of patients will require operative intervention. Neurosurgeons play a crucial role in managing these patients and raising awareness of the dangers of these weapons to the public.

Conflicts of Interest

All authors certify that they have no conflicts of interest.

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Research Article

Defining New Research Questions and Protocols in the Field of Traumatic Brain Injury through Public Engagement: Preliminary Results and Review of the Literature

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Traumatic brain injury (TBI) is the most common cause of death and disability in the age group below 40 years. The financial cost of loss of earnings and medical care presents a massive burden to family, society, social care, and healthcare, the cost of which is estimated at £1 billion per annum (about brain injury (online)). At present, we still lack a full understanding on the pathophysiology of TBI, and biomarkers represent the next frontier of breakthrough discoveries. Unfortunately, many tenets limit their widespread adoption. Brain tissue sampling is the mainstay of diagnosis in neuro-oncology; following on this path, we hypothesise that information gleaned from neural tissue samples obtained in TBI patients upon hospital admission may correlate with outcome data in TBI patients, enabling an early, accurate, and more comprehensive pathological classification, with the intent of guiding treatment and future research. We proposed various methods of tissue sampling at opportunistic times: two methods rely on a dedicated sample being taken; the remainder relies on tissue that would otherwise be discarded. To gauge acceptance of this, and as per the guidelines set out by the National Research Ethics Service, we conducted a survey of TBI and non-TBI patients admitted to our Trauma ward and their families. 100 responses were collected between December 2017 and July 2018, incorporating two redesigns in response to patient feedback. 75.0% of respondents said that they would consent to a brain biopsy performed at the time of insertion of an intracranial pressure (ICP) bolt. 7.0% replied negatively and 18.0% did not know. 70.0% would consent to insertion of a jugular bulb catheter to obtain paired intracranial venous samples and peripheral samples for analysis of biomarkers. Over 94.0% would consent to neural tissue from ICP probes, external ventricular drains (EVD), and lumbar drains (LD) to be salvaged, and 95.0% would consent to intraoperative samples for further analysis.

1. Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in the age group below 40 years. 1.4 million people attend Emergency Departments (ED) with a recent head injury annually in England and Wales alone [1]. TBI is a significant public health concern and has been estimated to contribute up to 41% of overall years of life lost (YLL) due to injuries [2]. In addition to the direct impact, there is a significant indirect impact on need for assistance with self-care, employment productivity, and social relationships, especially given that the majority of those with severe TBI are young adults [3]. Primary injury occurs at the time of impact, whereas secondary injury, also termed "delayed nonmechanical damage," occurs due to disruption of the normal metabolism often resulting in inflammation and necrosis. Primary injury cannot be modulated once the injury has occurred, but the focus of TBI care is on preventing or attenuating secondary injury.

The 2016 Brain Trauma Foundation Guidelines [4] advocate management of severe diffuse TBI conservatively in Intensive Care Units (ICU) with neuroprotective measures, guided by intracranial pressure (ICP) monitoring, with the potential to provide cerebrospinal fluid (CSF) drainage by

inserting an external ventricular drain (EVD) if the ICP remains high. In cases where there is a haematoma amenable to surgical evacuation, patients may undergo a craniotomy or craniectomy to decompress the brain. Thus, current therapeutic options are limited to relieving pressure (by evacuating haematomas, removing bone, or draining CSF) and supporting the patient with ICU care [5]. Despite many trials there are still no therapeutic options which alter the TBI, and treatment centres on supporting the patient while the brain injury runs its course.

Although progress has been made in unpicking the pathophysiology of TBI [6], this has not translated into clinical practice. Despite significant research effort, there are currently no therapeutic options, other than decompression and support, which actively alter the course of the injury. Numerous studies into biomarkers released in the acute phase have been conducted [7–27]; however, it is important to note that these samples are obtained peripherally, and we have no knowledge of how much information is lost when brain venous blood mixes with systemic venous blood.

