A Profile of Children with Traumatic Brain Injury Admitted to the Red Cross War Memorial Children's Hospital Paediatric Intensive Care Unit in Cape Town, South Africa, between 2015 and 2019

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MASTER OF PHILOSOPHY (MPHIL) PAEDIATRIC CRITICAL CARE
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DECLARATION

I, ……*Elri du Plooy*……, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background:

Paediatric traumatic brain injury (TBI) is a public health problem with high morbidity and mortality.

Objectives:

We aim to highlight risk factors and describe associated morbidity and mortality of children admitted to our Paediatric Intensive Care Unit (PICU) at Red Cross War Memorial Children's Hospital in Cape Town.

Methods:

We retrospectively documented the hospitalization of all children with TBI admitted into our PICU between 2015 and 2019.

Results:

Of 272 children identified, 232 were enrolled: 190 (81.9%) had severe TBI (Glasgow Coma Scale [GCS] ≤8), 32 (13.8%) moderate TBI (GCS 9-12) and 10 (4.3%) mild TBI (GCS ≥13). Median age was 6.5 (IQR 3.5-9) years; 144 (62.1%) were male. Motor vehicle accidents accounted for 77% (179) of injuries.

Two hundred (86.2%) children were invasively ventilated for a median of 3.5 (IQR 1-7) days; 26 children (13%, n=200) had a failed extubation and 16/200 (8%) required tracheostomies. Ninety-eight children (42.2%) had intracranial pressure monitoring. Almost 30% (67/232) required vasopressor support. Approximately a third (83/232) developed trauma-related seizures; 25 children (10.8%) required a Thiopentone infusion and 9 children (3.9%) a decompressive craniectomy. Common complications were post-extubation stridor (29/200 [14.5%]), hemiparesis (20/232 [8.6%]) and diabetes insipidus (15/232 [6.5%]).

Median PICU stay was 3 (IQR 1-8.3) days, and hospitalization 11 (IQR 5-20) days. Eighty-three (35.8%) children were transferred for further rehabilitation; 24 (10.3%) died.

Conclusion:

Despite marked improvement since the 1990's, children admitted to PICU with TBI had considerable morbidity and mortality. Enhanced primary preventative strategies, especially for motor vehicle accidents, are imperative to prevent TBI in children.

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- My main supervisor, Dr Shamiel Salie, for his support and guidance
- Prof Anthony Figaji for his insights
- The team at Red Cross War Memorial Children's Hospital records department for assisting with compiling the inpatient folders of study participants

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ABBREVIATIONS

ABBREVIATION	DEFINITION
CI	Confidence interval
CLABSI	Central line-associated bloodstream infection
CRF	Case report form
EVD	External ventricular drain
GCS	Glasgow Coma Scale
HAI	Hospital-acquired infection
HREC	Health Research Ethics Committee
IQR	Interquartile range
LMIC	Low- and middle-income countries
MVA	Motor vehicle accident
NHLS	National Health Laboratory Service
PACS	Picture archiving and communication system
PICU	Paediatric intensive care unit
RCWMCH	Red Cross War Memorial Children's Hospital
REDCap	Research Electronic Data Capture
RTI	Respiratory tract infection
SAJCC	South African Journal of Critical Care
TBI	Traumatic brain injury
UCT	University of Cape Town
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

DEFINITIONS

TERM	DEFINITION
Central line-associated bloodstream infections	A bloodstream infection that manifests after 48 hours of hospitalization in a patient with a central line in situ
Hospital-acquired infection	Infections acquired after hospitalization that manifest after 48 hours of hospital admission
Polytrauma	Two or more severe injuries in at least two areas of the body
Mild traumatic brain injury	Glasgow Coma Scale more than 13 out of 15
Moderate traumatic brain injury	Glasgow Coma Scale between and including 9 to 12 out of 15
Severe traumatic brain injury	Glasgow Coma Scale less than or equal to 8 out of 15
Ventilator-associated pneumonia	Pneumonia after 48 hours of ventilation and hospitalization

PUBLICATION-READY DISSERTATION

CHAPTER 1:

INTRODUCTION

1.1 CONTEXT

1.1.1 Introduction:

Paediatric traumatic brain injury (TBI) is a major global public health problem associated with high morbidity and mortality in children and adolescents.(1) It involves a wide range of pathology caused by closed, penetrating and/or blast injuries to the cranium and underlying brain.(2,3) The subsequent neuronal damage is categorised into 1) primary injuries, due to the mechanical forces of the focal and/or diffuse initial injury itself, and 2) secondary injuries in the form of additional tissue and cellular damage after the primary injury.(3)

The most common TBI severity classification is the 3-tiered Glasgow Coma Scale (GCS) classification that divides TBI's into Mild (GCS ≥13), Moderate (GCS 9-12) and Severe (GCS ≤ 8). More than 80% of paediatric TBIs are classified as Mild, while Severe TBI accounts for 3 to 7% of total traumatic brain injuries. Internationally, motor vehicle accidents (MVAs) (6-80%) and falls (5-87%) are the most prevalent mechanisms of injury in paediatric traumatic brain injury, and mortality rates range from 1 to 7%.(2)

The aim of our study was to provide a comprehensive profile of all children admitted to the Paediatric Intensive Care Unit (PICU) of Red Cross War Memorial Children's Hospital (RCWMCH) between 2015 and 2019. The follow-on objectives focused on differences between children with Severe and Moderate/Mild TBI; general measures undertaken (including ventilation, sedation, feeding practices); review of complications (failed extubation and tracheostomy, hospital-acquired infections, diabetes insipidus, pressure sores); duration of PICU and hospital stay, and mortality.

