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THE PREVALENCE OF HYPOTENSION AND HYPOXAEAMIA IN THE
PREHOSPITAL SETTING OF TRAUMATIC BRAIN INJURY IN JOHANNESBURG,
GAUTENG

By

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STSWIL001

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Faculty of Health Sciences

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# TABLE OF CONTENTS

## PART A: DISSERTATION

1. DECLARATION .................................................................................................................. 1
2. ABSTRACT .......................................................................................................................... 2
3. BACKGROUND ................................................................................................................... 3
4. LITERATURE REVIEW ....................................................................................................... 3
   a. Introduction and Classification of Traumatic Brain Injury ........................................... 3
   b. Search strategy ............................................................................................................... 4
   c. Epidemiology .................................................................................................................. 4
   d. Primary vs. Secondary Brain Injury and factors that affect mortality ......................... 8
   e. Hypotension ................................................................................................................... 11
   f. Hypoxaemia ................................................................................................................... 13
   g. The Role of Prehospital Care in Traumatic Brain Injury ............................................ 21
   h. Summary and Conclusion ............................................................................................ 23
5. METHODS ......................................................................................................................... 25
   a. Aim and Objectives ........................................................................................................ 25
   b. Study Design and Methods ............................................................................................ 25
   c. Data Management and Analysis ................................................................................... 26
6. RESULTS ........................................................................................................................... 28
   a. Sample Size and Quality of Data .................................................................................. 28
   b. Demographics ................................................................................................................. 29
   c. Hypotension and Hypoxaemia ....................................................................................... 32
   d. Hypotension, Hypoxaemia and Concomitant Injuries ................................................ 34
   e. Trends in Prehospital Treatment .................................................................................. 35
7. DISCUSSION ....................................................................................................................... 38
   a. Demographics ............................................................................................................... 38
   b. Hypotension .................................................................................................................... 39
   c. Hypoxaemia .................................................................................................................... 40
8. LIMITATIONS ..................................................................................................................... 42
   a. Bias ................................................................................................................................. 42
   b. Quality of Data .............................................................................................................. 43
   c. Limitations in methodology ......................................................................................... 43
   d. Validity ............................................................................................................................ 43
9. RECOMMENDATIONS ....................................................................................................... 44
10. CONCLUSION .................................................................................................................... 45
11. BIBLIOGRAPHY ............................................................................................................... 46
12. APPENDIX A: SEARCH STRATEGY .................................................................................. 50

## PART B: ADDENDA FOR UNIVERSITY PURPOSES

1. ORIGNAL PROTOCOL ......................................................................................................... 51
2. DATA CAPTURE SHEET ..................................................................................................... 63
3. NONDISCLOSURE AGREEMENTS OF DATA CAPTURERS .............................................. 64
4. INSTITUTIONAL CONSENT ......................................................................................................... 66
5. SURGICAL DRC-APPROVAL ........................................................................................................ 68
6. ETHICAL APPROVAL ................................................................................................................... 69
7. ACKNOWLEDGEMENTS ............................................................................................................. 70

**TABLES AND FIGURES**

Table 1: Summary Table – TBI epidemiology around the world ............................................................ 5
Table 2: Evidence Table – Hypotension and Traumatic Brain Injury ................................................... 18
Table 3: Evidence Table – Hypoxaemia and Traumatic Brain Injury ................................................... 20
Table 4: Number of patients with hypotension and injuries and those without .................................... 34
Table 5: Number of patients with hypoxaemia and injuries and those without .................................... 34

Figure 1: Tracking profile of record exclusion ....................................................................................... 28
Figure 2: Sample gender distribution .................................................................................................... 29
Figure 3: Sample race distribution ....................................................................................................... 29
Figure 4: Sample Glasgow Coma Scores (GCS) .................................................................................... 30
Figure 5: Sample mechanism of injury distribution .............................................................................. 30
Figure 6: Mode of transport to hospital ................................................................................................. 31
Figure 7: Prevalence of concomitant injuries with TBI ........................................................................ 31
Figure 8: Sample systolic blood pressure (SBP) values ........................................................................ 32
Figure 9: Sample Pulse-oximetry values .............................................................................................. 33
Figure 10: Prevalence of hypoxaemia, hypotension or both ................................................................ 33
Figure 11: Prehospital airway management .......................................................................................... 35
Figure 12: Means of prehospital intubation .......................................................................................... 35
Figure 13: Total prehospital Morphine dosages administered ............................................................ 36
Figure 14: Total prehospital Midazolam dosages administered ........................................................... 36
Figure 15: Total prehospital fluid volumes infused .............................................................................. 37
PART A: DISSERTATION

1. DECLARATION

MPhil (Emergency Medicine)
2012

DECLARATION

Name: Willem Stassen

THE PREVALENCE OF HYPOTENSION AND HYPOXAEMIA IN THE PREHOSPITAL SETTING OF TRAUMATIC BRAIN INJURY IN JOHANNESBURG, GAUTENG

1. I know that plagiarism is wrong. Plagiarism is to use another’s work and pretend that it is one’s own.

2. I have used the Vancouver convention for citation and referencing. Each contribution to, and quotation in, this essay/report/project from the work(s) of other people has been attributed, and has been cited and referenced.

3. This dissertation is my own work.

4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

Signature: 

Date: 29/01/2013
2. ABSTRACT

Introduction: Prehospital hypotension and hypoxaemia have been found to adversely affect the outcome of patients who have sustained a traumatic brain injury (TBI). This study aimed at determining the prevalence of prehospital hypotension and hypoxaemia in Johannesburg, Gauteng among patients who sustained a moderate to severe TBI.

Methods: A retrospective cross-sectional descriptive (chart review) design was used. Patient report forms were obtained from two institutions by searching for ICD 10 codes that denote “Injuries to the head”, for any mechanisms of injury that might lead to a TBI and hand-searching through helicopter case sheets. Results were limited to primary, adult patients with a GCS of 13/15 or less who sustained their injury between 1 January and 31 December 2011.

Results: A total of 299 patient records were identified, 66 were eligible for analysis. The mean age of the sample was 33.59 (± 10.95) years and the male/female ratio were 2.9:1. 51% (n=33) of patients were black, 20% (n=14) were white, while a single patient (2%) was Indian. 27% (n=18) of the sample did not have any racial data available for comment. The average lowest SBP was 106.7mmHg (±34.8mmHg) while the average lowest SpO\textsubscript{2} was 89.65 (±18.42%). The prevalence of prehospital hypotension and hypoxaemia were 33.3% (n=22) and 43.9% (n=29) respectively while 21.2% (n=14) had double insults suffering both hypotension and hypoxaemia. Hypotension and hypoxaemia was associated with haemorrhage (p = 0.011) and chest injuries (p = 0.001).

Conclusion: The prevalence of hypotension in this study was similar to that observed in international studies but the prevalence of hypoxaemia was much higher in the current sample (possibly due to a variance of case definition for hypoxaemia). This has significant implications on the current practice of monitoring and action in response to hypoxaemia in the prehospital setting.
3. BACKGROUND
Following a Traumatic Brain Injury (TBI), any minor insult may be detrimental to patient outcome. The brain is particularly susceptible to these insults in the acute phase immediately post-injury. Hypotension and hypoxaemia have been associated with increased mortality in patients who have sustained moderate and severe TBI and many of these patients have sustained trauma to other body systems that might precipitate secondary insults. Patients are particularly prone to these insults in the acute phase of their care and the cerebral tissue is especially vulnerable to hypotension and hypoxaemia in the time immediately following a TBI. Prehospital care is therefore essential in order to prevent these insults and improve morbidity and mortality in an economically active population so that these individuals can recover fully and return to being tax paying citizens. However, the prevalence of hypotension and hypoxaemia in the prehospital environment of Johannesburg was largely still unknown prior to this study.

This study was aimed at determining the prevalence of hypotension and hypoxaemia in this acute, prehospital phase and to describe the demographic profile of patients who have sustained TBIs in Johannesburg, Gauteng.

4. LITERATURE REVIEW

a. Introduction and Classification of Traumatic Brain Injury
Traumatic Brain Injury (TBI) is a term used to describe any injury of the intracranial structures and cerebral parenchyma that might result from trauma to the head. Included in this definition is the cascade of pathophysiological events that lead to progressive worsening of the initial injury such as intracranial haemorrhage and cerebral oedema. (1) An injury like this may result in altered brain function and could present as confusion, altered consciousness, coma, convulsions and focal neurology. (2) TBI should not be confused with that of “Head Injury” which is a blanket term used to describe any injury to the head and includes soft tissue and skeletal injuries with TBI. (2) Injury can result from blunt or inertial forces (as with road traffic collisions) to the head or from penetrating forces such as gunshot and stab wounds. (1)

TBI might be classified by severity at initial presentation by applying the Glasgow Coma Scale (GCS). Three categories are identifiable using this scale namely, minor head injury (GCS 14-15), moderate head injury (GCS 9-13) and severe head injury (GCS ≤ 8). (1) This classification is commonly known, easy to use by a wide variety of healthcare providers and has been assessed and validated in the use of gauging the severity of head injuries. For these reasons it is commonly applied in the prehospital environment. (3,4) Yet, this scale is not without limitations. (5) Firstly, the method of painful stimulus application might falsely lower the GCS by not eliciting a response; secondly, the addition of sedation and paralysis and other clinical factors such as ocular injuries might also affect the GCS score. (5) One
study did not find a clinical significant impact of blood alcohol level and GCS in patients with a TBI. (6) A final limitation of the GCS is that of scoring an intubated patient. (5) Disparities between the assignment of values for these patients have been seen between trauma facilities and might make interpretation of the literature difficult. (7)

The discussions that follow will only focus on the moderate to severe population of TBI (accounting for approximately 20% of all TBI (1)), as this is the population where early aggressive management in the prehospital phase might have the greatest impact on eventual outcome (8,9) and will review key concepts currently trending in the literature relating to TBI management principles.

b. Search strategy
A PubMed search was conducted on 17 August 2012. The following Medical Subject Headings (MeSH) were used in multiple permutations to refine the search: “Brain Injuries”, “South Africa”, “Emergency Medical Services”, “Hypotension” and “Hypoxia, Brain”. Searches were limited to English studies among humans conducted in any country and to the following study designs: Clinical trials, guidelines, randomised controlled trials, systematic review articles and meta-analyses. The publication period was limited to articles published between 2000 and 2012 in order to include only the most recent studies. All abstracts were included for relevance at face value and revised later on detailed screening. Paediatric studies (inclusion of patients under the age of 18) were also excluded during abstract screening. Any articles deemed relevant were reviewed in full text and cited accordingly. References of pertinent articles were finally examined for additional resources not included in the online search. The full search strategy is shown in the appendix.

c. Epidemiology
As estimated in 2009, each year an approximate 89 000 new cases of head injury (of any severity) are reported in South Africa (180/100 000), according to the National Institute for Occupational Health. (10) Of these cases, 50% are due to road accidents (bicycle, vehicle or pedestrian), 25% are due to falls and a further 25% are due to violence. (10)