S100B [7, 11, 12] is perhaps the most extensively studied biomarker in TBI; however, it has been found elevated in patients with polytrauma suggesting concentrations are affected by extracerebral injuries. Galectin-3 (GAL3) [8, 21] is a proinflammatory protein expressed during inflammation of the central neurological system, with a positive correlation being identified between plasma concentrations of GAL3 and Glasgow Coma Scale (GCS) scores, suggesting it may reflect trauma severity. Copeptin [23, 26] levels also show correlation with poor outcomes, and elevated levels of neuron-specific enolase (NSE) [7, 13, 14] have been demonstrated to be an indicator of mortality. The combination of ubiquitin C-terminal hydrolase L1 (UCH-L1) [9, 22, 27] and glial fibrillary acidic protein (GFAP) [10, 22] have been shown to produce superior sensitivity and specificity when distinguishing patients with TBI from healthy controls. Release of matrix metalloproteinase 9 (MMP9) [8] can be found up to 8 hours after mild TBI, whereas myelin basic protein (MBP) [7, 15, 16] often peaks between 48 and 72 hours after injury and can remain elevated for up to 2 weeks. MBP is also considered to be a potential biomarker of intracranial haemorrhage and traumatic axonal injury [18], and MBP along with myelin-associated glycoprotein (MAG) are products of oligodendrocyte demyelination which can be predictive of functional outcomes in patients with mild TBI [17]. The measurement of tau protein in CSF in patients who have sustained severe TBI has a proven correlation with outcome; however, it is a poor predictor when measured in peripheral blood or in mild TBI [24]. As demonstrated by this brief summary on the state of the art of TBI-specific biomarkers, the research interest into this area of neurotrauma is on the rise specifically for the expected leap forwards in terms of understanding of the physiopathology and possibility to design much sought after prognostication tools (see Table 1).

Animal models analysing the microscopic and cellular effects of TBI [28–30] have been conducted; however, these have limited application because they do not necessarily translate accurately to humans and human data remain scarce [31]. Brain tissue sampling outside of tumour surgeries has been done very occasionally, with Harish et al. [32] obtaining intraoperative open biopsy samples from 26 patients who had sustained TBI and correlating them to CT scans and Pyykkö et al. [33] obtaining cortical brain biopsies using a biopsy needle from 102 patients with normal pressure hydrocephalus (NPH).

For these reasons, among others, prognosis in TBI remains extremely difficult. Various models exist such as the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) trial in TBI [34]; however, their reliability in predicting an unsurvivable injury or a very poor neurological outcome is not high enough to permit withdrawal of care. Although the abovementioned biomarkers bring new hope, further research into their sensitivity and specificity is needed to appraise their possible role in clinical practice. As such, current management still revolves solely around prolonged ITU care and rehabilitation with significant resource implications which not infrequently result in patients left in a vegetative or minimally conscious state.

The authors propose a novel prospective study to obtain fresh brain tissue samples from patients suffering severe TBI, in order to correlate the cellular, proteomic, metabolomic, and, in the future, genomic data to clinical outcome. We also propose obtaining pure brain venous blood from jugular bulb venous catheters to analyse brain venous biomarkers and compare them to paired peripheral samples.

Patients suffering severe TBI will, by definition, not be able to consent to participate in research, and often, next of kin are often not immediately available. According to the guidelines set out by the National Research Ethics Service, we conducted a community consultation survey of patients and their families in order to establish their perception of what we propose.

2. Methods

A pilot survey was created and administered to 26 patients and families of patients who had been treated at our Institution for traumatic brain injury. This survey was registered as a service evaluation and obtained ethical approval by our Institutional Review Board. It was conducted at the Royal London Hospital, which serves a population of >5mln people; it represents the busiest Major Trauma Centre in London and accounts among the biggest neurotrauma hubs in the United Kingdom. The aim of the survey was to gauge public perception of whether taking samples that would usually be discarded for further analysis was acceptable. We included the question of collecting additional blood tests and inserting a jugular bulb venous catheter to collect venous drainage from the brain.

Feedback gathered from the pilot survey was used to create a further survey (Survey 1), containing more information. We introduced the question of obtaining a brain biopsy at the time of insertion of an ICP bolt and urine, saliva, and stool samples taken concurrently for evaluation of biomarkers.

Survey 1 was administered to four groups of patients from our hospital and its catching area (East London): patients suffering head injury and their family members on neurosurgical wards; patients attending the TBI follow-up

Table 1: Biomarkers and their applications.