The literature overview below will briefly review the epidemiology of paediatric TBI in low- and middle-income countries (LMICs), describe the current management principles of TBI, as well as comment on morbidity and future research.

1.1.2 Epidemiology of Paediatric Traumatic Brain Injury in LMICs

Little TBI-related data are available in Sub-Saharan Africa, even though low- and middle-income countries (LMICs) have triple the TBI burden of high-income countries (HICs).(1,4) A 2021 systematic review evaluating the morbidity and mortality in children with TBI in LMICs between January 2000 and May 2020, emphasized how little good-quality data is available, with published data on the volume and extent of paediatric TBI only available from 32 countries (less than 25% of all LMICs). (5)

Children in LMICs were found to be 4.4 times more likely to have Mild TBI (95% confidence interval (CI) 1.9-6.8), than Moderate or Severe TBI. A quarter (24%) had cognitive and physical dysfunction post hospital discharge, and the median case fatality rate was 7.3 per 100 cases (interquartile range (IQR) 2.1-7.7).(5)

The review highlighted 3 key points: 1) Children with TBI in LMICs are younger with more profound long-term neurodevelopmental, financial and broader societal ramifications; 2) Males are disproportionately affected, odds ratio (OR) 1.8:1, 95% CI 1.6-2; and 3) Pedestrian motor vehicle accidents are the main cause for traumatic brain injury, with total motor vehicle accidents (passenger and pedestrian) contributing to 39% (16 275/41 979) of all paediatric TBI in these countries.(5)

This emphasizes not only the need for better documentation of TBI cases in low- and middle-income countries, using for example trauma registries, to gain proper insight into the pandemic, but also the need to invest in public health, civil and road traffic initiatives to improve road- as well as general safety for children in LMICs.(5)

1.1.3 Diagnosis, Treatment and Management of TBI

Modern TBI management has been influenced by multiple individual and multicentre studies since the 1970's, but despite progress, clinical TBI trials are frequently unsuccessful and high-quality evidence remains lacking, mostly due to the changing demographics and wide scope of TBI, leading to continued high morbidity and mortality.(6)

Modern neuro-critical care has identified the pitfalls of approaching traumatic brain injury management with a one-size-fits-all protocol strategy, as variability exists in both the modifiable and non-modifiable factors from the time of injury to eventual death or rehabilitation and recovery.(6) The 2019 consensus and algorithm-based guidelines for the treatment of severe traumatic brain injury by Kochanek, et al, is the present-day best practice base to which future and new evidence-based treatment strategies will be added.(7)

It is due to the heterogeneity of traumatic brain injury, as well as advancements in the fields of technology and molecular studies, that the development of more individualised and advanced diagnostic strategies and multimodal physiological intracranial monitoring has been researched and developed, to assist with understanding the intricate dynamics and links between brain-tissue oxygenation, intra-cranial pressure, autoregulation, and energy metabolism. These strategies are, however, still in their infancy, limited by the localized nature of measurements and difficulty in interpreting the extensive real-time collected data. The role of precision medicine is becoming more prominent and has led to the incorporation of molecular, mechanistic and genetic factors into the diagnostic systems that previously solely relied upon the Glasgow Coma Scale Score and/or CT scan findings.(6)

As the evolution and progression of secondary injury after the initial traumatic insult determines the morbidity and mortality in these children, current TBI management aims to find and treat secondary brain injury before its consequences become irreversible.(8) Treatment strategies are not only focusing on known entities, such as the use of 3% hypertonic saline versus mannitol (3% hypertonic saline shown to be the longer acting in reducing raised intracranial pressure of the two)(9), but also new more novel measurements, like micro-dialysis catheter sampled brain glycerol levels as a correlate of evolving brain injury(8), to guide real-time treatment strategies.

1.1.4 Morbidity & Mortality

As mortality rates slowly decline, TBI-related morbidity and the prevention thereof has become an area of increased interest, as survivors of especially severe childhood traumatic brain injury often have enduring physical, cognitive and behavioural impairments. These disabilities frequently require long-term care and cause financial burden to families.(10,11)

In the shorter term, during their hospitalization, children with severe and even Moderate TBI, are prone to a host of secondary complications. These include endocrine complications like hypopituitarism in up to a third of patients, as well as central diabetes insipidus that is associated with increased injury severity, raised intra-cranial pressure and death. (12)

Up to a third of TBI patients in ICU develop infections during their stay, with lower respiratory tract infections contributing to 50-60% of this burden, and surgical site infections 5-15%. Ventilator-associated pneumonias and hospital-acquired infections prolong length of ventilation, length of ICU and hospital stay, worsen outcome, and increase costs. All efforts should be undertaken to prevent them.(12)

1.1.5 Future Research

In low- and middle-income countries future research should focus on the documentation of TBI data, as well as the long-term neuro-developmental, psychosocial, and financial implications of TBI. This in turn should be utilized in the developing and implementing appropriate preventative and management strategies to reduce the burden of TBI.

As medical science and technology advances, we should also focus on developing more reliable trials to promote evidence-based management of paediatric TBI, to not only rely on adult and consensus data.

1.2 ETHICAL CONSIDERATIONS

This study was performed in concordance with the principles set out in the Helsinki Declaration of 2013.

It commenced after ethics approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town, (HREC Ref Nr 135/2021, see Appendix 2 and 4), as well as the Chief Executive Officer / Head of Clinical Services at Red Cross War Memorial Children's Hospital (see Appendix 3).