However, determining the true extent of TBI is difficult because of a wide heterogeneity in studies with regards to methods, study population and demographics of patients. (2) The biggest methodological error in these studies is the inclusion of only patients who were admitted and the exclusion of patient who died out-of-hospital or those who never sought medical advice. This will result in an underestimation of the overall incidence and that of milder TBI and an overestimation of severe (requiring admission) TBI. (2) Table 1 summarises the epidemiologic data.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Country and Year of Origin</th>
<th>Incidence cited (1/100,000)</th>
<th>Methodological Flaws</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang, (12)</td>
<td>China, 1982</td>
<td>56</td>
<td>All deaths were excluded.</td>
</tr>
<tr>
<td>Tiret, (13)</td>
<td>France, 1986</td>
<td>280</td>
<td>Head injuries other than TBI were included</td>
</tr>
<tr>
<td>Guerrero, (14)</td>
<td>United States of America, 1995</td>
<td>392</td>
<td>All prehospital and EC deaths were excluded</td>
</tr>
<tr>
<td>Meerhoff, (15)</td>
<td>Netherlands, 1997</td>
<td>217</td>
<td></td>
</tr>
<tr>
<td>Corrigan, (16)</td>
<td>International Review, 2010</td>
<td>America: 506.4, Finland: 118, New Zealand: 1100 - 2360/100,000</td>
<td>Search strategy not defined, Heterogeneity not mentioned</td>
</tr>
<tr>
<td>Brown, (17)</td>
<td>South Africa, 1986-1987</td>
<td>316</td>
<td>All prehospital and EC deaths were excluded, Alternative classification of TBI severity</td>
</tr>
</tbody>
</table>

Table 1: Summary Table – TBI epidemiology around the world
A 2003 review study included 10 epidemiological studies that investigated the incidence of TBI in a variety of different settings across the world. This study is however dated, with much of the data originating in the late 80’s and early 90’s. A South African study from the 90’s was also cited - newer studies of this kind could not be found. (2)

A telephonic survey conducted among Americans investigated reported evidence of TBI. They estimated the incidence to be 825/100 000 population between 1977 and 1981. (11) In contrast a Chinese study conducted in 1982 paints a whole different picture and reports an annual incidence of 56/100 000. (12) This massive difference in incidence might be related to the different transport conditions in China at that time but is probably a product of inappropriate sampling techniques (only TBI cases that presented to an EC was included and all deaths were excluded). (12) A 1986 French study that included all prehospital deaths within the sample suggested the incidence to be 280/100 000. (13) However, non-TBI head injuries were also sampled and might have falsely inflated the incidence. (2,13) A second American study published in 1995 showed a decrease in the incidence from the 1981 findings to 392/100 000. (14) Worth mentioning however, is that the incidence might have been underestimated in this study as all prehospital and EC deaths were excluded from the sample. (14) A Dutch study that investigated the incidence of Head Injury estimated the incidence of TBI to be 217/100 000 in 1997. (15) A South African study will be discussed in a later section.

Another review article published in 2010 cites more recent statistics. One of the major drawbacks in this study is the lack of detail on the search strategy. (16) This raises questions on the accuracy of the presented results. (16) The overall incidence of TBI in the United States is estimated at 506.4/100 000, 118/100 000 for Northern Finland and a much higher incidence in New Zealand at 1100-2360/100 000. (16) The most plausible reason for these discrepancies in the epidemiology is related to heterogeneity in methods and not as a result of variance in population or geographic factors. Notably, one study estimates the incidence of TBI in South Africa to be 1.5-3.5 times higher than the global rate. (18) It is suggested that this is due to higher rates of road-traffic collisions in developing countries. (16)

A South African prospective study published in 1991 identified 1181 cases of TBI within Johannesburg between 1986 and 1987. (17) Patients who were admitted to 5 public hospitals and 3 private hospitals with confirmed or suspected TBI were included in the study if they were residents of Johannesburg for at least 3 months prior to the injury occurring. TBI was defined as cerebral contusion or laceration with or without loss of consciousness or coma and amnesia directly attributable to trauma. Patients with skull fractures, cranial nerve injuries, traumatic complications and nervous system or endocrine diseases were included if unconsciousness, seizures, headache, vomiting or cerebrospinal fluid rhinorrhoea occurred within 5 days of admission or history of trauma. Patients were excluded if they were not from
Johannesburg or if demographic data were unavailable. (17) Prehospital and Emergency Centre deaths were not included in the sample which might lead to underestimation of incidence. (2,17) Exclusion left the incident sample eligible for analysis at 599 and reports the overall incidence of TBI in this time at 316/100 000. Mild TBI accounted for 87.5% of cases, moderate for 7.9% and severe TBI for 4.6% of cases. Worth mentioning however is a difference in the GCS classification of severity in this study. Mild was described as a GCS of 13-15, moderate 7-12 and a GCS of 6 or less denoted a severe TBI. (19)

The severity distribution reported in international studies is comparable to those recorded in the Johannesburg-based study and loosely denotes 80% of cases as mild and 10% as moderate and severe respectively. (2,17,19) Large differences in the classification methods between studies complicate comparison of findings.

Further subclass analysis in the Johannesburg study reveals that the incidence in Black males was higher (581.69) when compared to Whites (224.07). In a pre-liberation Johannesburg, the distribution of race-specific designation between hospitals would bias these results and make subclass analysis difficult. The researchers did however, take this into account and allowed for statistical correction of these differences by using a relative standard error instead of 95% confidence intervals that was based on each hospital’s race designation. This might allow for comparison of subclasses at the same standard errors despite differences in sample size. (17) The RSE for Blacks and Whites were 1.31 and 3.30 respectively. (19) The highest risk group by age was 24-44 year olds (408.79/100 000; RSE: 2.11) and the male to female ratio for TBI was 4.8:1. (19) This is different to other studies that report male-female ratios of 1.5-2.8:1. (2)

When considering the aetiology of TBI in South Africa the majority (42.7%) of cases were due to road traffic collisions (RTCs) followed by interpersonal violence at 36.4%, suicide (6%), railway accidents at 5.85% and falls at 5.6%. (19) Comparably, international studies show similar representation of RTCs but much lower rates for interpersonal violence. (2) These differences can be attributed to the milieu in which these injuries occur. (2) In San Diego 50% of TBI was attributable to traffic incidents, 20% to falls and 10% to sports activities. (20) Similarly in Australia RTCs accounted for 40% of all TBIs while falls and recreational incidents denoted 21% and 25% respectively. (2) A Chinese study attributes 30% of TBIs to RTCs, 24% to occupational accidents, 22% to falls and 16% to recreational or sporting activities. (12) 2006 data from the United States identify falls (28%) as the leading aetiology in TBI followed by RTCs (20%), objects impacting the head (19%) and assault (11%). (16) Finally, in France RTCs account for 60% of TBI and falls for 33%. (13)
The incidence of TBI seems to range from as low as 56/100 000 to as high as 2360/100 000. These discrepancies between studies are a product of huge heterogeneity between methodology and definitions of TBI – resulting in conflicting inclusion and exclusion criteria. Many studies excluded prehospital and EC fatalities, while others only studied cases that were admitted. An overestimation of severe TBI and an underestimation of mild TBI might result. Uniformity between studies should be sought in order to get a global picture of TBI incidence that is comparable between countries and states. Whatever the extent, TBI places a massive burden on society by being the largest contributor to post-trauma morbidity. When considering that the highest incidence of head trauma is in the economically active population, this burden becomes even more pronounced as disability or death would have far-reaching consequences for the families affected and loss of macro-economic growth. Lifetime care and social and fiscal support and rehabilitation for these patients might be exorbitant. (1,16)

d. Primary vs. Secondary Brain Injury and factors that affect mortality

The brain is a semisolid organ that is encapsulated by a rigid skeletal cranial vault and is suspended in cerebrospinal fluid. The brain has an exceptionally high metabolic demand and enjoys 20% of total body oxygen consumption and 15% of the total cardiac output. In order to ensure uninterrupted supply to this high demand, cerebral perfusion pressure (CPP) is maintained by means of autoregulation (the automatic control of cerebral blood flow by constriction or dilation of the cerebral blood vessels in response to changes in CPP). (1,21) CPP in turn is determined by mean arterial pressure (MAP) and intracranial pressure (ICP). This relationship may be illustrated by the equation:

$$\text{CPP} = \text{MAP} - \text{ICP}.$$  

Autoregulation is able to function in a MAP range of between 50 and 150mmHg yet numerous external stimuli may affect autoregulation and CPP. Hypertension, alkalosis and hypocapnoea lead to cerebral vasoconstriction while cerebral vasodilation results from hypotension, acidosis and hypercapnoea. Autoregulation is also often disrupted directly after a TBI. (1,21,22)

Another factor that affects CPP is ICP. Total ICP is a product of the volume of the intracranial contents (blood, cerebrospinal fluid and brain tissue). This relationship may be illustrated by the Monro-Kellie Doctrine that states: should the volume of any of the intracranial contents increase, the other contents will have to compensate to return the state to volume equilibrium and maintain a normal ICP. This compensation will only occur up to a critical point, after which the ICP will increase, the adult cranium being rigid. In TBI this volume equilibrium may be altered by intracranial haemorrhage or cerebral oedema. (1,21,22)

Primary brain injury refers to the initial insult that the brain is subjected to in TBI as a result of the mechanical forces that act on the cerebral structures. These forces result in shearing,
tearing and compression of the intracranial structures and cause focal injury to axonal and vascular tissues. These injuries cannot be reversed or treated by any therapy of surgical intervention and the mainstay of acute management in TBI is therefore aimed at preserving the CPP despite failure of autoregulatory mechanisms. (1,23) Physical disruption of neural cell membranes, ionic homeostasis and increased permeability of cell membranes may result. A cascade of neurotoxic events ensues and culminates in neuronal swelling and hypoperfusion. (21,23)

Secondary brain injury is further injury to the brain that occurs from the physiological sequelae of the primary injury. (1,23,21) Following a TBI excitatory amino-acids are released, which are associated with an influx of calcium into the neural tissue. Excessive intracellular calcium concentrations promote oxygen radical reactions that in turn produce and release nitric oxide. Nitric oxide release stimulates excitatory amino-acid release and the cycle perpetuates. Widespread neuronal necrosis and apoptosis result. (21,24) This pathological cascade may be mediated by secondary insults that have been shown to significantly increase mortality and will be discussed briefly in the paragraphs that follow. (1,21,22) Cerebral hypoperfusion (hypotension), hypoxaemia, hypercapnoea and hypocapnoea, hyperthermia, hyperglycaemia and raised intracranial pressure are all factors that can lead to secondary brain injury. (1,21,22) Unfortunately, little can be done to minimise the devastation of the primary injury and all efforts are therefore directed at controlling the mechanisms that cause secondary brain insults. (23) Hypotension and hypoxemia will both be discussed in a separate section that follows.

Intracranial Hypertension
Cerebral oedema and intracranial haemorrhage all contribute significantly to increasing ICP and thereby lowering CPP. (1,22,25) As a consequence, management of ICP is essential in the treatment of patients with suspected TBI. There are pharmacological and non-pharmacological measures that can be taken to limit increasing ICP and prevent cerebral herniation. Some of these measures will be discussed shortly and the level of evidence (LOE) that supports these practices is provided in brackets. LOE was determined using the United States Preventive Services Task Force classification criteria.