Biomarker	Key features	References
S100B	Serum concentrations >0.48 μg/L in <6 hours predictive of Glasgow Outcome Scale Extended (GOSE) scores of <5 (severe disability) at 1 month post injury Extracerebral injuries have significant impact on predictive ability of S100B	[7, 11, 12]
GAL3	High plasma levels associated with GCS and in-hospital mortality	[8, 21]
Copeptin	Independent predictor of progressive haemorrhagic injury and acute traumatic coagulopathy and outcome at 1 year after injury	[23, 26]
NSE	>10 μg/L in <6 hours associated with headaches at 6 months Elevated levels indicator of mortality	[7, 13, 14]
UCH-L1	Plasma and CSF levels shown to be elevated for several days and associated with diffuse injuries	[9, 22, 27]
GFAP	Elevations primarily found in patients with a focal mass lesion (V to Marshall VI) When Marshall is combined with GFAP, it produces superior sensitivity and specificity for TBI	[10, 22]
MMP9	Elevated levels up to 8 hours after TBI; smaller increase maintained at 24 hours	[8]
MBP	Serum concentrations peak 48–72 hours after injury and can remain elevated for 2 weeks Potential biomarker of intracranial haemorrhage and axonal injury	[7, 15, 16, 18]
MAG	Strong predictors of functional outcome in mild TBI	[17]
Tau	Raised CSF levels associated with poor clinical outcome	[24]

clinic; a population of previous general trauma patients who had expressed an interest in assisting with research questions using Survey Monkey; TBI patients attending the East London Headway (a UK-based brain injury charity) centre. All responses were anonymised. All respondents had the capacity to fill out the questionnaire unaided. Apart from the Survey Monkey group, all participants had the opportunity to ask for additional information, which was provided by the staff administering the survey if required.

Feedback from Survey 1 regarding the anonymity and storage of samples was incorporated into a further version of the survey (Survey 2) to address those concerns and provide additional information. Overall, respondents had more understanding following these changes and seemed more satisfied with the amount of information provided.

When analysing the data, the pilot survey figures were considered separate to those of the main survey. The responses to Survey 1, Survey 2, and Survey Monkey responses were collated and analysed.

The pilot survey, Survey 1, and Survey 2 are attached as supplementary materials (available here).

3. Results

The pilot survey demonstrated that 92.3% of respondents were willing to support research on the neural tissue adherent to ICP probes and EVD/LD requiring appropriate storage and analyses meant to identify cellular and molecular changes. Furthermore, 96.2% of respondents were willing to support research on necrotic brain tissue resected at the time of surgery for the same purposes, and 80.8% were willing for a jugular bulb catheter to be inserted to ascertain the biomarker load directly from the venous drainage of the brain (see Table 2, and Figure 1).

After updating the survey, a further 100 responses were collected. The results show that only 7.0% of respondents would not consent to brain biopsy at the time of ICP bolt insertion, whereas 75.0% would agree to brain biopsy at time of ICP bolt and 18.0% declared to be unsure. This distribution highlights how difficult it may be for the general population to understand these concepts, particularly in online surveys where the opportunity to ask further questions is restricted. Additionally, the 18 "do not know" respondents to brain biopsy, 7 "no's" and 75 "yes's," although not posing any conceptual issue of our surveys, may demonstrate the potential indecisiveness of people dealing with an immediate decision in an acute trauma situation.

This said, our surveys indicate that 94.0% would consent to brain tissue adherent to ICP probes and 96.0% would consent to neural tissue adherent to EVD and LD tips, to be used for further analysis. Of note, 95.0% would agree to have intraoperative samples being taken, both from blood at the

Table 2: Results from pilot survey.

Question		Answers (n)	%
Brain attached to ICP tip	Yes	24	92.3
	No	2	7.7
CSF from drainage bag	Yes	24	92.3
	No	2	7.7
Neural tissue attached to EVD/lumbar drain tip	Yes	24	92.3
	No	2	7.7
Peripheral blood tests	Yes	26	100
	No	0	0
Jugular bulb catheter insertion	Yes	21	80.8
	No	5	19.2
Blood from operation site	Yes	24	92.3
	No	2	7.7
Necrotic brain	Yes	25	96.2
	No	1	3.8

operating site and necrotic brain that would otherwise be discarded, and 70.0% would agree to a jugular bulb catheter to be inserted for obtaining venous samples from the brain (see Table 3, and Figure 2).