As this was a retrospective descriptive study where only data on the completed routine treatment and management of children with traumatic brain injuries were reviewed and collected from already existing sources (patient folders, the National Health Laboratory Service (NHLS) and the picture archiving and communication system (PACS)), a waiver for informed consent was granted.

This was deemed appropriate as:

1. There was no active intervention done on the study population (risk) as all data was retrospectively collected from patient folders
2. Patient confidentiality was a priority
    a. Only Dr E du Plooy collected and handled patient data and transferred it to the secured RedCap data collection forms (see Appendix 1)
    b. Child data remained anonymous. No patient identifiers, such as names or hospital numbers will be entered on the case report forms (CRFs). Each CRF contained a unique study number that has been used to identify related child data.
    c. Only study identifiers were used in electronic data files. A single record was kept that links the patient identifiers to the case name and record. This file is protected on a password protected computer.
    d. No patient identifiers were included in the data-analysis and will be omitted from any future reports, publications or presentations.
3. The benefit of our research includes the identification of areas of concern or promise in the treatment of, especially, severe TBI in children, with the aim to conduct further research and improve the treatment and future outcomes.
4. The benefit of this research outweighs any risks and unlikely breach of autonomy or confidentiality.

1.3 PUBLICATION GUIDELINES

We chose the South African Journal of Critical Care (SAJCC) as the most appropriate publication for presentation of our research findings.

The complete set of author guidelines for a research article is attached in Appendix 5.

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CHAPTER 2:

PUBLICATION-READY MANUSCRIPT

A PROFILE OF CHILDREN WITH TRAUMATIC BRAIN INJURY ADMITTED TO THE PAEDIATRIC INTENSIVE CARE UNIT OF RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL IN CAPE TOWN, SOUTH AFRICA, BETWEEN 2015 AND 2019

ABSTRACT

Background:

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We aim to highlight risk factors and describe associated morbidity and mortality of children admitted to our Paediatric Intensive Care Unit (PICU) at Red Cross War Memorial Children's Hospital in Cape Town.

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Results:

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Two hundred (86.2%) children were invasively ventilated for a median of 3.5 (IQR 1-7) days; 26 children (13%, n=200) had a failed extubation and 16/200 (8%) required tracheostomies. Ninety-eight children (42.2%) had intracranial pressure monitoring. Almost 30% (67/232) required vasopressor support. Approximately a third (83/232) developed trauma-related seizures; 25 children (10.8%) required a Thiopentone infusion and 9 children (3.9%) a decompressive craniectomy. Common complications were post-extubation stridor (29/200 [14.5%]), hemiparesis (20/232 [8.6%]) and diabetes insipidus (15/232 [6.5%]).

Median PICU stay was 3 (IQR 1-8.3) days, and hospitalization 11 (IQR 5-20) days. Eighty-three (35.8%) children were transferred for further rehabilitation; 24 (10.3%) died.

Conclusion:

Despite marked improvement since the 1990's, children admitted to PICU with TBI had considerable morbidity and mortality. Enhanced primary preventative strategies, especially for motor vehicle accidents, are imperative to prevent TBI in children.

1. INTRODUCTION

Paediatric traumatic brain injury (TBI) is a major global public health problem associated with high morbidity and mortality in children and adolescents.(1) International paediatric TBI data from 1995 – 2015 indicated that males are more commonly affected, with a median age at injury of 6.8 years (mean ages 3.2 – 10.4 years), with a bimodal distribution peaking in very young children (0-3 years) and adolescents (15 – 18 years). More than 80% of paediatric TBIs are classified as mild TBI (Glasgow Coma Scale (GCS) ≥ 13), with severe TBI (GCS ≤8) accounting for between 3 and 7% of all TBIs in most populations. Motor vehicle accidents (MVAs) (6-80%) and falls (5-87%) are the most common mechanisms of injury, and mortality rates range from 1 to 7%, or between 2.8 and 3.8 children per 100 000 annually.(2,3)

In recent years there has been a major uptake in both adult and paediatric TBI-related research, with specific interest in improvement of patient management and the prevention of secondary brain injury and resultant morbidity, poor functional outcomes, and mortality. Despite cutting-edge advances in neuro-monitoring and -intervention, with marked improvement in the outcomes of this population group in the past 3 decades, there is scope for further progress.

Our aim was to document the profile of children with TBI admitted into our Paediatric Intensive Care Unit (PICU), with special focus on the risk factors, morbidity, and mortality, in order to guide future planning and interventions for improvement of quality of care to this subset of patients.

2. METHODS

2.1 Study Sample

Red Cross War Memorial Children's Hospital (RCWMCH) is a dedicated paediatric tertiary hospital located in Cape Town, South Africa. It is the referral centre for all paediatric major trauma and brain injury cases in the public health sector in the Western Cape province. The hospital's 22-bed combined medical-surgical PICU has approximately 1400 admissions annually, of which the annual average of trauma- and TBI-related admissions are approximately 135 and 50-60 respectively.

We conducted a retrospective descriptive review of all the children with traumatic brain injury admitted into the PICU at RCWMCH between 1 January 2015 and 31 December 2019.

2.2 Inclusion and Exclusion Criteria

All children with traumatic brain injury admitted to the PICU during the study period were eligible for enrolment. Exclusion criteria included previous enrolment in the study, unavailability of the inpatient notes and confirmed brainstem death prior to PICU admission.