To aid in gravitational cerebral venous return, patients with suspected head injury should be transported and nursed at a 15-30° angle (LOE II). (26) Another effort to prevent cerebral venous congestion is to avoid tight-fitting neck collars or endotracheal securing devices around the jugular veins (LOE III). (26) This will ensure that the jugular veins remain non-occluded, allowing for free blood drainage. (22)

Mannitol (LOE II) (27) and hypertonic saline (LOE II and III from paediatric studies) (27,28) administration increases the blood-brain osmotic gradient, thereby aiding in withdrawing
oedematous fluid from the cerebral tissue. Both have been found to be effective in the management of ICP and intracranial hypertension however, their role in prehospital care is yet to be determined by good-quality randomised trials. (1,8,9,22,25,29)

**Hypercapnoea and hypocapnoea**

Carbon dioxide is potently vaso-active in the cerebral vasculature and can easily influence the ICP and CBF as hypercapnoea (from hypoventilation) causes cerebral vasodilation (increasing blood component, refer to Monro-Kellie Doctrine) while hypocapnoea (from hyperventilation) causes cerebral vasoconstriction (decreasing blood component). (1,9,21,30) It has been suggested that each 1mmHg decrease in PaCO₂ is associated with a 3% decrease in CBF. (9)

A decrease in CBF of this magnitude might lead to significant cerebral hypoperfusion and ischaemia, aggravating the secondary brain injury. This is particularly true in the acute phase directly after injury, when the brain is vulnerable to hypoperfusion. (9,22,25,31) A 2010 study in a small sample found that mortality was 77% and 61% in patients who presented with hypocapnoea and hypercapnoea respectively in the EC following inappropriate prehospital ventilation. The effects of carbon dioxide derangements are placed into perspective when noting that the normocapnoeac mortality rate was merely 15%. Records with potential confounders were excluded from the study. (31) Another larger study found that mortality increased from 21% to 34% in cases of inappropriate ventilation. (32) Brain Trauma Foundation guidelines on prehospital head injury management therefore recommends (LOE III) that all patients be placed on continuous end-tidal CO₂ (ETCO₂) monitoring during field ventilation with the intent of keeping the values between 35-40mmHg, aiming at the lower range. (8,29)

**Hyperthermia and hyperglycaemia**

Hyperthermia has been associated with increased morbidity and mortality in patients with TBI. (22,33,34) A systematic review on fever and its association with outcome in brain injury reports that for every 1 °C increase in temperature above 38.3 °C in patients with subarachnoid haemorrhage; a 22-fold increase in mortality is appreciable. (33) Patients with TBI have a 68% prevalence of pyrexia within the first 72 hours. 79% of patients with TBI will have pyrexia within the first week of their recovery. (33) In a 2012 retrospective chart review of 126 patients, hyperthermic patients had lower mean CPPs than normothermic patients. (34) Aggressive management of hyperthermia is therefore recommended in patients with TBI. (22,33,34)

As with temperature, glucose control is also recommended in TBI as hyperglycaemia is associated with worse outcome. (22,23,26) In one study a blood glucose concentration of 11.1mmol/l was associated with a 3.6-fold increase in in-hospital mortality among patients
with severe TBI. (35) Glucose control to a blood glucose concentration of <10mmol/l is recommended in order to maximise outcome. (22,23,35,36)

e. Hypotension
Hypotension is defined as a systolic blood pressure (SBP) of 90mmHg or less and is associated with worse outcome in trauma patients. (37) However, the value of maintaining normotension in TBI is even more pronounced as MAP is a major determinant of eventual CPP. (1) Numerous studies have demonstrated the effect that hypotension has on the outcome of patients who have sustained a TBI. Table 1 summarises the evidence. Finally, the prevalence of hypotension in the setting of TBI will be discussed and factors associated with an increased risk of developing hypotension in this setting will be outlined.

One of the largest studies to evaluate the effect of hypotension on the outcome of brain injured patients was published in 1993. (38) In this prospective study, 717 patients with severe TBI were followed-up to determine outcome, specifically looking at the effect of hypotension (and hypoxaemia) on mortality. The prevalence of hypotension was 34.6% in the time period from injury to the end of EC resuscitation. (38) Hypotension was associated with a doubling in mortality from 27% in non-hypotensive patients to 64.8% in their hypotensive counterparts. This increase in mortality was also independent of age, admission GCS and pupillary status. Hypotension was in fact, counted among the five most significant predictors of outcome in TBI and decreased favourable outcome from 51.5% to 19.4%. (38) Late hypotension (in the Intensive Care Unit) occurred in 32% of patients and was the only hypotensive episode in 24% of cases. Despite only suffering delayed hypotension, 66% of these patients either died or were left in a severely vegetative state. Only 17% of patients who had not suffered a hypotensive episode died or remained vegetative. (39)

A prospective cohort study of 107 patients with moderate to severe TBI found that the relative risk of mortality increased 8-fold when a patient had two or more hypotensive episodes during his or her recovery. (40) A 2003 single-centre retrospective chart review aimed at establishing the effects of eleven factors on mortality (occurring in the first 24 hours post-injury) that have been implicated in the development of secondary brain injury. 81 adult patients with severe TBI (GCS ≤8/15) were included over a five year study period. (41) 68% of patients had at least one episode of hypotension (defined as a MAP of <70mmHg) during the first 24 hours post-injury. Jer Mitsky et al. found that patients who died had 50% more hypotensive episodes than survivors, that hypotensive patients had a longer length of hospital stay and fewer hypotensive patients were discharged home. Hypotension was also independently related to mortality after multivariate analysis. (41) These findings were corroborated in an Australian study that described an additive dose relationship between hypotension and mortality – i.e. the longer the patient remains hypotensive, the worse the outcome. (23) The
effects of hypotension on outcome are particularly pronounced in the acute stages following TBI. (42)

A more recent study – the IMPACT Study (International Mission for Prognosis and Analysis of Clinical Trials in TBI) aimed at combining the results of numerous randomised controlled trials conducted among moderate and severe head injuries in a meta-analysis to establish the relationship between hypoxia and hypotension at admission or in the prehospital phase and outcome. (43) Seven studies were included in the meta-analysis and yielded a combined sample size of 6629 patients. The IMPACT study used a proportional odds modelling methodology and found that patients who had hypotensive episodes before or at admission had worse outcomes (OR 2.7). (43)

A Cape Town-based single centre study published in 2002 aimed at establishing the incidence of hypotension and hypoxaemia in the pre-admission and hospitalisation phases (first 72 hours of admission only) of patients with moderate to severe TBI. (44) 96 patients (adult and paediatric) were included in a 3 month prospective data collection period. 8.3% of patients had a pre-admission episode of hypotension - either on scene or during transfer from referral centres, 6.3% of patients had hypotension in the EC while 13.5% of patients had a hypotensive episode during their ward stay. (44)

In patients with moderate to severe TBI, can TBI alone cause hypotension? It is unlikely, and usually due to blood loss and haemorrhagic shock. (45,46,47) A dated study from 1998 found that no identifiable cause for hypotension could be found in only 8.5% of TBI patients, and suggests that TBI in isolation might be the aetiology of hypotension otherwise unattributed in a small portion of the trauma population. (45) A 5 year retrospective chart review study evaluated the cause of hypotension among 231 blunt trauma patients. They found that 49% of patients had a haemorrhagic aetiology to their hypotension while only 13% of patients had only an isolated brain injury identifiable as potential cause of hypotension. (46) The mortality among the isolated TBI patients with hypotension was 80% and 64% of patients in the haemorrhagic group had a concomitant TBI. (46)

It has been suggested that neurologically intact recovery was likely if cerebral perfusion pressure is maintained regardless of the intracranial pressure and this has caused a shift in focus from ICP control to CPP maintenance. (47) Overzealous blood pressure support to supra-normal levels resulted until a millennial randomised controlled trial and subsequent follow-up study found that patients with supra-normal blood pressures had a 5-fold increased risk in developing acute respiratory distress syndrome (ARDS) (this might have had an association with increased frequency of inotrope use). (48,49) So, if hypotension negatively affects outcome and hypertension complicates the ventilator status of the patient, what is the optimal blood pressure for patients with TBI? It might be more than we think.
Two papers published recently (50) (51) aimed at establishing the optimum blood pressure targets to maximise good (neurologically intact) outcome in patients with moderate to severe TBI. Brenner prospectively studied sixty patients at a single tertiary trauma centre and recorded blood pressure measurements at 6 second intervals over 72 hours and expressed SBP as a pressure over time dose. Blood pressure thresholds (among others) were defined as SBP <90mmHg, <100mmHg, <110mmHg and <120mmHg. Pressure time doses of <110mmHg and <120mmHg predicted 12, 24 and 45 hour mortality while pressure time doses of <110mmHg and <120mmHg in the first 24 hours were predictive of unfavourable neurological outcome at 12 months. (50) Berry et al. in 2012 published a multicentre retrospective chart review of 15 733 patients (>15 years) over a five year period and aimed at establishing an optimal definition of hypotension as it relates to mortality in three age groups (15-49 years, 50-69 years and 70 years) by using a best fit model and adjusted odds ratios. The SBP threshold that best determined outcome was 100mmHg for patients 50-69 years and 110mmHg for both the youngest and oldest groups. (51) Another paper published from the IMPACT-study data suggests that an SBP of up to 135mmHg is the optimum target for favourable outcome in the setting of TBI. (52)

In summary, the evidence cited above points to the very strong association of hypotension increasing morbidity and mortality – close to doubling it in most studies. TBI alone is also often rarely responsible for hypotension and different aetiologies should be sought in these patients. It is important however, to be cognisant that most of the data available is of low quality evidence (Class II or II) with only one meta-analysis cited. Conducting randomised controlled trials would now be considered unethical and the sheer volume of large observational studies combined will dictate our knowledge and recommendations on this topic in the future.

f. Hypoxaemia

Most traumatic brain injuries are followed by a period of apnoea – even if just for a brief period. (9) Numerous studies have revealed the impact that hypoxaemia (PaO_2 <60mmHg or SpO_2 < 90%) has on the eventual outcome of patients who have sustained a TBI. Some of these studies will be outlined in the coming sections and the prevalence of hypoxaemia in TBI will be discussed. Table 2 summarises the evidence. Finally, the role of prehospital intubation in preventing hypoxaemia and its effect on outcome in TBI will be mentioned briefly.

Chesnut et al. in their large prospective study found the admission prevalence of hypoxaemia in moderate to severe TBI to be 22.4%. Hypoxaemia was associated with a near-doubling in mortality from 27% to 50%. (38) Manley et al. prospectively collected saturations and blood pressure data in 107 patients with an admission GCS of 12/15 or less. 38% of patients presented with hypoxaemia (defined in this study as a pulse oximetry reading of ≤92%).
Hypoxaemic patients carried a mortality of 44% and mortality was not associated with duration of hypoxaemia or the amount of hypoxaemic episodes. (40) In contrast, an earlier (1994) prospective in-hospital study of 127 patients with varying severities of TBI, reports that mortality was independently predicted by duration of hypoxaemia (p=0.024). (53)

A local study investigating the incidence of hypotension and hypoxaemia in the pre-admission and hospitalisation phases of patients with moderate to severe TBI found that 7.3% of patients suffered a hypoxaemic episode in the pre-admission phase, 2.1% of patients had hypoxaemia in the EC and 11.5% of patients had hypoxaemia while admitted in the wards. (44)

A prospective cohort study published in 2006 aimed at determining the incidence and duration of hypotension and hypoxaemia in 150 patients transported to 4 trauma centres by helicopter over a 2 year period. (54) The association between hypotension, hypoxaemia and their duration and mortality was established using multivariate logistic regression. 24.6% of patients suffered hypoxic episodes during transport. Hypoxaemia was associated with a higher incidence of mortality (OR 2.66). Among patients who were hypoxaemic, the mortality rate was 37% while this rate was only 20% among patients without hypoxaemia. Prehospital intubation appeared to have no significant variance on the incidence of hypoxaemia. (54)

When hypoxaemia is present a close to two-fold increase in mortality is appreciable. (38,40,53,54) The mortality of a patient is also proportional to the duration of the hypoxaemic event. (53) A theoretical advantage therefore exists for early airway intervention and possibly intubation in the prehospital phases of care.