4. Discussion

This community consultation has revealed an overwhelmingly positive opinion among TBI patients and their families regarding the prospect of further research into TBI, particularly with respect to obtaining brain biopsies at the time of insertion of ICP monitors, insertion of jugular bulb catheters, and using brain tissue and CSF samples that would otherwise be discarded. Patients with severe TBI are incapacitated due to the nature of the TBI and are thus unable to consent for themselves; therefore, public and patient surveys are vital as they explore the surrounding ethical issues and gauge acceptance of the proposed research. We chose not to involve families of nonsurvivors of TBI to eliminate the emotional bias that may be encountered in their responses when compared to rational answers.

The support and enthusiasm we received during the course of this community consultation highlight the recognition from people who have been affected by TBI that further work is required in understanding the physiopathology of TBI, thereby potentially improving prognostication and furthering treatment strategies.

Although the question of surrogate consent was not included in our survey, this is dealt with specifically by the 2005 Mental Capacity Act (sections 30–33) which provides lawful authority for intrusive research to be carried out involving people without capacity provided that the research has been approved by an appropriate body. Previous community consultations in emergency neurosurgical procedures in incapacitated patients have shown this is an acceptable method of inclusion in studies involving these patients [35–37]. While this is a good starting point, we should highlight that each of those studies related to the use of potential treatment that may have had direct benefit to the subject. In fact, the Corticoid Randomization after Significant Head Injury (CRASH) Trial [35] evaluated tranexamic acid in TBI; Clark et al. [36] was evaluating the role of decompressive craniectomy for evacuation of an acute subdural haematoma, and Scotton et al. [37] was evaluating a subdural evacuating port system as a minimally invasive alternative to burr-hole evacuation. On the contrary, the study outlined in our surveys, although not influencing our standard of care, might not necessary lead to any direct benefit for the participants. For this very reason, community consultation are considered prior to starting such type of investigational clinical trial, where the patient is unlikely to have capacity to consent to enrolment in the trial, but the proposed brain biopsy is for exploratory biomarker research that would not have a potential direct benefit to that subject.

There are many proposed hypotheses regarding the pathophysiology behind TBI; however, there remains limited information, and there are suggestions of increasing inpatient mortality rates following TBI over the last three decades [38, 39]. The reasons for this are multifactorial with many attributing the reason for the lack of improvements being made in the field to the lack of understanding of the underlying mechanisms and the restriction to experimental models [32]. In addition, prognostication remains a significant challenge as previously pointed out [41] despite the models proposed by the IMPACT and CRASH trials mentioned above.

Harish et al. [32] obtained brain tissue from 26 patients who had sustained TBI and underwent craniotomy and found distinct alterations specific to contusions and pericontusions at both the tissue and cellular levels in one of the first studies to investigate anatomical, cellular, and molecular changes in human TBI. Among their key findings was that pericontusional areas were susceptible to cytotoxic factors released by contusions, offering a window for repair and neuroregeneration and implying therapeutic options may be available. We believe that this study is crucial and opens the possibility for further work in human TBI, which is likely to provide more relevant information than histopathological research into animal models or postmortem studies.

Pyykkö et al. [33] obtained cortical brain biopsies from 102 patients with NPH and investigated the association between proinflammatory cytokines and biomarkers of neuronal damage in CSF. This study sets a precedent for obtaining *in vivo* brain tissue samples via needle biopsy outside the realm of brain tumour surgery. As the current study demonstrates, this concept is not straight-forward; however, only 7% stated that they would not consent to this.

Techniques such as microdialysis for the sampling of biomarkers in CSF interstitial space are well established, however limited in their application due to the difficulty in effectively estimating the concentration of the protein of interest *in vivo* [41]. Further work into point-of-care diagnostics has greatly enhanced the possibility of quick and inexpensive methods of detecting proteins of interest, and these tests can be performed in the emergency department or at the bedside. Besides saliva and plasma, attention is being given to CSF to show meaningful changes or imbalances in neural tissues [17].

