THE IMPACT OF BARBITURATE THERAPY IN CHILDREN WITH SEVERE TRAUMATIC BRAIN INJURY (TBI)

MMED IN NEUROSURGERY CANDIDATE (UCT):	Dr Andrew Appiah-Baiden
STUDENT NUMBER:	APPAND002
SUPERVISOR:	Prof. Anthony Figaji
CO-SUPERVISOR:	Dr. Nqobile Thango

INSTITUTION

Red Cross War Memorial Children's Hospital

University of Cape Town (UCT)

CONTENTS

APPENDICES

PLAGIARISM DECLARATION AND SUPERVISOR AUTHENTICATION

Section A: Student Declaration

I, the undersigned, declare that:

1. **Turnitin Submission:** This thesis/dissertation has been submitted to the Turnitin module (or an equivalent similarity and originality checking software) as required for the completion of my degree.
2. **Original Work:** The work presented in this thesis/dissertation is my own, and any references to the work of others have been appropriately cited and acknowledged.
3. **Supervisor Review:** My Turnitin report has been reviewed by my supervisor, and any concerns identified regarding similarity or potential plagiarism have been resolved through consultation.

Student Name: Andrew Appiah-Baiden

Student Number: appand002

Signature: Signed by candidate

Date: 23/10/2024

Section B: Supervisor Authentication

I, the undersigned, confirm that:

1. **Review of Turnitin Report:** I have reviewed the Turnitin report for the thesis/dissertation submitted by **Andrew Appiah-Baiden**. The similarity index percentage and details have been thoroughly examined.
2. **Assessment of Concerns:** Any issues or concerns revealed by the Turnitin report have been discussed with the student and resolved to ensure compliance with the university's academic integrity standards.
3. **Originality Confirmation:** Based on my review, I verify that the thesis/dissertation is original, and the content adheres to the required academic standards for citation and referencing.

Supervisor Name: Professor Anthony Figaji

Signature:

Date: 23/10/2024

DECLARATION

I, **Andrew Appiah-Baiden**, hereby declare that the work on which this research paper 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.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 23/10/2024

ACKNOWLEDGEMENTS

I would like to extend my deepest gratitude to those who have supported me throughout this research journey.

First and foremost, I want to express my heartfelt thanks to my wife, **Malebo**, my daughter, **Elizabeth,** and my **entire Family**. Your unwavering love, patience, and encouragement have been my greatest source of strength. Without you all, this achievement would not have been possible.

I am also profoundly grateful to my parents, **John and Mercy Appiah-Baiden**, whose constant support and belief in me have provided the foundation upon which I have built this work. To **God**, I give thanks for the guidance, wisdom, and strength that have sustained me through this challenging endeavor.

I would like to extend my sincere appreciation to my supervisors, **Professor Anthony Figaji** and **Dr. Nqobile Thango**, for their invaluable input, guidance, and mentorship throughout this project. Your expertise and insights have been instrumental in shaping this research.

Lastly, a special thank you to the **Red Cross research team** for their dedicated assistance with data collection and analysis. Your contributions have been crucial in bringing this project to fruition.

CERTIFICATION

The undersigned certify that they have read and thereby recommend for examination the Publication Ready Manuscript, titled **'The Impact of Barbiturate Therapy in Children with Severe TBI'**, in partial fulfilment of the requirements for the degree of Master of Medicine (Neurosurgery) of the University of Cape Town.

Prof. Anthony Figaji

Signature:

Date: 8/10/2024

Dr. Nqobile Thango

Signature:

Date: 18/09/2024

CHAPTER 1:

Literature Review

LITERATURE REVIEW: THE IMPACT OF BARBITURATE THERAPY IN CHILDREN WITH SEVERE TBI

Authors: A. Appiah-Baiden, D. van Eck, N. Thango, T. Mlambo, J. Enslin, U. Rohlwink, S. Salie, A. Figaji

INTRODUCTION

Severe traumatic brain injury (TBI) is a heterogenous entity reflecting either focal or global modes of injury. Focal findings include haematomas (extradural, subdural and intraventricular) and contusions. Global findings include post-traumatic subarachnoid haemorrhage, diffuse axonal injury, brain swelling and/or ischaemia and post-traumatic hydrocephalus (1). Severe traumatic brain injury (TBI) commonly causes raised intracranial pressure (ICP), which occurs in 50 to 80% of cases (2). The degree and duration of raised ICP adversely impacts patient outcomes (3), therefore ICP management is a fundamental step of limiting secondary brain injury.

Less is known about paediatric TBI when compared with the data and guidelines for adult TBI. TBI in children differs in both pathophysiology and management compared to adults. The differences are attributable to age-related structural changes, mechanism of injuries based on physical ability of the child, and the difficulty of neurological evaluation of the paediatric population. Therefore, children are considered to exhibit a specific pathological response to brain injury and accompanying neurological symptoms (4).

TREATMENT PROTOCOLS

Standardized protocols and guidelines have been developed in the last decade based on current evidence and consensus groups to guide ICP directed therapy for severe TBI (5, 6, 7). A 3-tier escalating approach has been adopted, according to which different treatment modalities are prioritized in their application. Treatments with more severe side-effects are classified as higher tier, while those with fewer side effects are considered lower tier. Tier-zero is management aimed at establishing a stable, neuroprotective physiologic baseline regardless of eventual ICP; this usually involves sedation and analgesia to target comfort and ventilator tolerance. Tier-one represents the first foray into managing medically refractory ICP (MRICP): escalation of analgesia and sedation, normocapnia, use of an external ventricular drain (EVD) to drain cerebrospinal fluid (CSF), electroencephalogram (EEG) monitoring and hyperosmolar therapy (7).

Second tier therapies are applied for patients with MRICP despite optimum first tier therapy. They have the potential for significant adverse effects and should therefore be used with caution and only if the MRICP poses a greater risk to the patient (8). These interventions include mild hypocapnia (32-35mmHg), neuromuscular paralysis, mean arterial pressure (MAP) challenge, mild hypothermia (35-36°C), decompressive craniectomy and barbiturate coma (7). Mild hyperventilation reduces ICP by reducing cerebral blood volume, however it carries a risk of causing cerebral ischaemia (9). Neuromuscular blockade may lower the ICP by lowering ventilation pressures and ventilator asynchrony, thus improving venous outflow from the brain. However, early or prolonged use of neuromuscular blocking agents is associated with increased rate of ventilator-associated pneumonia, prolonged intensive care unit (ICU) stay and ICU neuromyopathy (10). Decompressive craniectomy reduces ICP and may reduce mortality, but there are surgical complications and the effects on long-term neurological outcome may still be poor (11, 12). MAP challenge evaluates static pressure autoregulation (sPAR) and can be used to adjust MAP and cerebral perfusion pressure (CPP) to lower ICP in patients with preserved autoregulation. On the other hand, this carries the risk of ICP spike in cases of impaired sPAR autoregulation and may be difficult to assess in patients on high dose of vasopressors or concurrent lung or cardiac pathology (13). In some countries, use of EVD to drain CSF is applied as a second-tier therapy (14).

BARBITURATE COMA THERAPY

Barbiturate coma therapy (BCT) is a second-tier treatment used when first-line therapies fail to control ICP. Despite barbiturate therapy being recommended as a second tier therapy option for the management of refractory intracranial hypertension in both adults and children, its impact as a therapeutic strategy is still not well evaluated in the children. In fact, the choice between second tier therapies is not clearly defined because of lack of data, and practice across the world varies considerably. Pentobarbital and Thiopentone are the most commonly used barbiturates for MRICP in severe TBI. Both drugs are potent sedatives that induce metabolic suppression and have anti-epileptic properties (15). In addition to lowering ICP, extracellular concentrations of lactate and excitatory amino acids are reduced after treatment with barbiturates (16). Overall, thiopentone appears to be more effective than pentobarbital at reducing ICP, although its effects may take up to four days to become noticeable (17). Which drug is used preferentially seems have geographic variation.

The breakdown of thiopentone produces five metabolites, one of which is pentobarbital, with the remainder being inactive compounds (18). This may explain the increased efficacy of thiopentone in controlling ICP elevation as compared with pentobarbital (18). Significant

complications have been reported, with the most prominent being systemic hypotension. As a result, continuous invasive arterial blood pressure monitoring is required with adequate cardiovascular support in order to maintain appropriate CPP. Other complications include renal dysfunction, hepatic dysfunction, hypokalaemia, respiratory complications and infections (19). Literature on use of barbiturate coma in children to manage MRICP is scarce. In some paediatric studies, the improvement in ICP may be counterbalanced by the risk of haemodynamic problems and so it may not actually result in improved overall outcomes (20).