Conflicting data exists regarding the value of prehospital intubation – in the setting of TBI; the debate is even more heated. Numerous studies have been conducted on endotracheal intubation in the field and many of these used implied variables to establish the value and safety of prehospital intubation. A meta-analysis published in 2012 (55) investigated the success rates of prehospital attempts at endotracheal intubation. 33 studies met inclusion criteria and were eligible for meta-analysis. A pooled success rate of 90% was appreciable. This rate was significantly higher when physicians (99%) attempted intubation than when non-physicians (85%) attempted intubation (p=0.0345). The use of paralytics and anaesthetic agents resulted in a much higher success rate (97%) when compared to the use of anaesthetic agents alone (81%). Important to note is that fewer patients were intubated in total by physicians (2 538) than by non-physicians (12 862), the number of attempts at success was not recorded and finally the studies were heterogenous ($I^2=97.8\%; p<0.0001$). (55) Such heterogeneity would preclude the dataset from being subjected to meta-analysis. Another meta-analysis showed similar success rates among non-physicians (86%) with significant improvement in success rates when rapid sequence techniques (RSI) were used.
(97%). Heterogeneity is not explicitly reported on, yet it is stated that the I^2 statistic was “high”. (56) Both of these studies failed to look at outcome and the incidence of adverse physiological effects related to prehospital intubation. The studies included in the meta-analysis were heterogenous and of low quality (most were retrospective observational studies). (55,56)

No meta-analyses could be found related to mortality and prehospital endotracheal intubation in patients with TBI. One retrospective chart review showed that prehospital intubation in patients with moderate and severe TBI was associated with a 5-fold increase in mortality when compared to patients who were not intubated in the field (AOR 5). This study looked at 2549 patients, only 2.6% (n=61) of whom were intubated prehospital. Despite the dramatic result, this study did not explicitly report on the differences in severity of injury between the two groups or on other confounding factors. The method of intubation (whether drug assisted or RSI) was not recorded. All of these factors limit the universal application of the study results. (57)

Another meta-analysis on mortality in TBI analysed a pooled sample of 15 335 patients. (58) Most studies were retrospective chart reviews or cohort studies. Not a single study was randomised. Conflicting results were appreciable and odds ratios for mortality ranged from 0.17 (CI 0.10-0.31; favours non-intubation groups) and 2.43 (CI 1.78-3.33; favours prehospital intubation). Heterogeneity was not explicitly stated. All studies where intubation was facilitated by neuromuscular blocking agents were excluded from the analysis. Other confounding factors that might influence outcome such as prehospital physiologic variables (hypoxaemia, hypotension, hypo- or hypercapnoea) and injury severity was not reported or corrected for in many studies. (58) No South African data was available on this topic.

When considering prehospital intubation within the South African context: only a selected group of paramedics have RSI on their scope of practice – the so-called Emergency Care Practitioner (ECP) who completes a four year Honours degree in Emergency Medical Care. (59) These ECPs are equipped with additional training and a greater skills-set in order to broaden their scope of practice in order to bring roadside anaesthetic and advanced monitoring capabilities to the patient in the field. (59) In 2012 there were 166 (60) Emergency Care Practitioners serving a population of 50 million. (61) Important to note is that the majority of patients do not require such advanced interventions, and intermediate ambulance technicians and paramedics have a sufficient scope and skills-set to manage the bulk of patients. (59) However, these confines to practice and relative shortage of ECPs might preclude safe intubation of TBI patients within the field (intubation with neuromuscular blocking agents improve success rates). (56)
The exclusion of confounders in analysis and reporting is an inherent flaw in the studies cited that investigate the impact of prehospital intubation on TBI mortality and creates a large room for bias. This is of particular relevance when considering that many patients are intubated in the field because they have refractory hypoxaemia or have critical injuries complicating their TBI. (29) The application of these studies in a clinical context is still up for debate and the jury is still out on whether evidence supports prehospital intubation or not.

The association between hypoxaemia and mortality in TBI is not as strong as that between hypotension and mortality but should the two occur simultaneously, the mortality might be as high as 75%. (41)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Description</th>
<th>Data Class</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chesnut, 1993</td>
<td>Prospective study of 717 patients to evaluate the effect of hypotension on mortality</td>
<td>III</td>
<td>Prevalence of hypotension of 34.6% and mortality increased from 27% to 64.8% with early hypotension</td>
</tr>
<tr>
<td>(38)</td>
<td></td>
<td></td>
<td>Delayed hypotension also contributes to bad outcome</td>
</tr>
<tr>
<td>Manley, 2001</td>
<td>Prospective cohort study of 107 patients to evaluate the effect of hypotension on mortality</td>
<td>III</td>
<td>Two or more hypotensive episodes yield an 8-fold increase in mortality</td>
</tr>
<tr>
<td>(40)</td>
<td></td>
<td></td>
<td>Two or more hypotensive episodes yield an 8-fold increase in mortality</td>
</tr>
<tr>
<td>Jeremitsky, 2003</td>
<td>Single centre, retrospective chart review of 81 records to establish the effect of 11 factors on mortality (including hypotension)</td>
<td>III</td>
<td>Patients who died had 50% more hypotensive episodes than survivors</td>
</tr>
<tr>
<td>(41)</td>
<td></td>
<td></td>
<td>Patients who died had 50% more hypotensive episodes than survivors</td>
</tr>
<tr>
<td>McHugh, 2007</td>
<td>Meta-analysis of 7 RCTs with combined sample of 6 629 to establish the effect of prehospital hypotension and hypoxaemia on outcome</td>
<td>I</td>
<td>Worse outcome in the setting of hypotension (OR 2.7)</td>
</tr>
<tr>
<td>(43)</td>
<td></td>
<td></td>
<td>Worse outcome in the setting of hypotension (OR 2.7)</td>
</tr>
<tr>
<td>Reed, 2001</td>
<td>Local prospective chart review to establish the incidence of hypotension and hypoxaemia at a single centre</td>
<td>III</td>
<td>8.3% of patients had pre-admission hypotension, 6.3% in the EC and 13.5% of patients had hypotension in the ward</td>
</tr>
<tr>
<td>(44)</td>
<td></td>
<td></td>
<td>8.3% of patients had pre-admission hypotension, 6.3% in the EC and 13.5% of patients had hypotension in the ward</td>
</tr>
<tr>
<td>Chesnut, 1998</td>
<td>Retrospective chart review of 248 records to examine hypotension in TBI not associated with hypovolaemia</td>
<td>III</td>
<td>No identifiable source for hypotension could be found in only 8.5% of patients with isolated TBI</td>
</tr>
<tr>
<td>(45)</td>
<td></td>
<td></td>
<td>No identifiable source for hypotension could be found in only 8.5% of patients with isolated TBI</td>
</tr>
<tr>
<td>Mahoney, 2003</td>
<td>Retrospective chart review of 231 records to identify the cause of hypotension in blunt trauma victims</td>
<td>III</td>
<td>Only 13% of patients with isolated TBI had hypotension with no other identifiable cause</td>
</tr>
<tr>
<td>(46)</td>
<td></td>
<td></td>
<td>Only 13% of patients with isolated TBI had hypotension with no other identifiable cause</td>
</tr>
<tr>
<td>Robertson, 1999</td>
<td>Unblinded RCT of 189 patients to establish whether CBF- or ICP-targeted management yielded better outcome in patients</td>
<td>II</td>
<td>ICP-targeted management increased the risk of cerebral ischaemia 2.4-fold but CBF-</td>
</tr>
<tr>
<td>(48)</td>
<td></td>
<td></td>
<td>ICP-targeted management increased the risk of cerebral ischaemia 2.4-fold but CBF-</td>
</tr>
</tbody>
</table>
Contant, 2001 (49)  
Follow up from Robertson, 1999 aiming to compare patients who developed ARDS with those who did not  
Induced hypertension is associated with the development of ARDS in patients with TBI

Brenner, 2012 (50)  
Prospective cohort study of 60 patients aimed at establishing the prognostic value of different BP values  
Systolic blood pressure targets closer to 120mmHg might be more efficacious than the traditional 90mmHg

Berry, 2012 (51)  
Retrospective chart review of 15 733 records that aimed at establishing an optimum blood pressure to improve mortality rates  
A new hypotensive threshold of SBP<110 mmHg was suggested for patients with isolated moderate to severe TBI

Butcher, 2007 (52)  
Retrospective chart review of 13 448 records to establish the relationship between admission BP and outcome  
Outcome improved as SBP increased up to 135mmHg

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contant, 2001 (49)</td>
<td>Follow up</td>
<td>Induced hypertension increased the risk of ARDS 5-fold</td>
</tr>
<tr>
<td>Brenner, 2012 (50)</td>
<td>Prospective cohort</td>
<td>Systolic blood pressure targets closer to 120mmHg might be more efficacious than the traditional 90mmHg</td>
</tr>
<tr>
<td>Berry, 2012 (51)</td>
<td>Retrospective chart review</td>
<td>A new hypotensive threshold of SBP&lt;110 mmHg was suggested for patients with isolated moderate to severe TBI</td>
</tr>
<tr>
<td>Butcher, 2007 (52)</td>
<td>Retrospective chart review</td>
<td>Outcome improved as SBP increased up to 135mmHg</td>
</tr>
</tbody>
</table>

Table 2: Evidence Table – Hypotension and Traumatic Brain Injury
<table>
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<tr>
<th>Reference</th>
<th>Study Description</th>
<th>Data Class</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chesnut, 1993 (38)</td>
<td>Prospective study of 717 patients to evaluate the effect of hypoxaemia on mortality</td>
<td>III</td>
<td>Prevalence of hypoxaemia of 22.4% and mortality increased from 27% to 50% with early hypoxaemia</td>
</tr>
<tr>
<td>Manley, 2001 (40)</td>
<td>Prospective cohort study of 107 patients to evaluate the effect of hypoxaemia on mortality</td>
<td>III</td>
<td>Hypoxaemic patients had a 44% mortality</td>
</tr>
<tr>
<td>Jones, 1994 (53)</td>
<td>Prospective study of 124 patients aimed at establishing the effect of secondary insult to outcome after TBI</td>
<td>III</td>
<td>Outcome is worse with longer episodes of hypoxaemia</td>
</tr>
<tr>
<td>Reed, 2002 (44)</td>
<td>Local prospective chart review to establish the incidence of hypotension and hypoxaemia at a single centre</td>
<td>III</td>
<td>7.3% of patients had pre-admission hypotension, 2.1% in the EC and 11.5% of patients had hypotension in the ward</td>
</tr>
<tr>
<td>Chi, 2006 (54)</td>
<td>Prospective, multicentre study to determine the incidence and duration of hypoxaemia in 150 patients transported and its associated with mortality</td>
<td>III</td>
<td>24.6% of patients had a hypoxaemic event which increased mortality from 20% to 37% (OR 2.66)</td>
</tr>
<tr>
<td>Lossius, 2012 (55)</td>
<td>Meta-analysis investigating success rates of prehospital ETI</td>
<td>III (I²:97.8%)</td>
<td>Pooled success rate of 90%. Improved success rates among physicians and when using RSI.</td>
</tr>
<tr>
<td><strong>Hubble, 2010 (56)</strong></td>
<td>Meta-analysis investigating success rates of prehospital ETI</td>
<td>III (heterogeneity not stated)</td>
<td>Improved success rates when RSI was used</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td><strong>Bukur, 2010 (57)</strong></td>
<td>Retrospective chart review investigating the influence of prehospital endotracheal intubation on mortality</td>
<td>III</td>
<td>Shows an increase in mortality with prehospital intubation (AOR 5)</td>
</tr>
<tr>
<td><strong>Von Elm, 2009 (58)</strong></td>
<td>Meta-analysis investigating mortality and ETI in TBI</td>
<td>III (heterogeneity not stated, no RCTs included)</td>
<td>Showed conflicting results with odds ratios ranging from 0.17 (CI 0.10-0.31) to 2.43 (CI 1.78-3.33)</td>
</tr>
</tbody>
</table>

Table 3: Evidence Table – Hypoxaemia and Traumatic Brain Injury
g. The Role of Prehospital Care in Traumatic Brain Injury

The cerebral tissue is particularly vulnerable to secondary insults in the time period immediately following a traumatic brain injury. (8,9,22,31,62) This is likely to be caused by failure of autoregulation immediately after injury and CPP then more loosely correlates with MAP. (1) The vulnerability of the brain in the early phases following injury has been demonstrated by an experimental animal study conducted in 2008. (62) The aim of the study was to investigate the effects of early versus late hypoxic and hypotensive insults in a sample of rats with simulated acceleration-deceleration TBI. Rats were randomly allocated to five study groups (early and delayed hypoxic and hypotensive insults and a control group) and then subjected to induced hypotension and hypoxaemia at 45 minutes and 225 minutes post-injury. Hypotension was induced by controlled haemorrhage to a MAP of 40mmHg while hypoxaemia was induced to a PaO\textsubscript{2} of 40mmHg by ventilation with 10% oxygen. CPP, cerebral tissue oxygenation and ICP monitoring was continued throughout the experiment. A significant decrease in brain oxygenation and CPP was appreciable when a hypotensive or hypoxic insult was induced, when compared to control groups. A disruption in cellular metabolism was also seen as evidenced by elevated brain lactate levels – these disruptions were only significant in the “early-insult” group. (62) Out of this study it can be extrapolated that early insults have a more devastating effect than later insults. A case can be made for earlier intervention to avoid these insults and thus illustrates the importance of prehospital care in TBI.