Biomarkers in TBI have been gathering increasing attention; however, the majority of published studies focus on

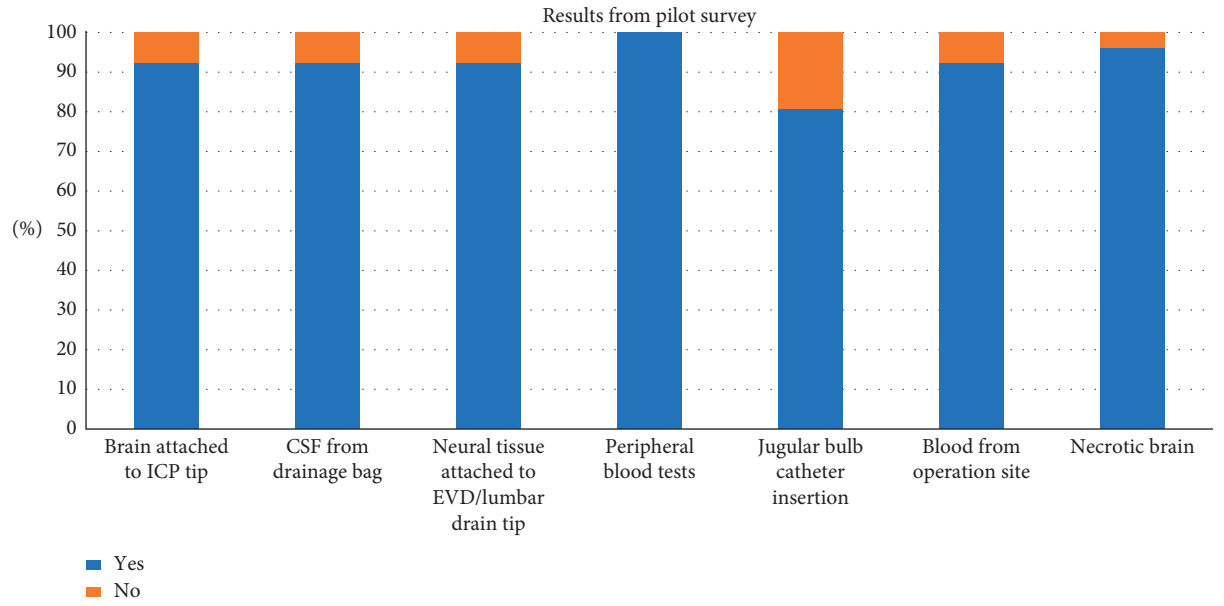

Figure 1: Results from the pilot survey.

Table 3: Results from survey.

	Question	Survey 1	Survey Monkey	Survey 2	Total (n)	%
Brain attached to ICP tip	Yes	33	28	33	94	94
	No	0	1	3	4	4
	Do not know	2	0	0	2	2
Brain biopsy	Yes	27	17	31	75	75
	No	2	2	3	7	7
	Do not know	6	10	2	18	18
CSF from drainage bag	Yes	32	29	33	94	94
	No	0	0	2	2	2
	Do not know	3	0	1	4	4
Neural tissue attached to EVD/lumbar drain tip	Yes	33	29	34	96	96
	No	0	0	2	2	2
	Do not know	2	0	0	2	2
Peripheral blood tests	Yes	33	27	33	93	93
	No	0	0	3	3	3
	Do not know	2	2	0	4	4
Urine, saliva, stool samples	Yes	33	27	34	94	94
	No	1	0	1	2	2
	Do not know	1	2	1	4	4
Jugular bulb catheter insertion	Yes	25	17	28	70	70
	No	7	3	5	15	15
	Do not know	3	9	3	15	15
Blood from operation site	Yes	33	29	33	95	95
	No	0	0	1	1	1
	Do not know	2	0	2	4	4
Necrotic brain	Yes	34	29	32	95	95
	No	0	0	2	2	2
	Do not know	1	0	2	3	3

peripheral blood samples. Insights on biomarker trends after TBI through samples obtained from pure brain venous blood (obtained from the jugular venous bulb) paired with those obtained from peripheral blood may prove useful to understand how much information is lost in peripheral venous blood, as proven in previous pilot studies [42]. In