EFFECTIVENESS OF BARBITURATE COMA IN REDUCING INTRACRANIAL PRESSURE

Barbiturate coma therapy has been shown to be effective in reducing ICP in children with MRICP. A study by Velle et al. demonstrated that BCT significantly reduced ICP levels in children with TBI, with median ICP decreasing from 22 mmHg before BCT to 16 mmHg within five hours of treatment initiation, and this reduction was maintained throughout the treatment period (21, 22). These findings are consistent with other studies that highlight the effectiveness of BCT in lowering ICP in severe TBI cases, thereby reducing the risk of further brain injury (1, 2, 17, 18).

COMPARATIVE EFFICACY OF PENTOBARBITAL AND THIOPENTONE

Pentobarbital and thiopentone are the most commonly used barbiturates in BCT. Both drugs are potent sedatives that induce metabolic suppression and have anti-epileptic properties, contributing to ICP reduction. However, evidence suggests that thiopentone may be more effective than pentobarbital. A randomized trial performed by Pérez-Bárcena et al. of pentobarbital versus thiopentone in the treatment of refractory intracranial hypertension in patients with TBI found that thiopentone was more effective in controlling MRICP in paediatric TBI patients compared to pentobarbital, with better-controlled ICP levels and fewer complications (18). Thiopentone's increased efficacy may be due to its pharmacokinetics, as it is metabolized into pentobarbital and other inactive compounds, enhancing its ability to control ICP. This superiority in controlling ICP has been observed in both paediatric and adult populations, suggesting a broader applicability of thiopentone in BCT (3, 16, 23, 24).

CLINICAL OUTCOMES AND COMPLICATIONS

The clinical outcomes of BCT in children with severe TBI are generally favourable when ICP is effectively controlled. Velle et al. reported that 82% of children treated with BCT had

favourable outcomes, defined as either good recovery or moderate disability at follow-up (21, 22). The occurrence of these side effects underscores the importance of administering BCT in a controlled environment, such as a neurointensive care unit (NICU), where continuous monitoring and prompt management of complications are possible (5, 6, 12).

LONG-TERM IMPACT AND RECOVERY

The long-term impact of BCT on children varies, with outcomes ranging from good recovery to moderate disability. While BCT is effective in controlling life-threatening ICP levels, its long-term efficacy in improving neurological outcomes remains variable. Continued rehabilitation and monitoring are essential for improving long-term outcomes in paediatric patients treated with BCT (4, 21). This underscores the need for individualized treatment plans that consider the potential benefits and risks of BCT in paediatric TBI (10).

SPECIFIC LITERATURE

According to the Brain Trauma Foundation (BTF) Guidelines (5), the use of barbiturate coma is considered a Level III recommendation for ICP control. High-dose barbiturate therapy is recommended in patients who have MRICP with stable haemodynamic parameters, despite maximal medical and surgical therapy. Failure to control refractory ICP with high-dose barbiturates results in a reduction in time to death as well as a trend towards a five-fold increase in death (23, 24, 25). These guidelines further utilize 1 retrospective study and 3 smaller treatment series in order to provide recommendations for the use of barbiturates in paediatric severe TBI.

Mellion and colleagues (23) conducted a study utilizing high-dose barbiturates (non-standardized dose) in the management of 36 children with severe TBI. Pentobarbital was utilized in the form of a loading dose followed by a continuous infusion. Other variables assessed from their study included: non-contrasted CT to assign a Rotterdam Criteria Score, mechanism of injury (motorized, non-motorized and non-accidental), markers of injury severity (GCS, Injury Severity Score or ISS, pre-hospital data such as cardiac arrest), transfer pattern (direct or indirect) and time from injury to trauma centre, hourly CPP and ICP data, use of vasopressors, laboratory results, ventilator settings, nosocomial infections and the development of renal insufficiency. Primary outcome measures in this study were the Paediatric Cerebral Performance Category (PCPC) score at discharge and then at 3 months (adequate 1-3, poor 4-6). The study ultimately concluded that high dose Pentobarbital achieved control of refractory hypertension in 30% of children, with other studies quoting

between 22-55% (22, 23, 24). This control was associated with an increased probability of acceptable long-term outcome.

Kasoff et al (20) documented a treatment series of 25 children with severe traumatic brain injury and aggressive physiological monitoring. This monitoring strategy was based on concerns surrounding unpredictable physiological consequences of high dose pentobarbital therapy in the management of refractory intracranial hypertension. Failure to control ICP by means of mannitol, hyperventilation or head elevation were the triggers to initiate pentobarbital therapy. In this series, pentobarbital was administered as an initial bolus (4-7mg/kg) and then by continuous infusion of 1-4mg/kg. Pentobarbital blood levels (25-50mg/l) or EEG monitoring (absence of brainstem function) were utilized to assess depth of therapy. Primary outcome variables included GCS and Trauma Score (TS), which is a 16-point cumulative, 5-parameter score, assessing respiratory rate (0-4 points), respiratory expansion (0-1 point), systolic blood pressure (0-4 points), capillary refill (0-2 points), and GCS (1-5 points). Secondary variables assessed in this study included causes of TBI (MVA, falls, child abuse, baseball assault), diagnostic evidence on admission (mass lesions, decerebrate posturing, bilateral fixed pupils and hemiparesis), CT evidence of head trauma, mortality rate (20%), the need for inotropic support (91%), EEG findings of absence of brainstem function, ICP, MAP and other such physiological parameters. Some of the notable conclusions in this study were that GCS was a good predictor of outcome and that lowering ICP correlated well with improved outcomes.

An older retrospective study was conducted by Pittman et al (26), assessing efficacy of barbiturate therapy (pentobarbital for at least 24 hours with a documented CPP <50 torr for >30 minutes) in the treatment of resistant intracranial hypertension in children with severe traumatic brain injury. This study only included 7 children between 1984 and 1986, all of which had raised intracranial pressure resistant to conventional medical therapies. A Pentobarbital bolus dose of 5mg/kg, followed by a continuous infusion of 1-2mg/kg/hr was used to a target blood level of 30-40mg%. Outcome was graded using a modified 5-point Glasgow Outcome scale. Additional variables assessed (compared against outcome) included CPP, duration of treatment with pentobarbital, serum levels, age and initial neurological examination. Of the 7 participants, 3 had good recoveries, 2 were moderately disabled, and 2 were in a vegetative state. Neither the CPP or pentobarbital coma were accurate predictors of outcome.

CONCLUSION

Barbiturate coma therapy, particularly with thiopentone, is effective in reducing intracranial pressure in paediatric patients with traumatic brain injury, leading to favourable outcomes in a significant proportion of cases. However, the treatment is associated with a risk of side effects that require careful management. No clear guidelines exist for sedation and thiopentone use as a second-tier option for refractory ICP in children. No large series of barbiturate use exists in the paediatric population, and none which examine its effects on other physiological parameters. The choice of barbiturate and the setting in which BCT is administered are crucial factors that influence both the efficacy and safety of the treatment. Further research is needed to refine treatment protocols, improve long-term outcomes for paediatric patients undergoing BCT and to assess its effects on other physiological parameters, including ICP, PbtO2, MAP and CPP.

REFERENCES

1. Menon D, Ercole A. Critical care management of traumatic brain injury. Handbook of clinical neurology. 2017;140:239-74.

2. Maas AI, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology. 2017;16(12):987-1048.

3. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. Journal of neurosurgery. 1991;75(Supplement):S59-S66.

4. Araki T, Yokota H, Morita A. Pediatric Traumatic Brain Injury: Characteristic Features, Diagnosis, and Management. Neurol Med Chir (Tokyo). 2017;57(2):82-93.

5. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the management of pediatric severe traumatic brain injury: update of the brain trauma foundation guidelines. Pediatric Critical Care Medicine. 2019;20(3S):S1-S82.

6. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017;80(1):6-15.

7. Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med. 2019;45(12):1783-94.

8. Vrettou CS, Mentzelopoulos SD. Second-and Third-Tier Therapies for Severe Traumatic Brain Injury. Journal of Clinical Medicine. 2022;11(16):4790.

9. Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. Critical care medicine. 2007;35(2):568-78.

10. Hsiang JK, Chesnut RM, Crisp CB, Klauber MR, Blunt BA, Marshall LF. Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? Critical care medicine. 1994;22(9):1471-6.

11. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive craniectomy in diffuse traumatic brain injury. New England Journal of Medicine. 2011;364(16):1493-502.

12. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. New England Journal of Medicine. 2016;375(12):1119-30.

13. Rosenthal G, Sanchez-Mejia RO, Phan N, Hemphill JC, Martin C, Manley GT. Incorporating a parenchymal thermal diffusion cerebral blood flow probe in bedside assessment of cerebral autoregulation and vasoreactivity in patients with severe traumatic brain injury. Journal of neurosurgery. 2011;114(1):62-70.

14. Chau CYC, Mediratta S, McKie MA, Gregson B, Tulu S, Ercole A, et al. Optimal Timing of External Ventricular Drainage after Severe Traumatic Brain Injury: A Systematic Review. J Clin Med. 2020;9(6).

15. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. XI. Anesthetics, analgesics, and sedatives. Journal of neurotrauma. 2007;24(Supplement 1):S-71-S-6.