Two articles published in the last decade investigate the role that prehospital care plays in the eventual outcome of patients that have sustained TBI. (63,64) The effect of prehospital ETI has already been discussed - ETI has been associated with an improved outcome when assisted by RSI, performed by experienced healthcare providers and when ventilation is monitored by continuous end-tidal carbon-dioxide measurements. (58) A dose response to secondary insults has been demonstrated. (23,53) Aggressive prehospital correction of hypotension is therefore essential to improve patient outcome. (9) In one study, hypotension that was not corrected by arrival in the Emergency Centre carried a higher mortality (60.2% vs. 50.0%). (9) From this information, it may be deduced that early correction of hypotension and hypoxaemia will effectively decrease mortality.

Outcome is not influenced by scene time. (63,65) A dated study (1998) investigated the relationship between the on-scene to EC time, interventions performed and mortality. Patients who had no procedures performed had an average scene time of less than 15 minutes and a mortality of 51.6%. Patients who received intravenous fluid therapy only had a typical scene time of 15-30 minutes and a mortality of 40%. A final group of who patients received intravenous therapy, intubation and ventilation and osmotic therapy had an average scene time of 30-60 minutes and had a significantly lower mortality (21.7%; p < 0.05). (65)
In the event of intracranial haemorrhage intracranial hypertension and cerebral compression might occur rapidly and neurosurgical evaluation and potential evacuation of the haematomas is extremely time dependant in order to increase the likelihood of functional outcome. (1,9,44) The mean incidence of intracranial haemorrhage following severe TBI is 12-38% and between 40% and 60% of these will require neurosurgical evacuation. (1) Reed and Welsh cite one study that found a 30% mortality rate in cases where evacuation had not been done within 4 hours of injury. This mortality rate increased 3-fold should intervention be delayed by another 4 hours. In South Africa, the mean time to surgical intervention has been reported to be as long as 7.5 hours. The main delay appears to be due to initial delivery of these patients to hospitals without neurosurgical capabilities and later referral to Level I trauma centres. (44) Studies also suggest that with appropriate prehospital care, transport time within this 4 hour window is non-influential on outcome. (9) It is therefore recommended that all patients who might require neurosurgical consultation and that can be stabilised initially on scene be transported to trauma centres with the appropriate resources, even if closer centres are bypassed. (8,9)

In order to shorten the time to definitive surgical management the use of aeromedical evacuation has been suggested. (66) A 2005 retrospective analysis of a trauma registry investigated the effect of aeromedical transport on outcome in patients with TBI. 10 314 patients met the inclusion criteria and of these 3 017 patients were transported by air. Demographics, secondary insults and injury severity were similar for the road and air groups. Favourable outcome was more prevalent in the patients transported by air (AOR 1.36; CI 1.18-1.58; p <0.001). Patients with more severe injuries appeared to benefit most from air transport. Patients who were intubated in the field and transported by air also had improved outcome when compared to patients who were transported by road and intubated in the EC (AOR 1.42; CI 1.13-1.18; p < 0.001). (66)

Another retrospective cohort study aimed at investigating the effect on outcome of ground versus air transportation in patients who sustained a TBI. (64) 194 patients met inclusion criteria - the ground (n=105) and air (n=89) sample sizes, demographics and injury severity were all comparable. Patients transported by air had a significantly lower prevalence of hypotension (18% vs. 36%; p < 0.001) and mortality was significantly lower in the helicopter group (21% vs. 25%; p < 0.05). Almost all (92%) of the patients transported by helicopter were intubated while only 36% of the road transported patients had an advanced airway in place. The mean fluid volume infused was also higher in the helicopter group (1056ml; ±678ml) than the ground group (581ml ±272ml). (64)

It is important to take cognisance of the different legislative confounders that influence these results. Staffing and scope of practice constraints differ from country to country and even between states. This leaves the cited data non-generalisable. These multiple confounders
also mean that we cannot ascribe the improved outcome to air transport – as it might be as a result of an improvement skill level, access to greater interventional capability (RSI for instance) or a lower threshold for airway interventions.

h. Summary and Conclusion
Definitions of traumatic brain injury were outlined. The incidence of TBI ranges from 56/100 000 to 2360/100 000 and is 316/100 000 in Johannesburg. About half of all cases of TBI are consistently due to road traffic collisions with falls and interpersonal violence also being important mechanisms depending on the geographical location and demography of the patient. Comparing epidemiological statistics between regions and studies are however, exceptionally difficult as these studies have a high heterogeneity with high variance in methodology, inclusion and exclusion criteria and diagnostic definitions.

The concept of raised ICP was discussed using the Monro-Kellie Doctrine and its relation to CPP and MAP was also outlined. The brain is particularly vulnerable to secondary insults (hyperthermia, hypo- and hypercapnoea, hyperglycaemia, hypotension and hypoxaemia) during the acute phase after injury and it is for this reason that aggressive prehospital management might be of benefit. The presence of prehospital hypotension doubles mortality and there appears to be a relationship between the length of time that a patient is hypotensive and their eventual outcome. It has also been suggested that higher blood pressure targets are set for patients with TBI. The prevalence of hypotension in the brain injured population ranges from 8.3% to 68% and most often has a haemorrhagic aetiology. The prevalence of hypoxaemia ranges from 7.3% to 38% and is also associated with a doubling in mortality. When hypoxaemia and hypotension occur together, the mortality can be as high as 75%. Prehospital intubation of patients with TBI was found to increase mortality however many of these studies are confounded. Other studies suggest that prehospital intubation by experienced providers and by means of RSI are associated with lower prevalence of hypoxaemia and better outcome.

The patient with TBI is one of few trauma populations that seem to benefit from prolonged scene time in order to stabilise the vital functions. Even though scene time was prolonged in patients where multiple interventions were performed, the mortality seemed to improve. It is also recommended that patients be transported directly to neurosurgical centres even if other centres are bypassed or if it prolongs transport time.
Economically active individuals are at greater risk of suffering TBI and aggressive goal directed care might make a difference in their outcome. This will hopefully aid in relieving the economic burden that TBI and neurological impairment have on a developing country like South Africa. Current data available on TBI are of low quality with a high concentration of confounders and high heterogeneity. Good quality studies (such as blinded randomised controlled trials) would be unethical to conduct and there is therefore a high reliance on well-designed observational studies that are similar in methodology in order to make meta-analyses possible.
5. METHODS

a. Aim and Objectives

This study primarily aimed to establish the prevalence of prehospital hypotension and hypoxaemia in moderate to severe traumatic brain injury in the Greater Johannesburg area, Gauteng, South Africa.

The Objectives of this study were:

- To describe the demographic characteristics of patients with moderate to severe TBI.
- To determine the prevalence of hypotension in patients with moderate to severe TBI before reaching definitive care.
- To determine the prevalence of hypoxaemia in patients with moderate to severe TBI before reaching definitive care.

b. Study Design and Methods

A retrospective cross-sectional descriptive (chart review) design was used. Patient report forms were obtained from the two institutions (ER24 – a private Emergency Medical Service and the University of Johannesburg’s electronic patient care record database) by one of three methods:

1) an electronic search through ER24s billing database for ICD10 codes that match the description for “Injuries to the Head” (S00-S09);

2) Electronic database search through the student Patient Care Records of the University of Johannesburg's EMDATA for any motor vehicle accident, pedestrian, explosion or sport related injury. The EMDATA search was limited to Adult patients who responded to verbal or painful stimuli and who were seen while working with any Emergency Medical Service other than ER24.

3) Hand-searching through ER24s helicopter patient report forms.

All patient records were limited to adult patients (18 years or older) who were seen in 2011 (1 January – 31 December) and had a GCS of 13/15 or less. This cut-off was selected as literature suggests that patients with a GCS score of 13/15 should be included in the moderate TBI category as they represent a similar risk set and complication rate as patients with a GCS of 9 to 12. (5,67,68) The initial or first recorded GCS was used to include or exclude patient records. All transfers and paediatric patients were excluded from the search.

If any essential pieces of data were missing (GCS, blood pressure measurements or saturations measurements) the patient record was excluded. The inclusion and exclusion criteria were:
Inclusion Criteria

- 18 years of age or older
- Clinical evidence of traumatic brain injury on the chart (ICD10 codes S00-S09, diagnosis of TBI or variations (head injury, isolated head) or positive mechanism for TBI (any motor vehicle accident, pedestrian vehicle accident, fall, assault, explosion or sport related injury))
- GCS 13/15 or less
- Cases arising between 1 January 2011 to 31 December 2011
- Patients residing within the greater Johannesburg Metropolitan area

Exclusion Criteria

- Paediatric cases
- Interhospital transfers
- GCS greater than 13/15
- Duplicate cases
- Patients who died before arrival of EMS or on scene prior to transport
- Penetrating TBI
- Cases outside of the Johannesburg area
- Incomplete crucial datasets. These crucial data were GCS, blood pressure and saturations

Demographic characteristics such as age, gender, race, mechanism of injury and concomitant injuries were extracted to an Excel® spread sheet from each record in addition to the essential data that answers the research questions. The prevalence of hypoxaemia (defined as a saturations reading of 94% or less) and hypotension (defined as a systolic blood pressure of 90mmHg or less) was recorded for each record. The reason for this higher saturation level than in the literature is that paramedics are taught to respond to a SpO\textsubscript{2} reading of less than 94% as hypoxaemia and administer oxygen. The initial saturations and blood pressure readings were recorded (Initial prevalence) as well as the lowest of readings for each (Prehospital prevalence). Finally, ancillary data regarding the treatment that these patients received prehospitaly were recorded. Ethical approval for this study and its methods was granted by the Human Research Ethics Committee of the University of Cape Town (Reference number 131/2012).

c. Data Management and Analysis

The data outlined above were recorded in a password protected Microsoft Excel © 2010 spread sheet by two data capturers independently and backed up onto two external hard drives. If demographic data was unknown, these fields were left blank for analysis. Should the saturations or blood pressure measurements be detailed as "unrecordable" (or similar) the
value was captured as zero (0). Should one of the critical fields (saturations and blood pressure) have been omitted, the entire record was discarded and left ineligible for analysis. Intubated patients were assigned a value of 1 for the verbal component of the GCS. Two parallel datasets were compared and discrepancies between the two data capturers were resolved by the principal investigator. All records and data were secured in a fireproof safe and only the primary investigator and research supervisor were allowed access to the data.