2.3 Data Collection

All admissions to the RCWMCH PICU from 1 January 2015 to 31 December 2019, as contained in a specifically designed Microsoft Access® database detailing all PICU admissions data, were reviewed for eligible participants by running a directed search/query on the 'Primary Diagnosis' and 'Diagnosis' fields. Folders of possible participants were requested from the records department and all candidates with available folders were enrolled. Data collected included demographics (sex, age, referring centre); traumatic brain injury severity (Glasgow Coma Scale-guided into mild (GCS ≥13), moderate (GCS 9-12) and severe (GCS ≤ 8)); mechanism of injury; associated injuries; type and duration of brain monitoring in PICU; incidence and management of trauma-related seizures; duration of invasive and non-invasive ventilatory support, including need for tracheostomy; PICU complications, including ventilator associated pneumonia, catheter related blood stream infections, pressure sores, deep venous thrombosis and endocrine complications like diabetes

insipidus. Duration of PICU and hospital stay, as well as PICU and hospital mortality were collected as measures of outcome.

Data collection and management was performed using secure, web-based REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Cape Town. The investigator populated all case report forms using patient medical folders, the National Health Laboratory Service database and the Picture Archiving and Communications Systems (PACS) radiology database.

2.4 Statistical Analysis

Microsoft Office Excel® 2015, TIBCO Statistica™ version 14 and IBM® SPSS® Statistics for Windows version 28 were used for data analysis. The characteristics of the patients were described using standard descriptive analysis, including measures of central tendency (mean, median, proportions) and dispersion (standard deviation, interquartile ranges and 95% confidence intervals).

More in-depth analysis was conducted using Mann-Whitney U testing to describe measures of central tendency on non-parametric data, as well as Chi square and Fisher's Exact tests for categorical data to review factors associated with ventilation duration, PICU and hospital stay, as well as mortality. A p-value of <0.05 was deemed statistically significant.

2.5 Ethical Considerations

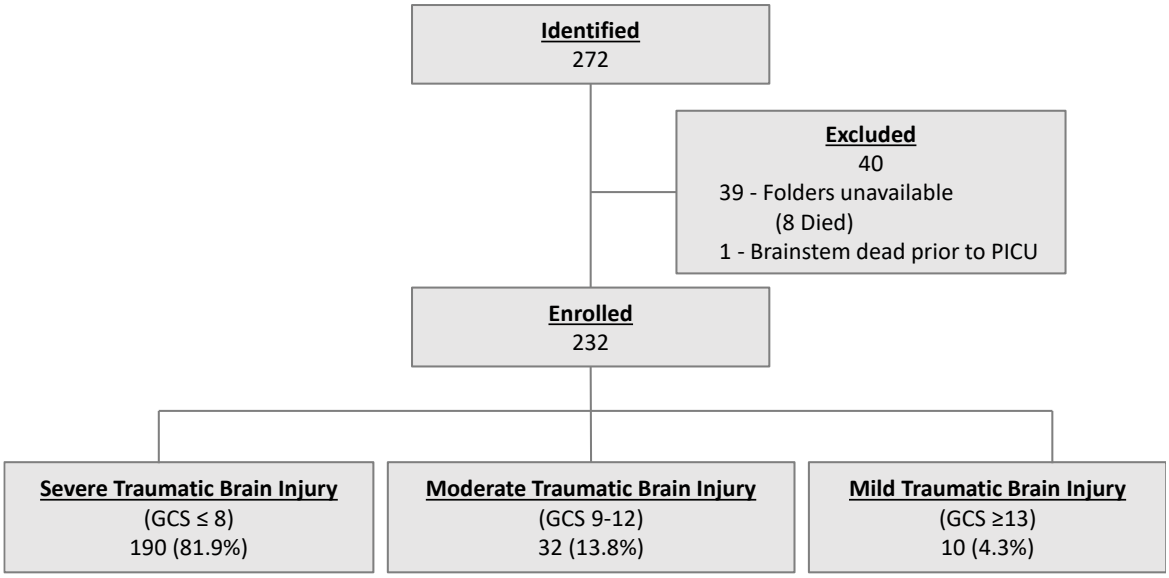
The study was performed in concordance with the principles set out in the Helsinki declaration. Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC Reference nr 135/2021) and the RCWMCH research committee, prior to commencement of data collection.

3. RESULTS

3.1 Demographics

Of the 272 children identified, 232 were enrolled into the study: One hundred and ninety (81.9%) children were classified as having severe TBI (GCS≤8), 32 (13.8%) moderate (GCS 9-12) and 10 (4.3%) mild TBI (GCS ≥13), see Figure 1.

Figure 1: Recruitment Process



GCS – Glasgow Coma Scale, PICU – Paediatric Intensive Care Unit

The children were 62.1% male (144/232), had a median age of 6.5 (IQR 3.5-9) years, and road traffic accidents accounted for 77% of all TBIs. Children were mostly referred from Khayelitsha District Hospital (32, 13.8%), Worcester Hospital (19, 8.2%) and Delft Community Health Centre (11, 4.7%). Forty-two children (18.1%) were brought directly to the RCWMCH Trauma Centre.

Five (2.2%, N=232) children had an acute life-threatening event requiring cardio-pulmonary resuscitation (CPR) after their injury. Four (80%, n=5) of these events occurred prior to PICU admission.

3.2 Injuries

During the study period 190 children were admitted to RCWMCH PICU with polytrauma (two or more severe injuries in at least two areas of the body), 158 (83.2%) of them with an associated head injury. Forty-three percent (100/232) of the children enrolled in the study had an isolated traumatic brain injury.

Skull fractures were present in 52.6% (122/232) of cases. The most common associated injuries were facial fractures (including frontal, mandibular, maxillary and orbital fractures) in 48 (20.1%) children, femur fractures (28, 12.1%), pneumothoraxes (25, 10.8%), lung contusions (23, 10.8%), as well as haemothoraxes and tibula/fibula fractures (19, 8.2% each). Additional injuries were not statistically associated with higher risk of death, $p>0.05$.