16. Goodman J, Valadka A, Gopinath S, Cormio M, Robertson C. Lactate and excitatory amino acids measured by microdialysis are decreased by pentobarbital coma in head-injured patients. Journal of neurotrauma. 1996;13(10):549-56.

17. Stover JF, Pleines UE, Morganti-Kossmann MC, Stocker R, Kossmann T. attenuates energetic impairment but fails to normalize cerebrospinal fluid glutamate in brain-injured patients. Critical care medicine. 1999;27(7):1351-7.

18. Pérez-Bárcena J, Llompart-Pou JA, Homar J, Abadal JM, Raurich JM, Frontera G, et al. Pentobarbital versus in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial. Critical Care. 2008;12(4):1-10.

19. Schalen W, Messeter K, Nordström CH. Complications and side effects during thiopentone therapy in patients with severe head injuries. Acta anaesthesiologica scandinavica. 1992;36(4):369-77.

20. Kasoff SS, Lansen TA, Holder D, San Filippo J. Aggressive physiologic monitoring of pediatric head trauma patients with elevated intracranial pressure. Pediatric Neurosurgery. 1988;14(5):241-9.

21. Velle F, Lewén A, Howells T, Enblad P, Nilsson P. Temporal effects of barbiturate coma on intracranial pressure and compensatory reserve in children with traumatic brain injury. Acta Neurochir (Wien). 2021;163(2):489-98.

22. Velle F, Lewén A, Howells T, Nilsson P, Enblad P. Intracranial pressure-based barbiturate coma treatment in children with refractory intracranial hypertension due to traumatic brain injury. J Neurosurg Pediatr. 2020;25(4):375-83

23. Mellion SA, Bennett KS, Ellsworth GL, et al: High-dose barbiturates for refractory intracranial hypertension in children with severe traumatic brain injury. *Pediatr Crit Care Med* 2013; 14:239–247

24. Eisenberg HM, Frankowski RF, Contant CF, et al: High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg* 1988; 69:15–23

25. Marshall GT, James RF, Landman MP, et al: Pentobarbital coma for refractory intracranial hypertension after severe traumatic brain injury: mortality predictions and one year outcomes in 55 patients. *J Trauma* 2010; 69:275–283

26. Pittman T, Bucholz R, Williams D: Efficacy of barbiturates in the treatment of resistant intracranial hypertension in severely head-injured children. *Pediatr Neurosci* 1998; 15:13–17

CHAPTER 2:

Abstract

THE IMPACT OF BARBITURATE THERAPY IN CHILDREN WITH SEVERE TBI

Authors: A. Appiah-Baiden, N. Thango ,D. van Eck, T. Mlambo, J. Enslin, U. Rohlwink, S. Salie, A. Figaji

ABSTRACT

INTRODUCTION

There are no clear guidelines on how to use sedation and second-tier therapies for the treatment of raised intracranial pressure (ICP) in children with severe traumatic brain injury (TBI). Specifically, evidence is limited on the use of barbiturate therapy as a second-tier treatment option for uncontrolled ICP in children, in part because cohort sizes are small and there are little data on physiological effects. To address this, we evaluated the impact of thiopentone on physiological variables and outcome in children with severe TBI.

METHODOLOGY:

In this retrospective study we collected data on children (<13 years) with severe TBI who had undergone multimodality monitoring and received thiopentone to control ICP. We examined 1) the effect of thiopentone on physiological variables, 2) clinical characteristics of the cohort, and 3) outcome.

RESULTS:

Data were analyzed from 74 children: most were male (67.6%), and most were road traffic accident victims (71.6%). The average time from admission to initiation of thiopentone therapy was 48 hours; the average treatment duration was 4.8 days. On average, patients were extubated 5.3 days after cessation of thiopentone infusion; 20.3% received tracheostomies, and the average duration of ICU stay was 13 days. Decompressive craniectomy (DC) was used in 23% of patients. The mortality rate was 20.3%. Thiopentone use was associated with a reduction in median ICP and median mean arterial pressure (MAP), and no change in cerebral perfusion pressure (CPP). Brain tissue oxygenation was slightly higher on thiopentone, but not significantly.

CONCLUSION:

This is the largest study to analyze barbiturate therapy in children with TBI. Thiopentone was useful in decreasing ICP. Although there was an associated decrease in MAP, CPP remained similar. Despite this being a selected group of patients on second-tier therapies, the mortality rate was acceptable. Thiopentone use may avoid the surgical morbidity of DC, but at the expense of longer stays in ICU.

***KEYWORDS*:** Intracranial Pressure (ICP), Thiopentone, Paediatric Critical Care, Decompressive Craniectomy

CHAPTER 3:

Publication Ready Manuscript

THE IMPACT OF BARBITURATE THERAPY IN CHILDREN WITH SEVERE TRAUMATIC BRAIN INJURY

Authors: A. Appiah-Baiden, D. van Eck, T. Mlambo, J. Enslin, U. Rohlwink, N. Thango, S. Salie, A. Figaji

INTRODUCTION

Various standardized protocols and guidelines have been developed over the last two decades based on current evidence and consensus groups to guide intracranial pressure (ICP)-directed therapy for severe traumatic brain injury (TBI) (1-4). The evidence base for these guidelines in children though, remain weak (2). In particular, there are no clear guidelines for how to use sedation and second-tier therapies for refractory ICP in children with severe TBI, and clinical practice across the world varies considerably. Barbiturate coma therapy (BCT) is recommended as an option for second-tier therapy for the management of medically refractory intracranial pressure (MRICP) in both adults and children. However, its impact as a therapeutic strategy is still not well evaluated in children. Pentobarbital and Thiopentone are the most commonly used barbiturates for MRICP in paediatric severe TBI. Both drugs are potent sedatives that induce metabolic suppression and have anti-epileptic properties (5). According to the Brain Trauma Foundation (BTF) Guidelines, the use of barbiturate coma is considered a Level III recommendation for ICP control. High-dose barbiturate therapy is recommended as an option for patients who have MRICP with stable haemodynamic parameters, despite maximal medical and surgical therapy (2). However, there is no clear guidance on which second-tier therapies should be employed and in which patients. There is some older data that suggested the improvement in ICP may be counterbalanced by mortality from haemodynamic problems and may not actually result in improved overall outcomes. Currently, barbiturate therapy is used uncommonly and variably in paediatric TBI, with decompressive craniectomy being a more commonly used strategy, accounting for as many as 35% of severe TBI cases in some series (6). Additionally, there is little data on the balance between effectiveness of barbiturate therapy in reducing ICP and its potential detrimental effects. Finally, the overall cohort sizes in the available literature are typically small.

In this study we evaluate the impact of thiopentone on physiological variables of children who sustained a severe TBI, the characteristics of the population, and their clinical course.

CLINICAL MATERIALS AND METHODS

This retrospective cohort study was conducted at the Red Cross War Memorial Children's Hospital (RCWMCH), the primary referral centre for children with severe TBI within the Western Cape Province of South Africa. Ethical approval for the study was obtained from the University Of Cape Town's scientific and human research ethics board (HREC Reference 499/2022). Data were collected over a 10-year period, spanning from January 1, 2010, to December 31, 2020.

Patient Selection

Inclusion criteria for this study were children <13 years of age admitted to the intensive care unit (ICU) with a diagnosis of severe TBI (Glasgow Coma Scale [GCS] ≤ 8) in whom thiopentone infusion was administered as second-tier management for refractory intracranial hypertension, defined as an intracranial pressure (ICP) ≥ 20 mmHg after failure of standard first-tier medical management (7) (Appendix A). Patients were excluded if had incomplete medical records.

Patient Management

In brief, patients with severe TBI are managed broadly in keeping with established clinical protocols. An intracranial pressure monitor (Codman ICP Express; Codman, Integra Neurosciences) and brain tissue oxygen monitor (PbtO2), (Licox; Integra Neurosciences) are standard at our institution if intracranial monitoring is considered. Typically, the PbtO2 catheter was placed in normal-appearing white matter in the right frontal lobe. Patients are admitted to the paediatric intensive care unit where they were ventilated and managed according to an institutional protocol that aims to maintain ICP < 20 mmHg, CPP greater than 50mmHg, and PbtO2> 20 mmHg, but these goals are adapted for individual patients depending on age, clinical condition, brain imaging findings, and clinical course. Standard therapies for intracranial hypertension including sedation, analgesia, neuromuscular paralysis, ventricular drainage (where considered applicable), hypertonic saline, and CO2 control. Where these measures do not control ICP, surgical decompression or barbiturate coma are considered (8, 9). Hypothermia is not used at our institution. The decision to use surgical decompression or thiopentone is at the treating clinician's discretion; it is influenced by the nature of and magnitude of the ICP increase, haemodynamic instability, and the brain imaging findings. Mean arterial pressure (MAP) was measured through continuous invasive measurements (arterial line) and CPP was calculated from MAP-ICP with the arterial line zeroed at the level of the heart.