A descriptive analysis method was employed to present the categorical data. Numerical data were analysed in Microsoft Excel © 2010 and means, standard deviations and interquartile ranges were calculated to a 95% confidence interval. The prevalence of hypotension and hypoxaemia is presented. Numerical data is presented according to demographics and the presence of concomitant injuries. Data was further subjected to Chi square testing to determine variance between the prevalence of hypotension and hypoxaemia as it relates to interventions (intubation, medication dose and fluid therapy) and the presence of concomitant injuries (long bone fractures, suspect occult or internal haemorrhage, external haemorrhage or chest injuries). Means were also recorded for ancillary data where applicable.
6. RESULTS

a. Sample Size and Quality of Data

A total of 299 (Method 1: 200; Method 2: 42; Method 3: 57) patient records were identified from the initial data search. Finally only 66 (Method 1: 7; Method 2: 14; Method 3: 45) patient records met the inclusion criteria. 192 records were excluded from the Method 1 sample, 28 records were excluded from the Method 2 sample and 12 records were excluded from the Method 3 sample. The majority of the records (45%, n=136) were excluded because patient did not have a moderate to severe head injury (GCS > 13/15). 11% (n=34) of records were paediatric patients, 6% (n=19) were excluded as transfers, 13% (n=39) had incomplete datasets (GCS, saturations or hypotension) and the remainder of the initial sample (2%, n=5) was excluded for other exclusion criteria. Figure 1 tracks the exclusion of records.

All records gained from the 2\textsuperscript{nd} data collection method were void of demographic data and data regarding concomitant injuries; yet all were identifiable as “Adult”. All other records had demographic data although exact ages were sometimes replaced with a range (e.g. 35-40 years old).

![Figure 1: Tracking profile of record exclusion](image-url)
b. Demographics

Figure 2: Sample gender distribution

The mean age of the sample was 33.59 years ± 10.95 years. Figure 2 illustrates the gender distribution of the sample. 56% (n=43) were male patients and 12% (n=8) were female patients while gender data were not available for 23% (n=15).

Figure 3: Sample race distribution

Figure 3 shows the racial distribution of the sample. 51% (n=33) patients were black, 20% (n=14) were white and while a single patient (2%) was Indian. 27% (n=18) of the sample did not have any racial data available for comment.
Figure 4 outlines the GCS frequency of the sample. Most patients (43.4%; n=28) had a GCS of 3/15. Another peak in frequency is appreciable at a GCS of 7/15 (16.7%; n=11). The median GCS was 5.

Figure 5 illustrates the mechanism of injury for each patient within the sample. The majority (41%, n=28) of the patients were injured in an RTC. PVAs accounted for 14% (n=9) of all cases while MBAs accounted for the third most head injuries (8%, n=5). Assaults and bicycle accidents and falls and falling objects accounted for 6%, and 2% of all cases respectively.
Finally, 21% (n=14) of patients did not have any recorded data regarding the mechanism of injury.

Figure 6: Mode of Transport to Hospital

Figure 6 shows the Mode of Transport to hospital of each patient. The majority of patients were transported by helicopter (68%; n=45), 11% of patients were transported by road (n=7) while 21% (n=14) did not have the mode of transport available.

Figure 7: Prevalence of concomitant injuries with TBI
When considering the prevalence of concomitant injuries (Figure 7), 28% of patients (n=19) sustained major fractures (defined as long bone fractures or suspected or confirmed pelvic fractures) while 12% (n=8) had facial fractures complicating their TBI. 16% (n=11) of patients sustained injuries to the chest (rib fractures, pneumothoraces, haemothoraces, aspiration and cardiac contusions) that might complicate oxygenation and ventilation. 27% and 12% (n=18 and 8) of patients had external and internal haemorrhagic potential. Patients were deemed to have external haemorrhage potential when there were reports of bleeding, soft tissue injury, amputations or open fractures. Patients were deemed to have a potential for occult (or internal) haemorrhage when a distended or rigid abdomen was reported or in patients with closed long bone or pelvic fractures. Only 15% of patients had an isolated head injury. 21% (n=14) of cases had no clinical description of injuries available.

c. Hypotension and Hypoxaemia

![Blood Pressure Frequency Chart]

The majority (Figure 8) of patients had a low SBP with 25.8% (n=17) and 39.4% (n=26) of the sample recording SBPs in the 80-99mmHg range initially and lowest, respectively. 4.5% (n=3) had initial and lowest “unrecordable” SBPs. The average initial SBP for the sample was 114.2mmHg ± 38.4mmHg while the mean for the lowest SBP was lower at 106.7mmHg ± 34.8mmHg. An initial SBP of less than 90mmHg was seen in 27.3% (n=18) of patients while 33.3% (n=22) of patients had hypotension at some point in the field.
60.6% (n=40) and 65.1% (n=43) of patients respectively (Figure 9) had initial and lowest oxygen saturation readings of 90-99%. Only two (3%) of patients had unobtainable oxygen saturations. Initial hypoxaemia was seen in 37.9% (n=25) while 43.9% (n=29) of patients had at least one episode of hypoxaemia prehospitaly. Finally, the mean oxygen saturation was 90.2 ± 18.6% and 89.65 ± 18.42% initially and lowest in turn.

The prevalence of hypotension and hypoxaemia within the sample is outlined in Figure 10. Initial hypotension was defined as a first systolic blood pressure (SBP) of 90mmHg or less while prehospital hypotension was defined as an SBP of 90mmHg or less at any time during
the prehospital phase. Initial hypoxaemia was defined as a saturations level of 94% or less recorded at first patient contact and prehospital hypoxaemia was defined as a saturations level of 94% or less recorded at any time during prehospital care.

d. Hypotension, Hypoxaemia and Concomitant Injuries

Injury data was only available for 52 (79%) patients. Only the cumulative prehospital prevalence of hypotension and hypoxaemia was used to determine the prevalence variance as it relates to injuries sustained. 28.8% of patients with clinical injury data experienced hypotension during the prehospital phase of their care and 86.7% (p=0.011) of these patients had injuries that had the potential to cause hypotension. Nineteen out of the 52 patients (36.3%) with clinical injury data recorded experienced prehospital hypoxaemia; 42.1% (p=0.001) of these patients had a chest injury that could be attributable as the aetiology for the hypoxaemia. Table 1 and 2 illustrate these relationships.

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Table 4: Number of patients with hypotension and injuries and those without

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Table 5: Number of patients with hypoxaemia and injuries and those without
e. Trends in Prehospital Treatment

Treatment data were only available for 52 patients.

Figure 11: Prehospital airway management
(ETI: Endotracheal Intubation, LMA: Laryngeal Mask Airway)

81% (n=42) of patients were intubated prehospitaly while one patient’s airway was managed by insertion of an LMA. 17% (n=9) of patients did not undergo any airway interventions.

Figure 12: Means of prehospital intubation
Out of the 42 patients who were intubated prehospitaly, the majority of intubations (71%; n=30) were assisted by means of deep sedation (Morphine and Midazolam) while 24% (n=10) were performed using a rapid sequence method (anaesthetic and paralytic) and 5% (n=2) were not intubated with any pharmacological assistance.

Figure 13: Total prehospital Morphine dosages administered

Figure 13 reveals some data regarding the trends of Morphine administration to the sample. Patients typically received 5-9mg (44%; n=23). The average Morphine dose was 8.1mg ± 5.5mg.

Figure 14: Total prehospital Midazolam dosages administered
The average Midazolam dose was higher than that of Morphine at 9.7mg ± 7.2mg. Much like with Morphine most patients (30.7%; n=16) received 5-9mg of Midazolam (Figure 14) during their prehospital phase of care.

![Graph showing volume of fluids infused](VOLUME_FLUIDS_INFUSED.png)

The mean total volume of fluid that the sample received prehospitaly was 919.2 (0 – 1921.1ml). Most patients (n=9; 17.3%) received between 400ml and 599ml of fluid. 60% (n=31) of patients received one litre or less fluid in their entire prehospital phase of care (Figure 15).
7. DISCUSSION

a. Demographics

The mean age of the sample was 33.59 years ± 10.95 years. 74% (n=40) of all the patients with demographic data available were in the age group of 24-44 years. Just over half of the patients were black and the male to female ratio was 2.9:1. The age and race data was comparable to that of an earlier Johannesburg-based (19) study reporting a higher incidence in black individuals between the ages of 24 and 44 years. The male to female ratio was quite lower in the current dataset than that of the earlier study but similar to a study from the New York Bronx that reported a ratio of 2.8:1. (2)

Similar to international data and that reported by Nell and Brown the current study found that RTCs accounted for 41% (Nell and Brown reported 42.7%) of TBIs. (19) Gauteng has an exceptionally high rate of RTCs with 23% of all RTCs in South Africa occurring within its borders and being responsible for 21.5% of all road fatalities. (69) Despite technological advances in motor vehicle safety patients are still getting seriously injured in accidents. This could potentially be a product of complacent drivers not wearing seatbelts. A 2005 study showed that only 75.1% of Gauteng drivers wore a seatbelt. (69) This figure was almost half for front seat passengers (44.5%) and even more startling when considering that only 13% of rear seat passengers buckled up. (69) Another possible explanation for this might be because the assessment tools used in New Car Assessment Programme (NCAP) ratings have been found to be poor predictors of TBI. (70) Only four patients (6%) were assaulted which is a much lower prevalence than reported in the study by Nell and Brown. (19) Most patients transported by private ambulance services in South Africa have medical aid and by default might be of higher socio-economic status. The incidence of interpersonal violence has been suggested to have an inverse correlation with socioeconomic status. (71,72) This might also be as a consequence of the improving crime rate (including fewer assaults, as reported by the South African Police Services). (73)

Most patients had a GCS of 3/15 (43.4%) and the median GCS was 5. Many patients that were transported by helicopter (68% of the sample) were sedated or intubated before the flight crews arrived on scene. Their initial GCS measure is therefore misleading and chemically altered. This might have overestimated the severity of TBI as measured by the GCS. Only 15% of patients sustained an isolated traumatic brain injury. This figure is consistent with international data reporting a prevalence of isolated TBI in 13% of 231 blunt trauma victims. (46) The prevalence of haemorrhage is however, slightly lower in the current sample than reported in the previous study (39% versus 49%). This study, by Mahoney et al. (46) was conducted on hypotensive trauma patients and it is therefore expected that a higher prevalence of haemorrhage will be observed.
b. Hypotension

Initially, a systolic blood pressure (SBP) of less than 90mmHg was seen in 27.3% (n=18) of patients while 33.3% (n=22) of patients had hypotension at some point during their prehospital phase of care. The prevalence of hypotension in the current sample is comparable to that seen in Chesnut et al.’s which reported a prevalence of 34.6% (however, this included the acute EC resuscitation phase) (38) but is much higher than a Cape Town-based study (8.3%). (44) The Cape Town-based study included patients who were transferred from referring facilities and many patients did not have prehospital data available. Episodes of hypotension might have already been corrected in the referring facilities or went unrecorded and would lead to an underestimation of hypotension. Conversely, the prevalence of hypotension is more than double in the study by Manley et al. (68%) yet, their study period included the first 24 hours of admission and comparison is therefore limited. (40) The mean lowest SBP of 106.7mmHg ± 34.8mmHg for the sample is much lower than the higher target SBPs suggested by the IMPACT study (135mmHg) and recommendations by Berry et al. (110mmHg). (51,52)

A statistically significant proportion (86.7%; p = 0.011) of patients with hypotension had concomitant injuries that had potential to cause haemorrhage and hypotension. This finding is supported in the literature that suggests hypotension in TBI most often has a haemorrhagic aetiology (45,46) and that TBI as a sole cause of hypotension is only seen in 8.5% (45) to 13% (46) of patients. It has been suggested that hypotensive patients with TBI should be approached as if they were suffering from haemorrhagic shock. (46) A vasodilatory mechanism to hypotension in isolated brain injury has also been postulated (46,74) and a benefit of inotropic support is therefore evident. (75) No patients were placed on inotropic support in this sample.