3.3 Course in PICU

Children were admitted to the RCWMCH PICU at a median of 9 (IQR 7.1-12.9) hours after injury. Table 1 summarizes the major general, first tier and second tier interventions (as documented in the *Management of Pediatric Severe Traumatic Brain Injury: 2019 Consensus and Guidelines-Based Algorithm for First and Second Tier Therapies*(4)), as well as outcomes of children with severe and those with mild/moderate traumatic brain injury.

Table 1: Profile of Children by Traumatic Brain Injury Severity

	All Children (N=232)	Severe TBI (GCS≤8) (N=190,81.9%)	Mild/Moderate TBI (GCS≥9) (N=42,18.1%)	P
DEMOGRAPHICS				
Male n(%)	144(62.1)	119(62.6)	25(59.5)	0.707
Age median(IQR) years	6.5(3.5-9)	6.7(3.8 - 9.3)	4.1(2.9-7.3)	0.013
Mode of Injury n(%)				
1 Pedestrian vehicle accident	126(54.3)	105(55.3)	21(50)	
2 MVA Passenger	53(22.8)	47(24.7)	6(14.3)	
3 Fall	22(9.5)	14(7.4)	8(19)	
GENERAL INTERVENTIONS				
ICP monitors n(%)	99 (42.7)	95 (50)	4 (9.5)	<0.001
Noradrenalin n(%)	67(28.9)	64(33.7)	3(7.1)	<0.001
Ventilated (IPPV) in PICU n(%)	200(86.2)	181(95.3)*	19(45.2)	<0.001
Packed Red Cell Transfusion n(%)	91(39.2)	81(42.6)	10(23.8)	0.017
FIRST TIER INTERVENTIONS				
Hypertonic Saline n(%)[∞]	118(50.9)	109(57.4)	9(21.4)	<0.001
Neuromuscular Blockade n(%)	16(6.9)	16(8.4)		
EVD n(%)	8(3.4)	8(4.2)		
SECOND TIER INTERVENTIONS				
Thiopentone infusion n(%)	25(10.8)	24(12.6)	1(2.3)	0.525
Decompressive Craniectomy n(%)	9(3.9)	9(4.7)		
OUTCOMES				
PICU Duration median(IQR) days	3(1-8.3)	4(1-9)	1(0-2)	< 0.001
Hospitalization Duration median(IQR) days	11(5-20)	11.5(5-21)	7(3-15)	0.023
Mortality n(%)	24(10.3)	24(12.6)		

EVD - External ventricular drain, GCS - Glasgow Coma Scale, ICP - Intracranial pressure, IPPV - Intermittent positive pressure ventilation, IQR - Interquartile Range, MVA - motor vehicle accident, PICU - Paediatric Intensive Care Unit, RCWMCH- Red Cross War Memorial Children's Hospital, TBI - Traumatic Brain Injury

* 3 children with severe TBI never ventilated, 4 extubated prior to PICU admission, 2 extubated on arrival in PICU

[∞] Hypertonic (5%) Saline is standard of care at RCWMCH, mannitol is not routinely used

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3.4 Complications and Morbidity

Table 2 summarizes the most common complications and morbidities encountered.

Table 2: Complications and Morbidities

	All Children (N=232)	
	N/n	
Trauma-related seizures* n(%)		83(35.8)
Post-extubation stridor n(%)	200	29(14.5)
Failed extubation n(%)	200	26(13)
Tracheostomy (n%)	200	16(8)
Hospital-acquired infection n(%)		42(18.1)
CLABSI n(%)		12(5.2)
VAP n(%)	200	32(16)
Hemiparesis n(%)		20(8.6)
Diabetes insipidus n(%)		15(6.5)
Deep vein thrombosis n(%)		6(2.6)
Transferred for further inpatient rehabilitation on RCWMCH discharge n(%)		83(35.8)

CLABSI - Central line-associated bloodstream infection, IQR - Interquartile Range, N/n - denominator if different from N=232, RCWMCH – Red Cross War Memorial Children's Hospital, VAP - ventilator-associated pneumonia

* Clinical seizures

3.4.1 Seizures

Seventy children (30.2%, N=232) developed trauma-related seizures within 24 hours, 4 (1.7%) between 24 and 72 hours, and 9 (3.9%) after 72 hours. Seizures were diagnosed clinically as not all patients in our setting get an electroencephalogram (EEG; 25/232, 10.8%), cerebral function monitoring (CFM; 28/232, 12.1%) or both (10/232, 4.3%). Four children had seizures on EEG, and 7 on CFM. Three of the 10 children monitored with EEG and CFM had confirmed electrical seizures on both modalities. Phenobarbitone (77.1%, 64/83) was the treatment of choice, followed by Sodium Valproate (8.4%, 7/83) and

Phenytoin (6%, 5/83). Levetiracetam was used in 2 cases (2.4%) in 2019 (its use only became more prominent in our setting after the study period). Seizure treatment was started at a median of 1 day post insult (IQR 0-1 days).

3.4.2 Respiratory and Ventilatory Complications

Children were ventilated for a median of 3.5 days (IQR 1-7 days, N=200): 4 (IQR 1-8) days in those with severe TBI (n=181) and 1 (IQR 0-7) day in mild/moderate TBI, p=0.03.

Patients failed extubation due to severe upper airway obstruction/stridor (21/26, 80.1%), increased work of breathing (11/26, 42.3%), and depressed level of consciousness (2/26, 7.7%).