Thiopentone Infusion Protocol

Thiopentone neat solution (25mg/ml) was administered as an intravenous infusion at 1ml/hr (dose Range 1-5mg/kg/hr). It was continued until the patient's ICP was adequately controlled or if further treatment was deemed necessary by the clinical team.

Data Collection

Data were extracted from a prospectively maintained database. Where data were missing from the electronic database, patients' clinical records were accessed. Usual protocol included high frequency physiological data (sampled at 50Hz) collected on bedside computers running specialized software (ICM+, Cambridge University); MAP was transferred via USB from a bedside monitor and ICP and PbtO2 were exported directly from the monitoring devices via an analogue-digital converter to the ICM+ system. Electronic data were averaged in 10 second intervals for data reduction and export. Occasionally ICM+ was not available or there were technical reasons why this could not be accomplished. In those cases, manual nursing records were collected. To compare time epochs before and after initiation of thiopentone, these recordings were analyzed for the 12-hour period before the drug was initiated, and compared to recordings for the duration that the drug was used. The following were collected: demographic data (age, sex), clinical data (mechanism of injury, initial GCS), physiological data and outcome. The use of decompressive craniectomy (DC) was classified as none, before thiopentone, or after thiopentone infusion. The use of tracheostomy in patients was dichotomised (yes/no) and time to extubation after thiopentone initiation was recorded.

The physiological data collected included ICP, cerebral perfusion pressure (CPP), PbtO2 and MAP. The first hour of PbtO2 was disregarded to exclude insertion artefact and to allow the catheters to stabilize. The length of ICU stay was recorded and mortality was recorded as dead/alive at 6 months.

Statistical Analysis

Descriptive statistical analysis was used, beginning with measures of central tendency, and based on the distribution of the data, the appropriate statistical tests were performed (parametric vs non-parametric). All *P*-values were two-sided, and a value of $p < 0.05$ was considered significant. All data were entered into a secure database and analysed using SPSS software (version 26.0, IBM Corp.).

Describing the Temporal profile of physiological variables of patients on Thiopentone Infusion

The measures of central tendency for ICP, MAP, CPP and PbtO2 were calculated per day for each patient. The median of physiological variables for before initiation of thiopentone, day 1, 2 and 3 were depicted on a temporal graph to display their change over the specified time course.

The effect of Thiopentone on physiological variables.

The median values of physiological variables (ICP, MAP, CPP, PbtO2) were calculated per patient for the periods before (12-hour period before drug started) and after thiopentone infusion. A paired t-test (parametric) and Wilcoxon signed-rank test (non-parametric) were used to asses if there was a difference in averages before and after treatment.

Describing the relationship between physiological variables, DC and outcome

An independent t-test for MAP/CPP/PBTO2 and Mann-Whitney U-test for ICP (non-parametric on normality test) was used to assess the relationship of physiological variables to outcome. Outcome was dichotomized to dead/alive. A Kruskal-Wallis test was conducted to assess the effect of decompressive craniectomy on physiological variables.

RESULTS

Demographic and Clinical Characteristics

Between January 1, 2010, and December 31, 2020, a total of 74 children with severe TBI were treated with thiopentone infusions as part of second-tier management. The median age of the cohort was 7.2 years. Of these, 24 children (32.4%) were female, and 50 (67.6%) were male. The most common mechanism of injury was road traffic accidents in 71.6% (53 patients), gunshot wounds (GSW) in 9.5% (7 patients), falls in 9.5% (7 patients), non-accidental injury (NAI) in 8.1% (6 patients), and crush injury in 1.4% (1 patient).

In terms of clinical course, decompressive craniectomy was performed in 23% of the participants (17 patients), of which approximately half were performed before (8 patients) and after (9 patients) initiation of thiopentone infusion.

Tracheostomies were required in 15 patients (20.3%), with all tracheostomies being successfully decannulated and no significant acute or long-term complications. The median

duration of thiopentone infusion was 95 hours (3.5 days). The average time to extubation following cessation of thiopentone infusion was 5.9 days and the average length of stay in the intensive care unit was 14.9 days. The overall mortality rate was 20.3% (15 patients, Table 1). Of these, 13 patients died with refractory ICP (6 of them had also had a craniectomy).

Table 1. Demographics and Clinical Characteristics of patients who received multi-modality monitoring and thiopentone at RCWMCH.

Characteristics	**Value**
Age*	7.2 (IQR 4.32-9.53)*
Sex	
Female	24 (32.4%)
Male	50 (67.6%)
Mechanism	
Road accident (passenger)	21 (28.4%)
Road accident (pedestrian)	32 (43.2%)
NAI	6 (8.1%)
GSW	7 (9.5%)
Fall	7 (9.5%)
Crush	1 (1.4%)
Outcome	
Alive	59 (79.7)
Dead	15 (20.3)
Decompressive Craniectomy	
None	57 (77%)
Before	8 (10.8%)
After	9 (12.2)
Tracheostomy	
No	59 (79.7)
Yes	15 (20.3%)

*Abbreviations: NAI - Non-accidental Injury, GSW – Gunshot Wound; *Age in years*

Physiological Outcomes

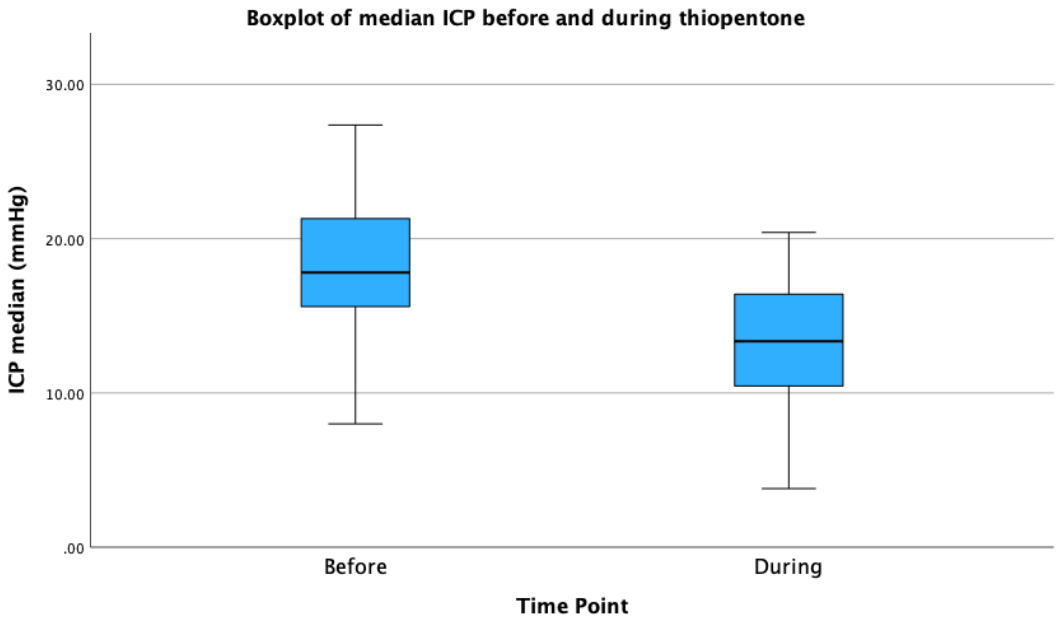
The primary outcomes assessed were changes in ICP, MAP, CPP, and PbtO2 before and during thiopentone infusion. In total, 20 patients did not have electronic high frequency data for either MAP and/or ICP and so manual recordings were used to calculate medians for these. In the 12-hour period prior to thiopentone infusion, the median ICP was 17.9 mmHg, compared to 13.6 mmHg over the period during the infusion. This represented a significant median reduction of 4.3 mmHg ($p < .001$). All patients had intermittent episodes of ICP greater than 20mmHg during this period, which prompted the initiation of thiopentone. Similarly, the median MAP showed a significant decrease, from 81.5 mmHg (before) to 75.7 mmHg (after) ($p < .001$), with a median reduction of 5.8 mmHg. PbtO2 was measured in 70 of the patients. The median PbtO2 showed a modest increase from 26.4 mmHg (before) to 29.4 mmHg during the infusion; however, this change was not statistically significant ($p = .258$). CPP showed a small, non-significant, median decrease from 62.5mmHg to 61.8mmHg. Slight differences are likely accounted for by summarising data per patient. These data are summarized in Table 2 and represented graphically in Graphs 1-4.