When considering that more patients developed hypotension than originally presented with low blood pressures one might ask whether paramedics adequately responded to a decrease in blood pressure or whether hypotension might be iatrogenic. To investigate this, results were subjected to Chi-square testing to establish whether a relationship existed between fluid volume and morphine and midazolam dosages administered and hypotension. The mean total volume of fluid that the sample received prehospitaly was 919.2 ml (0 – 1921.1ml). Fluid therapy had no statistically significant effect on the prevalence of hypotension regardless of the volume infused (p = 0.15). Patients who were hypotensive were given more fluid than those who were not. This was probably in an attempt to correct the hypotension. Aggressive fluid resuscitation is recommended in patients with isolated TBI to prevent hypotension (47,76) but more caution should be taken when there are potential sites of uncontrolled haemorrhage. (76) The mean fluid volume of this sample is comparable to that administered to the sample in an international study (1056ml) who had a much lower incidence of hypotension in their TBI patients (18%) at these volumes. (64) Assuming that the
fluid volume is adequate, these patients would have benefited from the uses of inotropes to improve their blood pressure and CPP. (75) However, the benefit of inotropes should be offset by the risk of hypertension and development of ARDS. (48,49)

The average Morphine dose was 8.1mg ± 5.5mg. The current data showed no association between the morphine dose administered and the prevalence of hypotension (p = 0.94). A 2011 systematic review of RCTs found however, that bolus doses of morphine might be deleterious to outcome by increasing ICP and decreasing the CPP. (77)

The average Midazolam dose in the current sample was higher than that of Morphine at 9.7mg ± 7.2mg. An association was appreciable between Midazolam dose and the prevalence of hypotension (p = 0.009) as corroborated by numerous international studies. (78,79) A 2004 study reported that Midazolam administration for induction in EC ETI was associated with a 10% decrease in the average SBP and a prevalence of hypotension of 19.5% when compared to 3.6% of patients induced with Etomidate. (79)

The use of Ketamine for induction in RSI of patients with TBI has been suggested to avoid hypotension and improve MAP and CPP. It might also have neuroprotective properties because of its effect on glutamate. (80) In the current sampled patients there was a tendency toward higher Midazolam doses in patients with higher SBP. One might speculate that these patients had higher levels of consciousness necessitating larger sedation requirements. Hypotension in our current sample might therefore be iatrogenic either by inadequate resuscitation efforts or by administration of Midazolam in high doses. As 81% of patients were intubated, this higher sedative demand might be interpreted as inappropriate airway management decisions in patients with a high level of consciousness (i.e. patients were intubated who did not need airway intervention). Yet the retrospective nature of the data does not allow for more direct conclusions other than mere speculation. Unfortunately, reliable data concerning patient weight was unavailable to evaluate medication doses and fluid volumes in relation to patient weight.

c. Hypoxaemia
The mean lowest oxygen saturation was 89.65% ± 18.42%. The prevalence of initial hypoxaemia was 37.9% (n=25) while 43.9% (n=29) of patients had at least one episode of hypoxaemia prehospitaly. Interestingly, the prevalence in this Johannesburg-based sample is much higher than that reported in the literature (22.4%), (38) even though 81% of patients were intubated. This study used a higher cut-off definition for hypoxaemia than that of Chesnut (SpO₂ 94% versus 90%) (38) – this might lead to an over-estimation of the hypoxaemic cases. The majority (68% n=45) of patients in this sample were transported by helicopter. A case can be made for the effects of altitude on the saturation levels of these patients and thus accounting for a higher prevalence in the current study. However plausible,
all patients were flown at an altitude lower than 6000 feet and on supplemental oxygen and this explanation is therefore unlikely. (81) 42.1% of patients with hypoxaemia had a concomitant chest injury that could be responsible for hypoxaemia. Much like in the case of hypotension, this relationship was statistically significant (p = 0.001).

Despite the controversies in prehospital intubation, the Brain Trauma Foundation recommends that all patients with a GCS of $\leq 9$/15, who do not have a self-maintained airway or where pulse oximetry readings remain $\leq 90\%$ have aggressive airway management in the most appropriate means plausible when considering the skill and experience level of the prehospital care provider and the milieu of the trauma system in which he or she functions. (8) Should endotracheal intubation be attempted, field RSI is the method of choice for patients with TBI. Despite these recommendations most patients (71%) were intubated using deep sedation which has been associated with more episodes of respiratory compromise and aspiration (82), however, there was no statistical difference in the prevalence of hypoxaemia in patients who were intubated in the field and in those who were not (p = 0.15). In the light of the association between hypotension and the use of Midazolam and the effects of hypotension on outcome in TBI (38,39) one should consider prehospital RSI for all patients requiring airway management after TBI. Numerous studies have demonstrated the feasibility of field RSI. (55,56,83,84,85,86) When comparing intubation by deep sedation to intubation using neuromuscular blockade successful tracheal placement improves from 81% to 97% in one study (55) and from 86% to 97% in another. (56) In the setting of proper training, experience and governance, prehospital ETI with RSI has been found to improve mortality and functional outcome in TBI from 39% to 51% (p = 0.046) in one study. (83) Other studies have agreed that RSI in TBI improves functional outcome. (84,85,86) Prehospital RSI has been associated with a mean increase in scene time of 6 minutes, (87) however; scene time has not been associated with mortality as long as adequate oxygenation, perfusion and ventilation are ensured. (63,65)

In South Africa, only paramedics with a 4-year degree in Emergency Medical care may perform prehospital RSI. (59) In 2012 there were 166 (60) of these paramedics serving a population of 50 million. (61) Even though international literature suggests that the extended scope to RSI be given to a “limited group of providers” (87) the current shortage of graduate paramedics might warrant extension of RSI scope to other prehospital practitioners in order to ensure maximum coverage to most patients. In essence, to give the most benefit to the most. This would however, require further training, monitoring tools, on-going research and continuous quality improvement measures to be in place. (87)

Forty out of 42 (95%) patients that were intubated prehospitaly were transported by helicopter while 89% of all patients that were transported by air had an advanced airway in place. This figure closely resembles that of Berlot et al who reported that 92% of all patients
with TBI flown to hospital were intubated. (64) According to standard policy and criteria, patients who have worse injuries are evacuated via helicopter preferentially and are therefore more prone to requiring advanced airway procedures and ventilation. (66,88) This might explain current trends in intubation and helicopter transport. Even though such a large amount of patients were intubated in the aeromedical group, the scene time still remained low, averaging at 10.25 minutes and ranging from as little as 3 minutes to 5 minutes. The average scene time in ground-transported patients was 31 minutes and ranged from 18 to 50 minutes. This is much lower than the scene times reported by Dybkowska et al who reported average scene times of 30 to 60 minutes (65) where scene time was related to greater intervention and lower mortality. It may be postulated that shorter scene time is over-emphasised and that intervention and stabilisation is suffering as a result. Consequently, patients are left hypotensive and hypoxaemic owing to a higher prevalence of these parameters in the current sample.

8. LIMITATIONS
Several limitations are to be considered in the analysis, interpretation and application of these results and will be outlined in the paragraphs that follow.

a. Bias
This study is limited by potential reporting, recall, measurement and selection bias. Reporting bias might have resulted as paramedics might inherently be less willing to record grossly abnormal values believing that this will negatively reflect on the quality of patient care that they provide. Reporting bias will skew the data by underestimating the prevalence of hypotension and hypoxaemia. Recall bias is the result of practitioners unable to remember the details and clinical data of patients after completion of the case. Even though it has likely influenced the results, quality assurance requires practitioners to complete their documentation as soon as they have handed over care of a patient to the EC – this influence might therefore be minimised effectively by this measure to negate the effect on results. The role of measurement bias in the interpretation of the results should not be underestimated as the accuracy of instrumentation used to measure hypotension and hypoxaemia might not be entirely calibrated to deliver accurate values. Literature however, addresses these issues: A study (2010) performed in Johannesburg on a provincial service found that 37% of sphygmomanometers were inaccurate within 3-10mmHg. (89) In addition, pulse oximeters in the emergency setting are generally said to have a sensitivity of 92% and a specificity of 90%. (90) The accuracy in the determination of the initial GCS could also be called into question and might sample patients into the study that do not actually fit the inclusion criteria, or yet exclude others. A 2010 study among prehospital providers in Johannesburg found that 67% of the sample studied was able to accurately calculate the GCS scores of patients. (3) Selection bias might result as patients were clinically diagnosed with TBI and the final diagnosis was not confirmed with more accurate diagnostic mechanisms (such as
computerised topographic scans). Follow-up was not feasible as many patients were anonymised and the study scope was limited by the resources available. Patients who therefore did not truly suffer a TBI but who might have decreased levels of consciousness from haemorrhagic shock and hypotension and hypoxaemia could therefore have been included in the sample, falsely elevating the results.

b. Quality of Data
Apart from the biases discussed above, the inherent quality of the documentation reviewed might limit the conclusions and interpretation that one may draw from the current findings. The quality of clinical data onto which inclusion and exclusion criteria were applied is fundamentally limited by the language proficiency and ability to communicate clinical findings in written format of the prehospital care providers. Often times patients (especially those airlifted) were sedated and intubated on scene and the pre-sedation GCS and pre-intubation saturation levels were not recorded. This falsely lowers the GCS and increases the oxygen saturation levels which could lead to overestimation of TBI severity and underestimation of hypoxaemic prevalence. Mechanism and injury data were not available for 21% (n = 14) of records and these could therefore not be included in further analysis. Even though a correlation was appreciable between injury and hypotension and hypoxaemia, many records did not have enough clinical information to determine an injury severity score and this could therefore not be correlated to hypotension and hypoxaemia. In the case of RTCs, the position of the patient (driver vs. passenger) was also not recorded. Correlation of these data with injury severity and seatbelt use would have been of interest. Finally, patient weight was not available for consideration in the relationship between drug dosage and fluid volume and the prevalence of hypotension.

c. Limitations in methodology
The current study used a retrospective chart review methodology of cases in 2011. Today, two years later, the data presented might not be representative of the current situation. The study is also affected by the inherent limitations of a retrospective design as outlined in the other sections. A retrospective study design can also not be used to determine association and causation but can only postulate on such relationships. Finally, the current study employed a higher cut-off definition than the other international studies cited (SpO₂ 94% versus 90%) for reasons outlined previously and could have resulted in an overestimation of the prevalence of hypoxaemia in this patient sample.

d. Validity
The generalisability of this study is poor as it was conducted on patients with moderate to severe head injury in Johannesburg and most data (79%; n = 46) were obtained from a single private emergency medical services company. National and international extrapolation is therefore limited by geographical confines and all associated socio-economic factors as well as a relatively small sample size. Nevertheless, despite not reaching the protocolled sample size, all patients that fit the inclusion criteria within the allotted timeframe were included. The
current investigation is purely an observational study using descriptive analysis and consequently the sample size becomes irrelevant.