The main reasons for a tracheostomy included prolonged ventilation (7/16, 43.8%), failed extubation/inadequate airway protection (11/16, 68.8%), and stridor (4/16, 25%). Tracheostomies were performed at a median of 13 (IQR 12-19) days post injury and required for a median of 17 days (IQR 14-23 days, n=15) before successful decannulation. Failed extubation and tracheostomy were associated with a statistically significant longer duration of IPPV, PICU stay and duration of hospitalization, $p<0.001$.

Eleven of the 200 ventilated children (5.5%) had an accidental/self-extubation: 9 (81.8%) occurred prior to PICU admission and 2 (19.2%) during their PICU stay. Two children (1%, n=200) required re-intubation for a blocked endotracheal tube, one (0.5%) sustained hypoxic brain injury due to very difficult intubation with multiple failed attempts, and another (0.5%) presented as an oesophageal intubation from the referring centre.

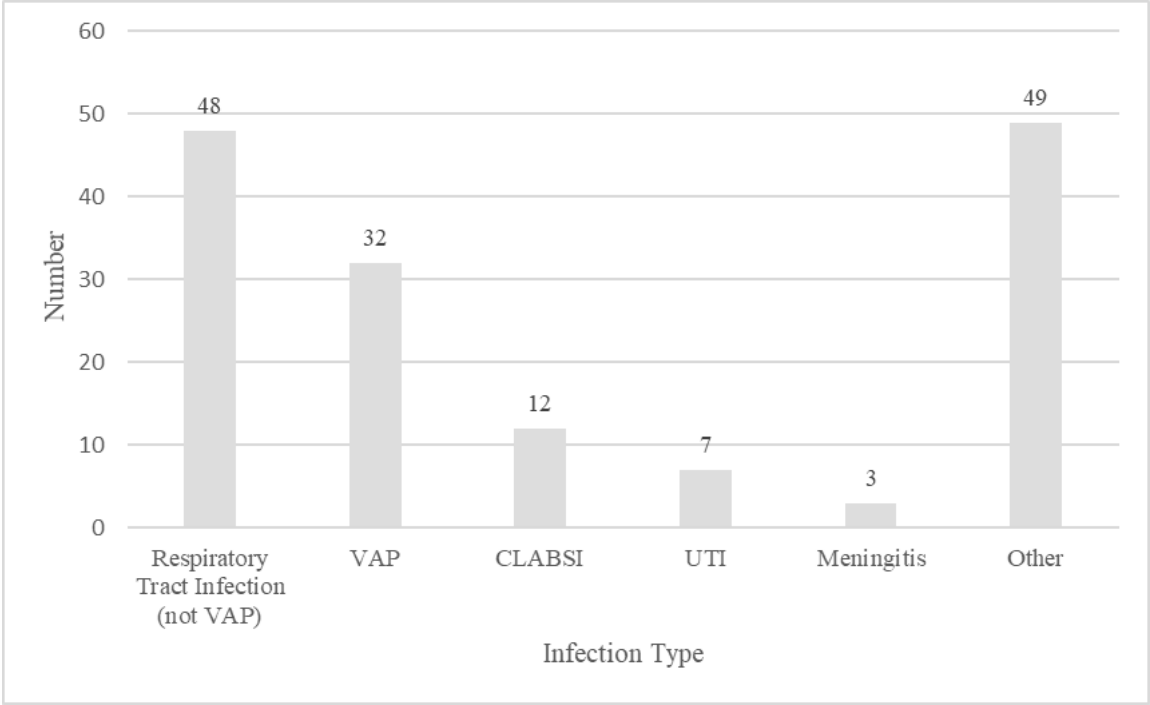
3.4.3 Infective Complications

Eighty children (40% of the 200 ventilated children) admitted to PICU with TBI developed a respiratory tract infection; 40% (32/80) of these were classified as a ventilator associated pneumonia (developed after 48 hours in hospital, VAP). Twelve children (5%) developed a central line-associated bloodstream infection (CLABSI).

Bacteria were most frequently cultured from tracheal aspirates, with the most common organisms being Methicillin sensitive Staphylococcus aureus (MSSA) in 11.2% of children (26/232) and Haemophilus influenza in 10.3% (24/232).

A third of patients (77/232) received no antibiotic treatment, while 57 (30%, N=190) of those with severe TBI, and 5 (15.6%, N=32) of those with moderate TBI received second-line antibiotics (Piperacillin-Tazobactam, Amikacin, Ertapenem, Meropenem, Vancomycin and Ciprofloxacin). No-one with mild TBI required second-line antibiotics.

Chart 1: Infections in Children Admitted to PICU with TBI



CLABSI – central line-associated bloodstream infection, PICU – Paediatric Intensive Care Unit, TBI – traumatic brain injury, VAP – ventilator-associated pneumonia, UTI – urinary tract infection

Other: Presumed sepsis (39), Wound site infection (8), Eye infection (1), Sinusitis (1)