Table 2. Change in physiological parameters

	n	Median (mmHg)	P
ICP (mmHg)			< .001
Before	74	17.9	
During	74	13.6	
Change		4.3	
MAP (mmHg)			< .001
Before	74	81.5	
During	74	75.7	
Change		5.8	
CPP (mmHg)			.104
Before	74	62.5	
During	74	61.8	
Change		0.7	
PbtO2 (mmHg)			.258
Before	70	26.4	
During	70	29.4	
Change		3	

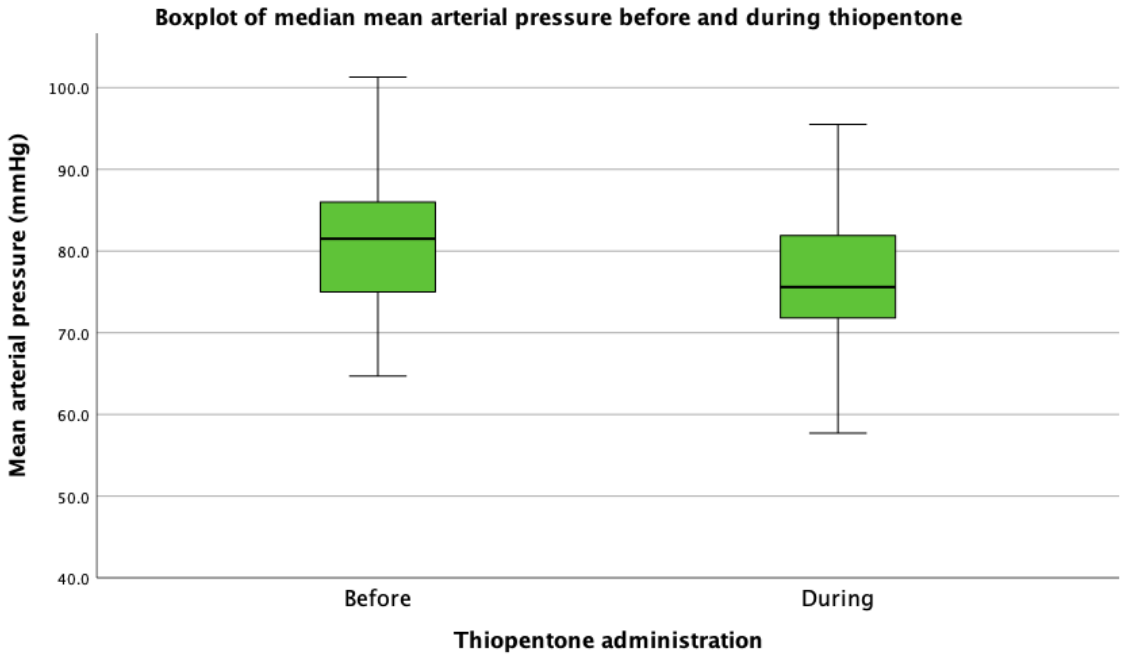
Table 2. N=74 patients, 4 patients did not have PbtO2 monitoring hence n=70 for PbtO2. Both ICP and MAP showed median reductions which were statistically significant; Both CPP decrease and PbtO2 increase were not statistically significant.

Graph 1. Median ICP before and during thiopentone infusion



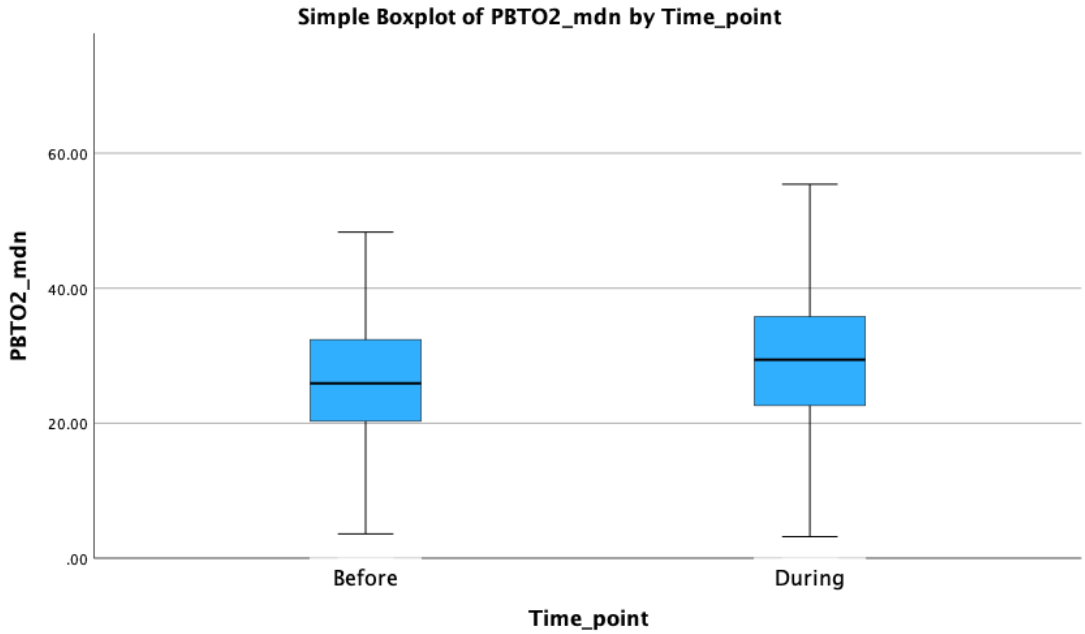
Graph 1 – Median reduction in ICP from 17.9mmHg to 13.6mmHg, (p < .001)

Graph 2. Median MAP before and during thiopentone infusion



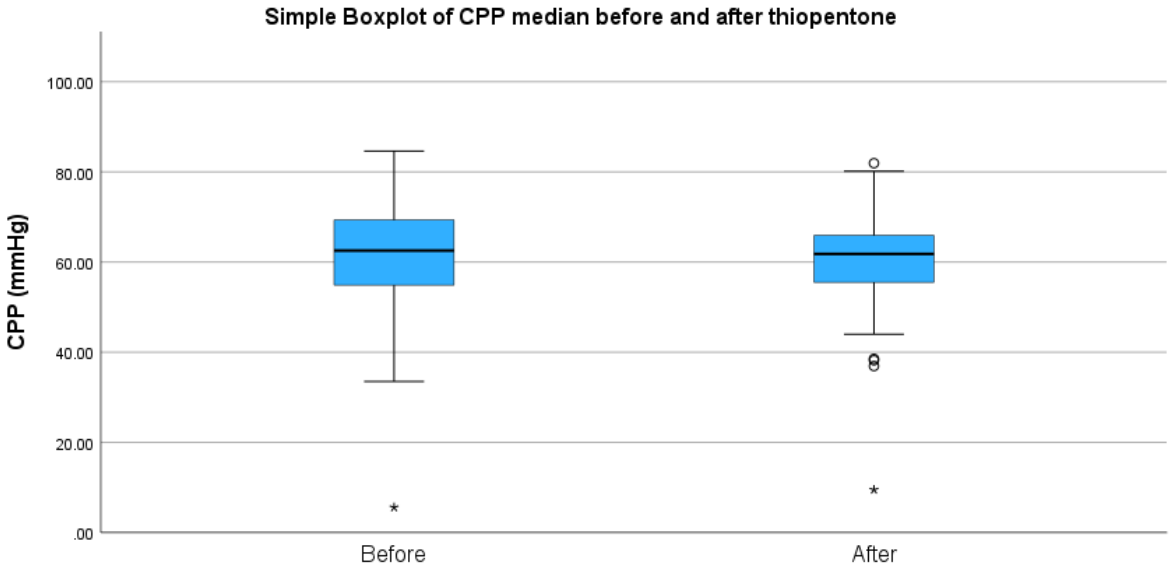
Graph 2 – Median reduction in MAP from 81.5mmHg to 75.7mmHg, (p < .001)

Graph 3. Median PbtO2 before and during thiopentone infusion



Graph 3 – Median increase in PbtO2 from 26.4mmHg to 29.4mmHg, (p = .258)

Graph 4. Median CPP before and during thiopentone infusion

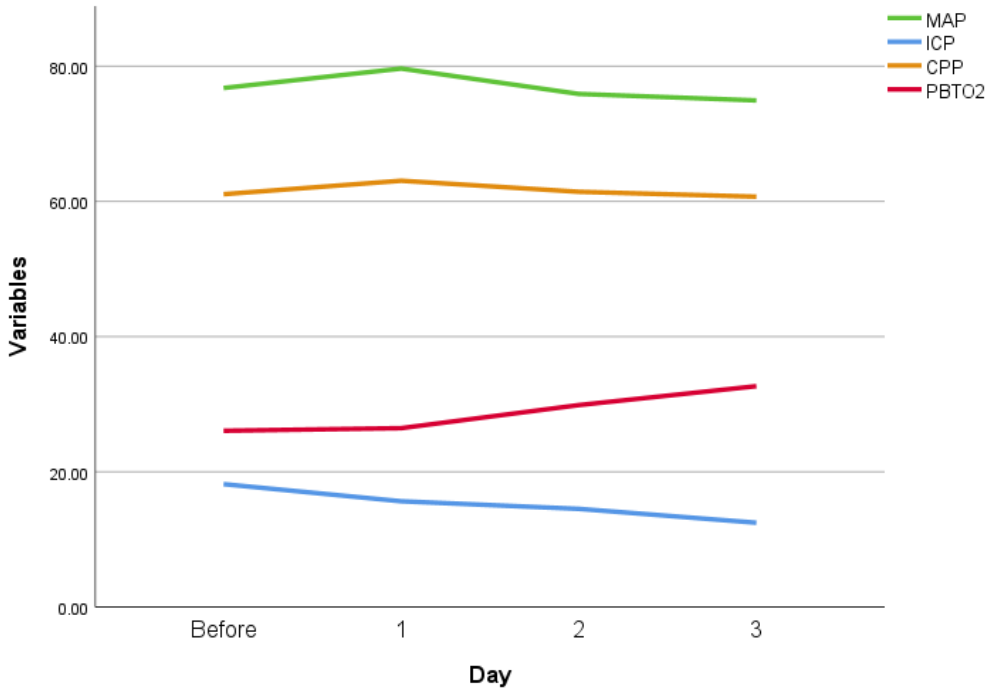


Graph 4 – Median decrease in CPP from 62.5mmHg to 61.8mmHg, (p = .104)

Temporal Analysis

A temporal analysis of the physiological parameters showed a maximal reduction in ICP over the first 2 days of thiopentone infusion, which stabilized within the first 72 hours of treatment. A similar pattern was seen for MAP and PbtO2 (Graph 5).