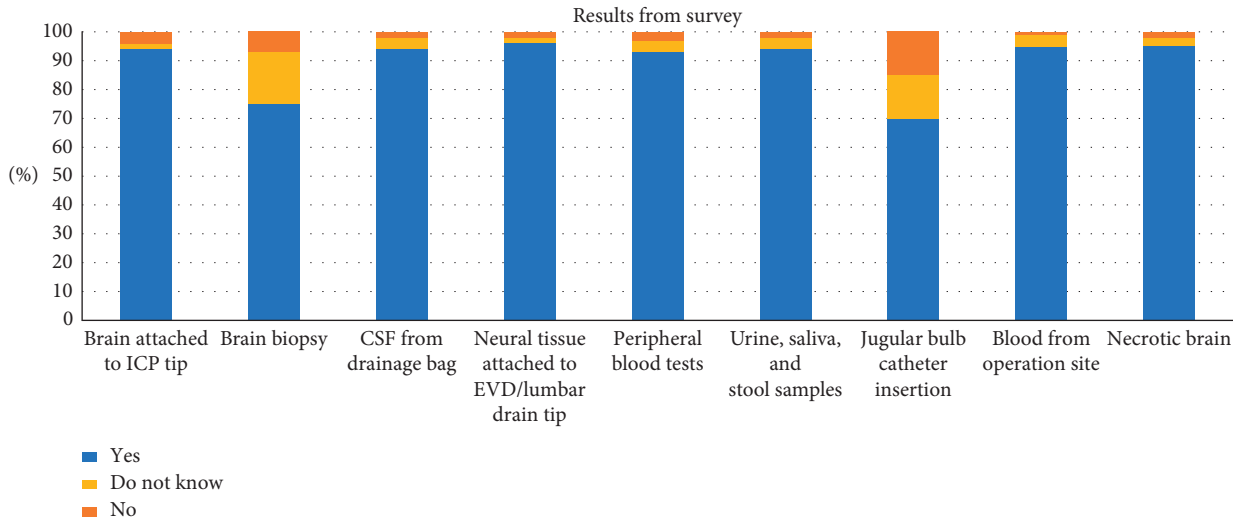

Figure 2: Results from the survey.

addition, this may permit correlation between the two and allow validation of peripheral samples.

5. Limitations of This Current Study

Responders to these surveys included patients who had previously sustained TBI and their families; an element of bias may therefore be present. In addition, although all respondents were able to complete the survey unaided, information pertaining to their education, intellectual capacity, and the degree of recovery was not recorded nor subject to further analysis.

Performing the pilot survey was important for the tool development and orientating the further steps in designing Survey 1 and improving it with Survey 2. Gathering all the data acquired in the course of this community consultation and conducting a final analysing can be criticized because of the slight difference of information received by participants at different stages and different methods of collection. Even though this has to be recognized as a limitation of the study, we considered this choice methodologically sounding because the questions asked in the surveys were basically very similar, if not identical.

6. Conclusion

Current management of TBI relies on decompression of salvageable brain and supportive care. There are currently no available treatments which aim to attenuate secondary injury. We hypothesise that the information gained from *in vivo* tissue sampling may direct future research into more accurate prognostic models and therapeutic options. As part of the research protocol, we conducted a community consultation aimed at investigating patients' understanding of the research challenges and their support toward future studies. The responses collected were overall very favourable, with many patients and their families recognising the utility and importance of this public engagement project and an overwhelming percentage willing to consent for samples being taken for this purpose in case of future studies. The responses to these surveys are particularly relevant because they suggest a wide community consensus in support of this type of research, hence partly answering the ethical questions revolving around participation of patients who have sustained severe TBI and therefore incapacitated and unable to consent to participation in research. Given the above, we hope that our study will contribute to provide evidence in support of research protocols requiring *in vivo* tissue sampling from patients suffering severe TBI.

Data Availability

The questionnaire data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All interactions with patients were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

All authors certify that they have no conflicts of interest.

Supplementary Materials

Supplementary material 1: pilot survey created to gauge response from head injury patients and their families to establish perceived acceptability to conducting laboratory analysis of neural tissue that may otherwise be discarded, obtaining peripheral blood samples, and for the insertion of jugular bulb catheters in patients with severe traumatic brain injuries. Supplementary material 2: Survey 1 created following feedback from the pilot survey. This contained further details and the response option of "do not know."

This also included new questions regarding obtaining additional tissue, i.e., brain biopsies at the time of insertion of intracranial pressure monitors, and obtaining extra samples of bodily fluids for analysis. Supplementary material 3: Survey 2 created following feedback from Survey 1 to answer questions regarding anonymity, the secure storage of samples in our laboratory, and that no further research investigations would be conducted at follow-up. (*Supplementary Materials*)

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