3.4.4 Diabetes Insipidus

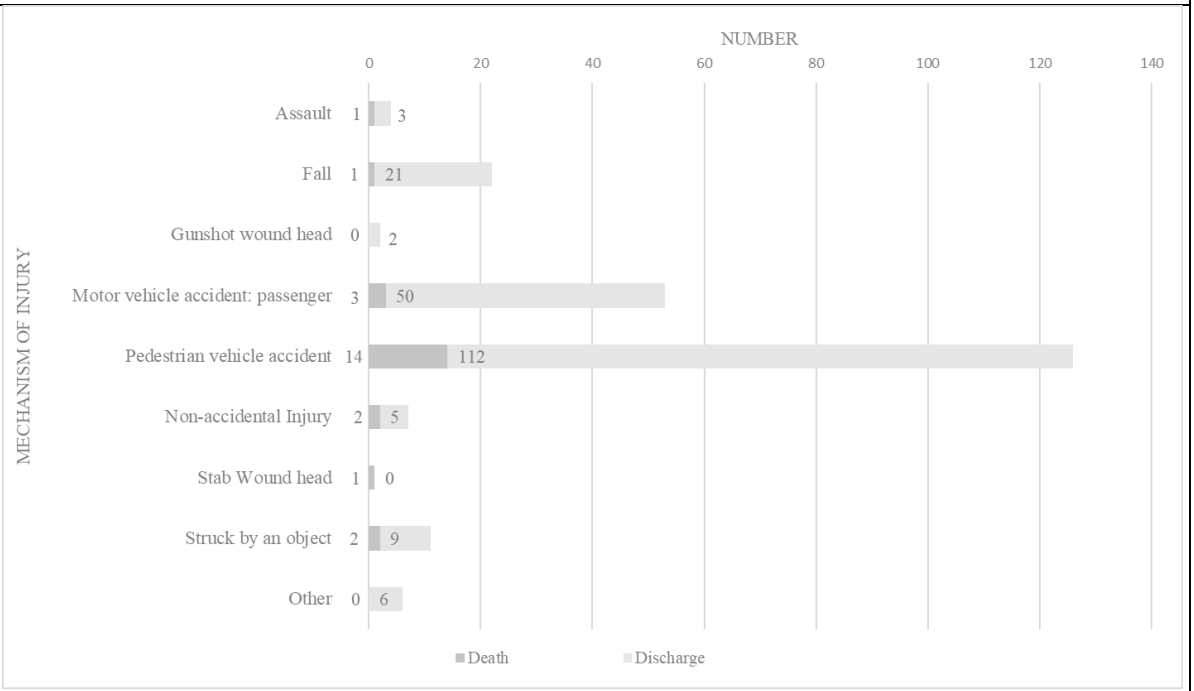
Fifteen children (6.5%, N=232), all with severe TBI (7.9% of 190), were diagnosed with diabetes insipidus (DI) using urine output >4ml/kg/hr and raised serum sodium criteria. There was a paucity in central DI-corroborating urine osmolality tests (5/15, 33%) and urine

specific gravities (3/15, 20%). The diagnosis was made on day 1 (IQR 1-2.5) after injury, with a median serum sodium of 159 (IQR 154-161, n=14). Twelve of the children (80%, n=15) received at least one dose of Desmopressin, median 1.5 (IQR 1-3) doses. Hypertonic (5%) saline was administered in most of these children (9/15, 60%), which may skew the validity of these results and underestimate possible iatrogenic hypernatraemia.

3.5 Mortality

TBI deaths (24/232, 10.3%) in our cohort, all due to severe TBI, accounted for 61.5% of the total of 39 trauma-related deaths during the 5-year study period. Life-sustaining treatment was withdrawn in 16 of the 24 children (67%): 15 (62.5%) due to brainstem death and 1 (4.2%) for poor neurological prognosis. See Chart 2 for a breakdown of deaths by mechanism of injury and Table 3 for factors associated with outcome in children with severe TBI. Total TBI deaths over the 5-year period were 12.1% (33/272); 9 children who died were not included in the study: 8 had unavailable folders and 1 was declared brain-stem dead prior to PICU admission.

Chart 2: Outcome in Children with TBI by Mechanism of Injury



TBI – Traumatic brain injury

Other: Pushed/fell from moving train (2), Wall/closet fell on child (2), Cycled into wall (1), Unknown (1)

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Table 3: Factors Significantly Associated with Outcome in Children with Severe TBI					
	Discharged		Died		P
	(N=166,87.4%)		(N=24,12.6%)		
	N/n		N/n		
GENERAL MEASURES					
Vasopressors and Inotropes					
Noradrenalin n(%)		47(28.3)		17(70.1)	<0,001
Adrenalin n(%)		11(6.6)		15(62.5)	<0,001
Maintenance Fluids and Feeds					
Crystalloid boluses n(%)	156	26(16.7)	23	11(47.8)	<0,001
FIRST TIER INTERVENTIONS					
EVD n(%)		5(4.8)		3(12.5)	0.0305
SECOND TIER INTERVENTIONS					
Thiopentone infusion n(%)		18(10.8)		6(24)	0.0510
Decompressive Craniectomy n(%)		5(3)		4(16.7)	0.0032
COMPLICATIONS					
Diabetes insipidus n(%)		6(3.6)		9(37.5)	<0,001
INFECTIVE COMPLICATIONS					
RTI (Total) n(%)		67(40.4)		3(12.5)	0.0082
Second-line Antibiotics n(%)		54(32.5)		3(12.5)	0.0453
OUTCOMES					
PICU Stay median(IQR) days		5(1-11)		1(0.5-4)	<0.001
Hospital Stay median(IQR) days		14(7-22)		1(1-5)	<0.001

EVD – External ventricular drain, IQR – Interquartile range, N/n = denominator if different from N total for column, PICU – Paediatric Intensive Care Unit, RTI – Respiratory tract infection, TBI – traumatic brain injury