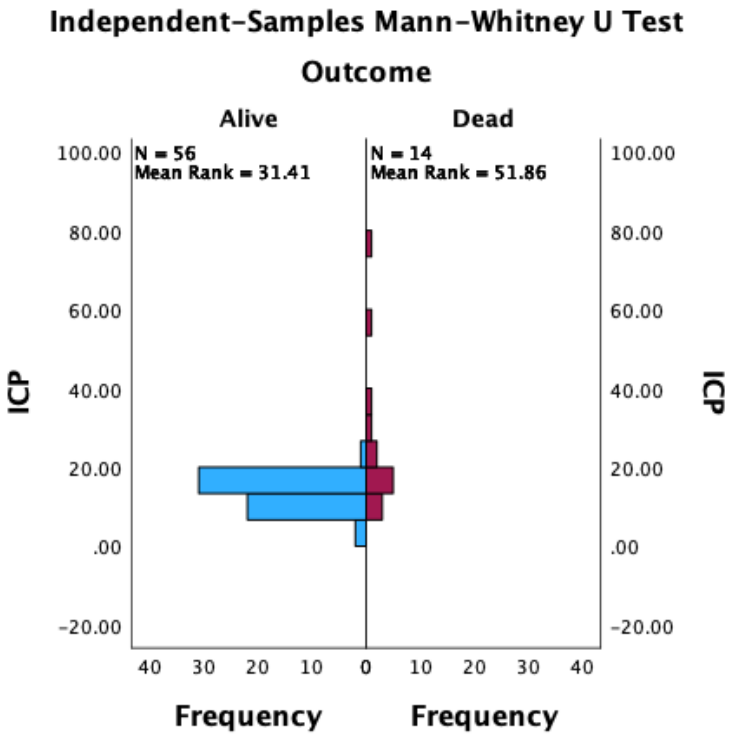
Graph 5. Temporal Profile of Physiological variables on Thiopentone



Correlation Analysis Results

When assessing the relationship that physiological variables had with outcome, only the median values before and during thiopentone infusion are detailed as follows. The Man Whitney U test revealed that the ICP was significantly lower in patients who survived (Md-13.8, n=56) than in patients who died (Md=17.3, n=14, U=621 ,Z=3.362) (P<0.00,1 r=0.4). No significant association was found between MAP, CPP and PbtO2 on outcome (Graph 6).

Graph 6. Man Whitney U test for Intracranial Pressure (ICP)



The **independent t-test** confirmed that there were no significant associations with outcome for MAP (p=0.1), CPP (p=0.06) and PbtO2 (p=0.07). (Table 3).

Table 3. Physiological variables in the alive and dead groups

Physiological variable	Mean (Alive)	Mean (Dead)	Standard deviation(SD) (Alive)	Standard Deviation (Dead)	Value of t	Significance value*p	Effect size Cohen's D
MAP	76	80.6	8.9	11	-1.18	0.1	-0.4
CPP	59	50	19.1	21	1.5	0.06	0.4
PBt02	29	21	10	17	1.5	0.07	0.5

*Levene's test showed the assumptions of homogeneity of variance were met for CPP, and not for MAP/PbtO2, the table shows results of the independent t-test

DISCUSSION

This study is the first large cohort study of thiopentone as a second-tier therapy for intracranial hypertension in paediatric TBI and the first to examine corresponding changes in physiological variables. Our results demonstrate a significant reduction in ICP and MAP following thiopentone administration, but maintenance of CPP and PbtO2. The effect sizes appeared most prominent after 48 hours of infusion: ICP (-3.88mmHg), MAP (-5.27mmHg) and PbtO2 (+6.4mmHg). In summary, the results show that there was a reduction in ICP that was adequate in most patients (only 12% of patients proceeded to require decompressive craniectomy), that the decrease in blood pressure was mitigated by the non-significant CPP and PbtO2 changes, and that overall mortality in a selected cohort of children with severe TBI requiring second-tier therapies was acceptable.

In terms of effectiveness, although 9 (12%) of the patients treated with thiopentone still required craniectomy, it is important also to note that conversely, 8 patients first had a craniectomy which failed to control ICP, necessitating thiopentone therapy thereafter. These results are useful to evaluate the relative value of using thiopentone as a second-tier therapy in children with TBI, but one would need to consider the impact also on probable increased duration of stay in the ICU and possible associated nosocomial infections (not evaluated in this study). These would have to be balanced against the complications typically associated with decompressive craniectomy. Further, additional analysis might identify patients who are more likely to fail thiopentone therapy.

Efficacy of Thiopentone vs Pentobarbital in the Management of MRICP

Of the two drugs, thiopentone appears to be somewhat more effective than pentobarbital at reducing ICP (10). The breakdown of thiopentone produces five metabolites, one of which is pentobarbital, with the remainder being inactive compounds (11). This may explain the slightly increased effectiveness of thiopentone in controlling ICP elevation as compared with pentobarbital. Significant complications with BCT have been reported, with the most prominent being systemic hypotension. Other complications include renal dysfunction, hepatic dysfunction, hypokalaemia, respiratory complications and infections (12)

Efficacy of Thiopentone in Reducing Intracranial Pressure

ICP was reduced on average by 4.3 mmHg ($p<0.001$) in patients on a thiopentone infusion. This reduction is consistent with previous studies that have demonstrated thiopentone's effectiveness in decreasing ICP, likely predominantly suppressing metabolism, decreasing metabolic demand, and reducing cerebral blood volume (13-17). Of course, effectiveness at ICP reduction is important in children, as in adults, because elevated ICP associates with poor neurological outcomes and increased mortality (18). Although the ICP reduction appears modest compared to typical ICP reductions after craniectomy, it is likely that this was sufficient to control ICP without needing craniectomy in most patients because there were fewer episodes of ICP elevated greater than an intervention threshold. As with all therapies, the reduction in ICP must be balanced against potential complications, including hypotension and other systemic complications (12). There were 13 patients who proceeded to refractory increased ICP that led to death, despite being on thiopentone. In 6 of these patients they developed refractory increased ICP despite having undergone a craniectomy also; 4 of these being after thiopentone had been started. In the remainder, it was likely that craniectomy was not considered for futility (on clinical and/or radiological grounds). In total, 9 patients underwent craniectomy after thiopentone, 4 of which developed refractory increased ICP despite surgery; therefore, the 5 survivors who had craniectomy after thiopentone, plus the 13 patients who died with refractory increased ICP, means that thiopentone failed to control increased ICP in 18 patients (24.3%).

Haemodynamic Compromise and Impact on MAP

While thiopentone effectively reduced ICP, it also reduced the MAP by 5.8 mmHg, from a median of 81.5 mmHg to 75.7 mmHg ($p < 0.001$), highlighting the previously reported blood pressure lowering effects of barbiturate therapy (6, 12). The balance between ICP control and haemodynamic stability is a well-known challenge in the management of severe TBI, given that this is a potential limitation of most, if not all sedative strategies. Although the median MAP reduction within our patient cohort was significant, the BP remained within clinically acceptable ranges for most patients. Thus, in cases where thiopentone use leads to significant MAP reduction, additional interventions, such as vasopressors, may be necessary to counteract the hypotensive effects while still achieving sufficient ICP control (2, 6, 12). Still, unless patients are hypotensive by formal definition, it is the CPP which is likely more important as a driver of brain perfusion. In this cohort, the reduction in ICP contributed to the maintenance of an adequate CPP; therefore, the reduction in MAP may be less clinically relevant. That said, it must be remembered that it is likely that blood pressure was actively

maintained at our centre, knowing the potential for thiopentone-induced hypotension, an important consideration when extrapolating these results to other centres.

Brain Tissue Oxygenation (PbtO2)

Despite the decreased MAP, the effect on PbtO2 was non-significant (p = 0.258). In fact, the median PbtO2 increased slightly (3 mmHg), rising from 26.4 mmHg to 29.4 mmHg. This lack of significant change could reflect several factors. First, it is possible that thiopentone's primary mechanism of action (reducing cerebral metabolic demands), may not directly translate into improvements in cerebral oxygenation, especially if the underlying pathology involves compromised cerebral perfusion or oxygen delivery, although if ICP is a diffusion-limiting factor this may be the case. If hyperaemia, for example, is driving increased ICP, then reducing MAP and ICP may not lead to improved oxygenation. Second, the heterogeneity of injury severity in our cohort may have contributed to the variable responses in PbtO2, with patients experiencing different degrees of ischaemic and metabolic injury at baseline. Given the limited change in PbtO2, future studies could focus on identifying subsets of paediatric patients with severe TBI who are most likely to benefit from thiopentone in terms of both ICP control and improvements in brain tissue oxygenation. At an individual level, where brain oxygenation is being monitored, the patient's clinical course can be directly monitored.

Outcome

The mortality rate of our patient cohort was 20.3%, which is consistent with previously reported *overall* outcomes in paediatric severe TBI cases (19, 20), despite this being a selected group. There are limited data in the literature regarding outcomes after treatment with thiopentone specifically. In this it is worth noting that this reflects outcome in a selected group of patients with refractory elevated ICP, not a general cohort of patients with severe TBI. One of the potential problems with thiopentone is that it may take some time before the sedative effects wear off after stopping the drug. Propofol is better in this regard, but is relatively-contraindicated for this indication in children. Patients remained intubated for almost 6 days after cessation of thiopentone. Furthermore, presumably because of the prolonged intubation, the tracheostomy rate was 20%. Fortunately, the tracheostomies all healed well with no major adverse complications, but this is an additional factor to consider.

Still, these are complicated patients by definition of the selection criteria. Ideally, their complication profile and outcomes should be compared to similar children treated with other second-tier therapies. Given the status of the ongoing discussion on this topic in adult TBI,

compounded by the difficulty in conducting clinical trials in children, it is uncertain that this will be subjected to a randomized controlled trial. It can also be argued that that direct comparison may not be worthwhile because ideal candidates for barbiturate therapy may be different from those who are ideal for craniectomy. Unfortunately no such clear criteria are published and clinical practice varies across different centres.

Decompressive Craniectomy

The timing of decompressive craniectomy, whether performed before or during thiopentone infusion, did not have any significant effect on the physiological variables (ICP, MAP, CPP and PbtO2), but the numbers are likely too small for meaningful analysis: 8 patients had craniectomy before thiopentone (of which 2 died and 6 had ICP control) and 9 patients had craniectomy after thiopentone (of which 4 died, 3 with refractory ICP). While decompressive craniectomy has been shown to be effective in reducing ICP (21, 22), like any therapy the effectiveness at changing a variable of interest must be balanced against the risk of the procedure. Compared with thiopentone, it is reasonable to assume that craniectomy would likely result in greater reductions in ICP (which may or may not be clinically relevant) and possibly shorter stays in ICU. This would have to be balanced against the known risks, including the need for further surgery (cranioplasty), wound infection rates (with potential bone flap loss), cerebral blood flow changes beneath the craniectomised area, syndrome of the 'trephined', and poor cosmetic results. At our centre, we do not consider this to be an either/or decision, but rather a decision about which patients would benefit from either strategy. In this regard, practice varies considerably across the world.

Limitations

This is a retrospective study and so is subject to all the limitations of retrospective work, including incomplete data and lack of clarity about indications for interventions, not being subject to prospectively defined criteria and depending on potentially variable clinician decisions. Although the strength of the study is the availability of high frequency data, this was not available in all patients. That said, most studies in the past have used charted data. Some discrepancies may result from using both charted and high frequency data, although there did not appear to be a significant difference between the groups. Direct comparison could not be made with the other commonly employed second-tier therapies such as decompressive craniectomy, because of selection differences for the interventions. Finally, we did not have data on nosocomial sepsis; however, final outcome measures such as length of stay in ICU

and mortality likely reflect the cumulative adverse outcomes and failure of therapy in these patients.

CONCLUSION

This is the largest study to analyze barbiturate therapy in children with severe TBI. We demonstrated a reduction in ICP without significantly compromising CPP and PbtO2. In our experience, the risk of haemodynamic compromise was not significant, although this might be because of interventions in anticipation of a decrease in blood pressure. Despite this being a selected group of patients on second-tier therapies, the mortality rate was acceptable, but in about 24% of patients thiopentone did not control increased ICP. Thiopentone use may avoid the surgical morbidity of DC, but possibly at the expense of longer duration of ventilation and ICU stay. Direct comparison with decompressive craniectomy cannot be made from this data. Further research is needed to explore the long-term outcomes and improve selection criteria for second-tier therapies in paediatric TBI.

Author Contributions

All authors contributed to data collection and/or analysis, had access to the database, and assisted with the preparation of the research paper.

Declaration of conflict of interest

None

Funding

None

References

1. Menon D, Ercole A. Critical care management of traumatic brain injury. Handbook of clinical neurology. 2017;140:239-74.

2. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the management of paediatric severe traumatic brain injury: update of the brain trauma foundation guidelines. Paediatric Critical Care Medicine. 2019;20(3S):S1-S82.

3. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury. Neurosurgery. 2017;80(1):6-15.

4. Hawryluk GW, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive care medicine. 2019;45:1783-94.

5. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. XI. Anesthetics, analgesics, and sedatives. Journal of neurotrauma. 2007;24(Supplement 1):S-71-S-6.

6. Kasoff SS, Lansen TA, Holder D, San Filippo J. Aggressive physiologic monitoring of paediatric head trauma patients with elevated intracranial pressure. Paediatric Neurosurgery. 1988;14(5):241-9.

7. Kochanek, P., Tasker, R., Tasker, R., Bell, M., Adelson, P., Carney, N., Vavilala, M., Selden, N., Bratton, S., Grant, G., Kissoon, N., Reuter-Rice, K., & Wainwright, M. (2019). Management of Pediatric Severe Traumatic Brain Injury: 2019 Consensus and Guidelines-Based Algorithm for First and Second Tier Therapies. *Pediatric Critical Care Medicine*, 20, 269–279

8. Figaji, A., Fieggen, A., Argent, A., Leroux, P., & Peter, J. (2008). Does adherence to treatment targets in children with severe traumatic brain injury avoid brain hypoxia? A brain tissue oxygenation study.. *Neurosurgery*, 63 1, 83-91; discussion 91-2 .

9. Rohlwink, U., Zwane, E., Fieggen, A., Argent, A., Roux, P., & Figaji, A. (2012). The relationship between intracranial pressure and brain oxygenation in children with severe traumatic brain injury.. *Neurosurgery*, 70 5, 1220-30; discussion 1231 .

10. Stover JF, Pleines UE, Morganti-Kossmann MC, Stocker R, Kossmann T. Thiopental attenuates energetic impairment but fails to normalize cerebrospinal fluid glutamate in brain-injured patients. Critical care medicine. 1999;27(7):1351-7.

11. Pérez-Bárcena J, Llompart-Pou JA, Homar J, Abadal JM, Raurich JM, Frontera G, et al. Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial. Critical Care. 2008;12:1-10.

12. Schalen W, Messeter K, Nordström CH. Complications and side effects during thiopentone therapy in patients with severe head injuries. Acta anaesthesiologica scandinavica. 1992;36(4):369-77.

13. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. XI. Anesthetics, analgesics, and sedatives. Journal of neurotrauma. 2007;24(Supplement 1):S-71-S-6.

14. Stover JF, Pleines UE, Morganti-Kossmann MC, Stocker R, Kossmann T. Thiopental attenuates energetic impairment but fails to normalize cerebrospinal fluid glutamate in brain-injured patients. Critical care medicine. 1999;27(7):1351-7.

15. Pérez-Bárcena J, Llompart-Pou JA, Homar J, Abadal JM, Raurich JM, Frontera G, et al. Pentobarbital versus thiopental in the treatment of refractory intracranial hypertension in patients with traumatic brain injury: a randomized controlled trial. Critical Care. 2008;12(4):1-10.

16. Velle F, Lewén A, Howells T, Enblad P, Nilsson P. Temporal effects of barbiturate coma on intracranial pressure and compensatory reserve in children with traumatic brain injury. Acta Neurochir (Wien). 2021;163(2):489-98

17. Velle F, Lewén A, Howells T, Nilsson P, Enblad P. Intracranial pressure-based barbiturate coma treatment in children with refractory intracranial hypertension due to traumatic brain injury. J Neurosurg Pediatr. 2020;25(4):375-83

18. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. Journal of neurosurgery. 1991;75(Supplement):S59-S66.