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4. DISCUSSION

The basic profile of children with traumatic brain injury admitted to the Red Cross War Memorial Children's Hospital PICU has remained mostly unchanged over the past 30 years. Children are still mostly male, approximately 6 years of age, with the most common mechanism of injury remaining motor vehicle accidents at almost 80%, with pedestrian vehicle accidents making up the majority of these at 54.3% of total TBIs. A positive, however, is that mortality rates have decreased markedly from 57% in the early 1990's to 14.6% between 2006 and 2011 and now to 12.1% (33/272) between 2015 and 2019. This decline in mortality is attributed to the increased zeal and precision in the approach to the medical and surgical management of traumatic brain injury over time.(1)

As mortality rates slowly decline, TBI-related morbidity and the prevention thereof has become an area of increased interest, as survivors of especially severe childhood traumatic brain injury often have enduring physical, cognitive, and behavioural impairments. These disabilities frequently require long-term care and cause financial burden to families.(5,6)

Severe TBI is especially of concern, as from the outset these children were ventilated longer ($p=0.030$) and had a longer PICU ($p<0.001$), and hospital stay ($p=0.23$) than those with mild/moderate TBI. All deaths (24, 10.3%) in our cohort were from the severe TBI group.

A systematic review and meta-analysis by Mariajoseph et al. on the incidence and risk factors for post-traumatic epilepsy following paediatric TBI concluded that early seizures (before 7 days), severe traumatic brain injury and intracranial haemorrhage were risk factors for post-traumatic epilepsy(7), and adult data from Taiwan showed that patients with post traumatic epilepsy had a 2-fold higher risk of mortality.(8) In our cohort post-traumatic seizures were associated with a longer ventilation time ($p<0.001$), but not PICU ($p=0.061$) or hospital stay ($p=0.377$). There was no associated increase in mortality ($p=0.1982$). Children with severe TBI admitted to RCWMCH are not routinely started on prophylactic anti-seizure medication but reviewed on a case-to-case basis.

Pulmonary complications after TBI are common and occur in up to 30% of cases.(9) Not much data are available on failed extubation and tracheostomy in children with TBI.

In the ICU arm of the Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injuries (CENTER-TBI) Study in adults admitted to 54 participating centres in 19 countries in Europe, 31.8% (433/1358) received a tracheostomy at a median (IQR) time of 9(5–14) days after ICU admission. This is much higher than the 16 (8%) in our cohort where tracheostomies were also performed later, at 13(IQR 12-19) days post injury. Interestingly, despite prolonged ventilation and hospital stay, all children with failed extubation and tracheostomy were discharged from Red Cross Cross Children's Hospital. Data on their eventual outcome is not available.

It is concerning to note that 11 children had an accidental extubation; nine of them prior to PICU admission, with an additional 5 requiring cardio-pulmonary resuscitation (4 pre-hospital). Careful attention needs to be paid to safety and sedation practices in these children, especially in the pre-hospital setting. Standardised protocols need to be set up and readily available and staff need proper training in the management of these patients.

Infections, including CLABSIs and VAPs, contribute to PICU morbidity and length of stay.(10,11) This was corroborated by our cohort, where VAP and probable HAI was associated with a statistically significant longer duration of ventilation, PICU stay and total hospitalization, $p < 0.001$. Neither, however, affected mortality ($p=0.0848$ and $p=0.102$). This is in keeping with data from the CENTER-TBI Study(12), as well as VAP data from an American paediatric TBI study between 2009 and 2012 that reviewed the epidemiology, risk factors and microbiology of VAP in children admitted to PICU with TBI.(11) Similar to our study, they found Methicillin-sensitive Staphylococcus aureus (34%) and Haemophilus influenzae (22%) to be the most commonly isolated organisms. In our cohort, VAP was associated with sedation (morphine and midazolam), thiopentone infusion, as well as use of noradrenalin and hypertonic saline. In contrast to the above study, neuromuscular blockade use was not statistically significantly associated with VAP, ($p=0.052$).

Central diabetes insipidus is known to be associated with increased severity of traumatic brain injury, raised intracranial pressure, as well as high mortality.(12) Our findings were no different, with DI being associated with severe traumatic brain injury and an increased risk of death ($p<0.001$), but not with increased length of ventilation (0.099), PICU stay ($p=0.313$) or hospitalization ($p=0.564$). Our findings may be biased by the lack of corroborating urine

osmolality and urine specific gravity measurements in all cases, as well as our use of hypertonic 5% saline in 60% of the presumed DI cases.

The mortality rate in children with severe TBI ranges between 16 and 22%.(13) At 12.1% (33/272), ours is in keeping with international trends. Most deaths are still from motor vehicle-related causes (17/24, 70.8%), followed by assault (4/24, 16.7%) and non-accidental injury (2, 8.3%). Use of adrenalin and noradrenalin infusions, administration of crystalloid boluses, need for EVD placement and/or decompressive craniectomy, and the presence of diabetes insipidus were all risk factors for death, ($p<0.05$), most likely as they are indicators of the severity of the children's clinical condition and treatment required.

We recognize the possible bias caused by retrospective file review, including the effect the missing folders may have on our data. Strengths of this study lie in the fact that RCWMCH PICU is the only dedicated centre for children with TBI requiring ICU care in the Western Cape. This assisted with standardization of treatment of all patients, as well as contributed to a reasonable sample size.

5. CONCLUSION

Children admitted to the RCWMCH PICU with TBI had considerable associated morbidity and mortality. Enhanced primary preventative strategies, especially for motor vehicle accidents, are imperative to prevent TBI in children.

Infective complications, such as ventilator-associated pneumonias, are important to prevent and the use of good aseptic practices and bundled care is important.

Future local research should include the long-term follow-up and neurodevelopmental outcomes of children admitted with TBI in our setting, with analysis of the resultant financial and social burden.

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