19. Chen, C., Chen, C., Chen, C., Hsieh, Y., Chung, C., & Liao, C. (2021). Predictors of In-Hospital Mortality for School-Aged Children with Severe Traumatic Brain Injury. *Brain Sciences*, 11.

20. Melo, J., Rocco, F., Blanot, S., Oliveira-Filho, J., Roujeau, T., Sainte-Rose, C., Duracher, C., Vecchione, A., Meyer, P., & Zérah, M. (2010). Mortality in Children With Severe Head Trauma: Predictive Factors and Proposal for a New Predictive Scale. *Neurosurgery*, 67, 1542-1547.

21. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive craniectomy in diffuse traumatic brain injury. New England Journal of Medicine. 2011;364(16):1493-502.

22. Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. New England Journal of Medicine. 2016;375(12):1119-30.

APPENDICES

APPENDIX A. MANAGEMENT ALGORITHM FOR CHILDREN WITH SEVERE TBI [7]

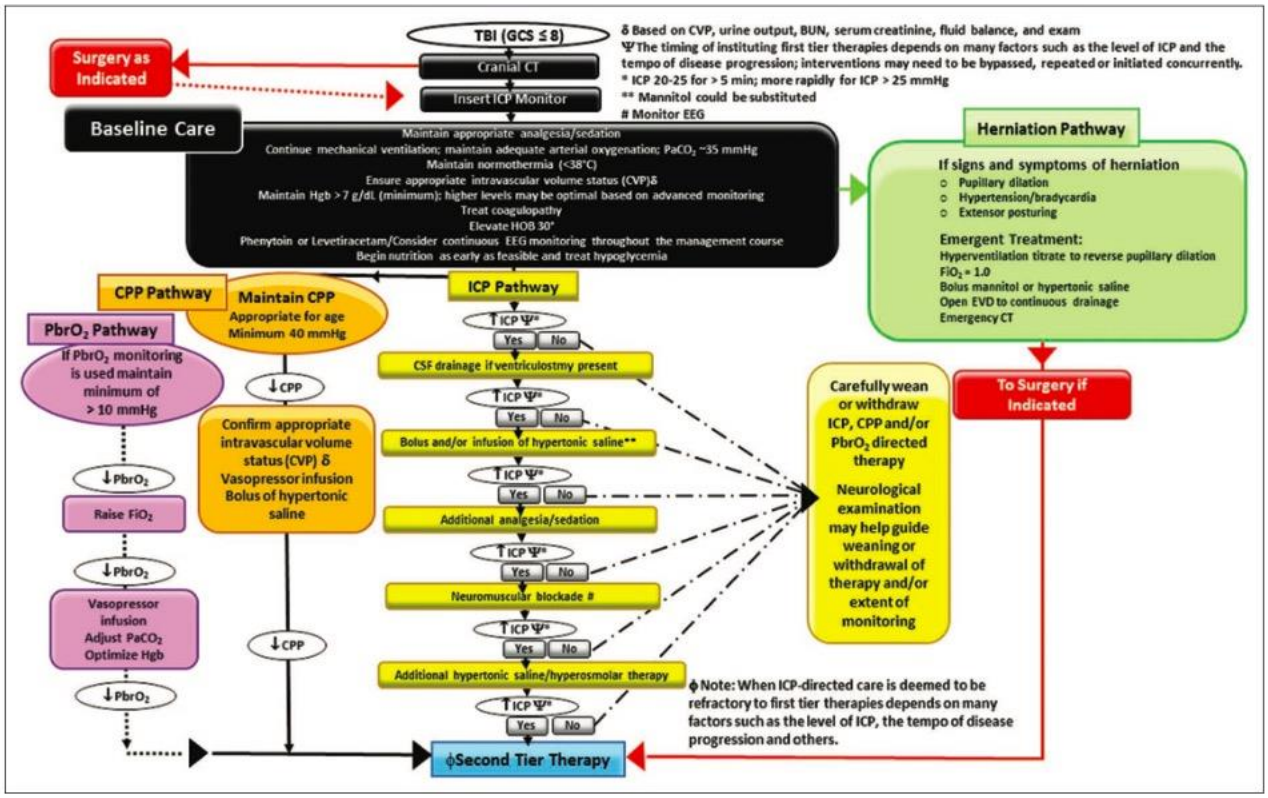


Figure 1. Evidence- and consensus-based algorithm of first tier therapies for the management of severe traumatic brain injury (TBI) in infants, children, and adolescents. The algorithm includes several components including Baseline Care (*black*), an Intracranial Pressure (ICP) Pathway (*yellow*), a Herniation Pathway (*green*), a Cerebral Perfusion Pressure (CPP) Pathway (*orange*), and a Brain Tissue Partial Pressure of Oxygen ($Pbro_2$) Pathway (*pink*). *Solid lines* identify the ICP and CPP pathways, reflecting their primary role, a *dashed line* identifies the $Pbro_2$ pathway given the fact that it represents a monitoring and management option that is less commonly used and has less literature support. A *dotted plus dashed line* identifies the weaning or withdrawal of the various interventions. As indicated in the text, the treating practitioner should integrate all of the available information and implement the Guidelines within the context of each patient's unique response to various therapies to craft the most optimal treatment regimen. In addition, although a linear approach in each pathway is provided, variations in "tempo" and timing during which therapies are implemented or weaned/withdrawn will depend on each given clinical context. For example, in some situations, a single intervention for raised ICP may suffice, whereas in others, multiple simultaneous interventions may be required. The approach will often need to be individualized to the patient's needs. If baseline care is insufficient to control intracranial pressure, then progression down the ICP and CPP pathways is indicated (*solid black line*). The *blue box* indicates the need for second tier therapy and represents the link to Figure 2. Please see text for details. BUN = blood urea nitrogen, CVP = central venous pressure, EEG = electroencephalogram, EVD = external ventricular drain, GCS = Glasgow Coma Scale, Fio_2 = fraction of inspired oxygen, Hgb = hemoglobin, HOB = head of bed.

APPENDIX B. INSTRUCTIONS FOR AUTHORS

CHILD'S NERVOUS SYSTEM ARTICLE SUBMISSION FORMAT:

Instructions for Authors

ORIGINAL RESEARCH ARTICLES

Original research papers report the results of laboratory or clinical studies and they should present original observations. The text should be arranged as follows: **structured Abstract** (and up to 4 keywords, excluding terms already present in the title), **Introduction, Methods, Results, and Discussion**. Original articles normally should not exceed 3,000 words, not be signed by more than 8 authors, not include more than 6-8 illustrations and tables, while references should be limited to 50 (exceptions at the discretion of the Editor in Chief) The authors number can exceed 8 in case of multicentre studies.

Raimondi Award papers: Original research articles meant at competing for the Raimondi Award should be accompanied by a specific letter to the Editor. They should be accepted for publication at least three months prior to the ISPN Annual Scientific Meeting.

REFERENCES

1. https://link.springer.com/journal/381/submission-guidelines#Instructions%20for%20Authors_Types%20of%20papers

---

APPENDIX C. ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

11 August 2022

HREC REF: 499/2022

Prof A Figaji
Department of Neurosurgery
Red Cross War Memorial Children's Hospital
Email: Anthony.figaji@uct.ac.za
Student: appand002@gmail.com

Dear Prof Figaji

PROJECT TITLE : THE EPIDEMIOLOGICAL PROFILE OF CHILDREN WITH SEVERE TRAUMATIC BRAIN INJURY: A SINGLE-CENTER ANALYSIS-MMED CANDIDATE-DR ANDREW APPIAH-BAIDEN

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Andrew Appiah-Baiden will also be involved in this study

Please quote the HREC REF 499/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC.REF499.2022

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC.REF499.2022

APPENDIX D. ABSTRACT ONLY PUBLICATION STATEMENT (INTS)

Dear Dr Andrew Appiah-Baiden

Please find attached The International Neurotrauma Society (INTS 2024) slide template should you wish to use it in preparation for your talk(s) detailed below.

Oral Presentations

Title	The Impact of Barbiturate Therapy in Children with Severe TBI
Paper Reference	O006
Paper Status	Accepted for Oral (Top Scoring Abstract)
Session Details	**Plenary 2: GCS at 50** Corn Exchange Tuesday, Sep 3, 2024 9:00 AM - 10:45 AM Corn Exchange
Presentation Time	10:35 AM - 10:45 AM
Presenting Author	Dr Andrew Appiah-Baiden

Permission to publish
Please note: by presenting at INTS 2024 you are agreeing for you abstract(s) to be published in a conference supplement of the Journal of Neurotrauma. If you do not wish your abstract(s) to be published please email ints2024@opening-doors.org.uk.

If you have any queries please don't hesitate to contact us.

We look forward to welcoming you to Cambridge.

Best wishes

Celia and Rose
INTS 2024 Conference Office

E: INTS2024@opening-doors.org.uk
T: +44 (0)1562 731788
Conference Website

ID 654