9. RECOMMENDATIONS

Research begets research – and true to this age-old adage the current results have answered some questions and ask many others. Ethically, well-designed prospective randomised controlled trials cannot be undertaken, yet it is recommended that a prospective prevalence study be designed at National level to determine the true extent of hypoxaemia and hypotension in moderate to severe head injuries. This study should allow for patient follow up and to determine whether these insults influence mortality in the specific context of the developing world. It should further definitively confirm the diagnosis of TBI via imaging and investigate a haemorrhagic aetiology for hypotension and a pulmonary aetiology for hypoxaemia. The prevalence of hypo- and hypercapnoea should also be investigated under these circumstances.

Educational interventions might result in stricter adherence to road and seatbelt safety in patients and decrease the burden of TBI in Johannesburg and the effect of such an intervention should be recorded and analysed. Similarly, educating prehospital care providers might ensure closer adherence to international TBI intervention guidelines in the absence of local prehospital TBI protocols which should be developed as a matter of urgency. Closer adherence to such guidance has been shown to decrease the prevalence of secondary insults and in turn, improving patient outcome. (91,92)

In the light of current literature showing a strong association between hypotension and mortality and the current results leaning toward a relationship between Midazolam dosage and hypotension, alternative means of prehospital intubation should be sought. A protocol review is needed, which might include RSI or use of Ketamine into the scope of other paramedics. Alternatively, more graduates should be delivered to supply such skills and legislation should support the sole use of RSI for ETI of TBI patients. Helicopters should solely be staffed by graduate paramedics or physicians who bring this higher scope of expertise to the roadside. Prospective studies should be designed to determine the effect of prehospital deep sedation vs. RSI on outcome in the TBI population.

In order to make South African data more comparable to international studies, the effect of scene time and aeromedical evacuation on outcome could be investigated, as data from the current study showed a tendency towards shorter scene times and a higher prevalence of hypoxaemia and hypotension.
10. CONCLUSION

Hypotension and hypoxaemia has been shown to significantly contribute to mortality and poor outcome in patients who have sustained TBI. These insults have a larger influence on mortality and morbidity when they occur in the acute (prehospital) phase following injury. This study was therefore aimed at establishing the demographic profile and the prehospital prevalence of hypotension and hypoxaemia in a Johannesburg-based sample of patients with moderate to severe TBI. Demographics and mechanism of injury were similar to international and earlier local studies. The group at highest risk for sustaining TBI was Black males between the ages of 24 and 44 years. Similar to previous and international literature the prevalence of hypotension and hypoxaemia in the current sample was 33.3%. A strong association existed between concomitant injuries that could lead to the development of hypotension and the dose of Midazolam that a patient received and the prevalence of hypotension. The study was however, not designed to reliably determine such associations. The prevalence of hypoxaemia was higher in the studied sample than that reported in international literature (43.9% vs. 22.4%). An association between hypoxaemia and chest injuries was also appreciable and further investigation to determine these associations is warranted. Good quality, prospective cohort studies produced locally, that follow up to definitive diagnosis and outcome investigating the influence of prehospital interventions on hypoxaemia, hypotension and mortality should be sought. Finally, the current study pointed towards a critical need for educational interventions and the development of a national TBI protocol for prehospital care providers that is based on sound clinical evidence and can guide their decision-making on the most appropriate interventions in the prehospital setting to maximise outcome. Further to this protocol, the paramedic scope should be re-evaluated on all levels to empower paramedics with the tools required to practice evidence-based medicine.
11. BIBLIOGRAPHY

### 12. APPENDIX A: SEARCH STRATEGY

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PART B: ADDENDA FOR UNIVERSITY PURPOSES

1. ORIGINAL PROTOCOL

THE PREVALENCE OF HYPOTENSION AND HYPOXAEMIA IN THE PREHOSPITAL SETTING OF TRAUMATIC BRAIN INJURY IN JOHANNESBURG, GAUTENG

By

Willem Stassen
STSWIL 0001

A RESEARCH PROTOCOL
SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfilment of the requirements for the degree

MASTER of Philosophy in Clinical Emergency Medicine

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission: 16 November 2011
Supervisor: Tyson Welzel
**TABLE OF CONTENTS**

1. BACKGROUND AND LITERATURE REVIEW .............................................. 1  
   a. Introduction and Background...................................................... 1  
   b. Literature review ....................................................................... 1  
      i. Definitions and Key Concepts ....................................... 1  
      ii. The Impact of Prehospital Care on Outcome ................. 2  
      iii. Limiting Secondary Brain Injury: Hypotension and  
           hypoxaemia .................................................................. 3  

2. AIMS AND OBJECTIVES............................................................................. 4  

3. METHODOLOGY .......................................................................................... 5  
   a. Study design and methods ......................................................... 5  
   b. Data Management ...................................................................... 5  
   c. Limitations and Bias ................................................................ 6  
   d. Sampling..................................................................................... 6  
   e. Data Analysis.............................................................................. 7  

4. ETHICAL CONSIDERATIONS ................................................................ 7  
   a. Permission to access patient records ......................................... 7  
   b. Consent ...................................................................................... 7  

5. WORK PLAN ........................................................................................... 8  
   a. Budget ........................................................................................ 8  
   b. Timeframe................................................................................... 8  

6. DISSEMINATION OF FINDINGS ............................................................... 9  

7. REFERENCES .......................................................................................... 10  

8. APPENDICES.......................................................................................... 13  
   a. Appendix A: Letter for Permission............................................. 13
1. BACKGROUND AND LITERATURE REVIEW
   a. Introduction and Background

   Following a head injury, any minor insult may be detrimental to patient outcome. Patients are particularly susceptible to these insults in the acute phase immediately post-injury. For this reason, prehospital care is of particular importance in order to prevent these insults and improve morbidity and mortality.

   This study will aim at determining the prevalence of hypotension and hypoxaemia in this acute, prehospital phase and secondly to describe the demographic profile of patients who have sustained head injuries in Johannesburg, Gauteng.

   b. Literature review
      i. Introduction and definitions

   Traumatic Brain Injury (TBI) or Head Injury (HI) refers to the damage (either real or potential) of intracranial structures due to blunt or penetrating trauma to the head. Included in this definition is the cascade of events that follows this injury such as intracranial haemorrhage and cerebral oedema. HI might be classified into three categories according to the modified Glasgow Coma Score (GCS) measured at initial presentation. These categories are Mild (GCS 14-15), Moderate (GCS 9-13) and Severe (GCS ≤8). On average mild head injury accounts for 80% of these cases, while moderate to severe head injury accounts for the remaining 20% (10% each). The discussion will focus on the latter 20%, as this is the population which will be studied.

   This specific population was chosen as these are the patients in which aggressive and correct prehospital treatment can make the most difference. 7, 14 The GCS measure of severity was chosen as this is the most widely used, most widely known, and one of the only measures that all levels of prehospital practitioners are trained to use. It was designed and validated to assess patients with head injuries. It is however less predictive in younger patients and patients with less severe head injuries. 19 This study will exclude this population, and the GCS is therefore a valid and reliable measure. 19, 20

   Each year an approximate 89 000 new cases of head injury (of any severity) are reported in South Africa, according to the National Institute for Occupational Health (2011). Of these cases, 50% are due to road accidents (bicycle, vehicle or pedestrian), 25% are due to falls and a further 25% are due to violence. 2 An epidemiology study conducted in Johannesburg, Gauteng in 1991 reports an annual incidence of TBI of 316 per 100 000, with an overall mortality in Johannesburg of 80 per 100 000 cases. 3

   An exhaustive outline of the pathophysiological mechanisms of traumatic brain injury is beyond the scope of this discussion however, some key concepts will be briefly mentioned next.
The brain is encapsulated in a rigid cranial vault, which is unforgiving for any changes in brain volume or intracranial pressure (ICP). Should the ICP rise, compensation will occur up to a critical point, where after the mean arterial pressure (MAP) needs to increase in order to overcome the ICP and maintain cerebral perfusion pressure (CPP). Should MAP not rise to counteract this, CPP will be compromised, causing cerebral ischaemia. 14

At present, it is not possible to reverse the damage caused by the traumatic event itself, and the aim of treatment is therefore focused on preventing further injury (the so-called secondary brain injury) in order to improve outcome.

ii. The Impact of Prehospital Care on Outcome
It has been suggested that the cerebral tissue is particularly vulnerable to all of these harbingers of secondary brain injury in the phase immediately following the primary injury. Reasons for this are thought to be related to ischaemia of cerebral tissue, cerebral inflammatory processes and failure to autoregulate CPP. 4,7,9,14,15 Studies suggest that with appropriate prehospital care delays in transport of up to four hours do not have an influence on outcome. 14 It is therefore recommended that all patients who might require neurosurgical consultation be stabilised on scene initially, if possible and be transported to trauma centres with the appropriate resources, even if closer centres are bypassed. 7,14 The prehospital phase of head injury management has been termed to be critical in final outcome 7 and prehospital care was said to be as important as time to definitive care. 14

iii. Limiting Secondary Brain Injury: Hypotension and Hypoxaemia
Secondary brain injury refers to further insults after the initial traumatic event that might mark the onset of further pathophysiological effects within cerebral tissue, which might worsen the condition of the patient and start their decline to neurological deficit or death. 4 These insults are categorised as systemic (hypotension, hypoxia, hypercapnoea, hypocapnoea and anaemia) or intracranial (intracranial hypertension, seizures, cerebral oedema and compressive haemorrhage). 1 Many of these are easily preventable or treated (limited at the least) in the prehospital setting. The impact of hypotension and hypoxaemia on outcome and management principles will be discussed next.

Hypotension
Hypotension (systolic blood pressure (SBP) <90mmHg) is associated with a worse outcome in patients with TBI as this interrupts CPP. 1,5 It is predicted that 35% of all patients with TBI will experience episodic hypotension at some point in their recovery process. The Traumatic Coma Bank Database reports that prehospital hypotension almost doubles the mortality (27% to 64.8%) and decreases good outcome from 51.1% to 19.4% in moderate to severe TBI. 1,5,6 Numerous other studies identify hypotension as an independent risk factor and important predictor of outcome in TBI. 1,4,9 For these reasons it is recommended that blood pressure (BP) should be monitored frequently in the prehospital setting and by the most accurate means available and should be treated aggressively. 7
Hypoxia

Hypoxia (PaO$_2$ < 60 mmHg or SpO$_2$ < 90%) occurs quite often after TBI and has been associated with a doubling of mortality in severe TBI. It has been found that a hypoxic event in the prehospital setting increases the mortality from 27% to 50% when hypoxia has not occurred. The odds of good neurological outcome are decreased from 51% to 29% when associated with hypoxia. When adding hypotension to hypoxia, this mortality rate increases to 75% and chances of good outcome decreases to 5.8%. A millennial study conducted in South Africa reported that 58% of patients experienced potential secondary brain injury (hypoxic or hypotensive event or both) in the pre-admission phase of their care. Continuous pulse oximetry monitoring during prehospital management is mandatory in order to have a measure of oxygenation. Rapid sequence intubation is recommended in the field should a patient be unable to protect their own airway, maintain a SpO$_2$ of greater than 90% despite oxygen supplementation or if their GCS is below 9.

(c. Importance of completing this project

Firstly, this study will provide valuable information regarding burden of head injury in Johannesburg. It will inform the areas and population that we need to focus on regarding prevention strategies. The literature presented identified prehospital hypotension and hypoxaemia as factors predictive of poor outcome in moderate to severe HI and it is therefore essential to establish its prevalence. Hereafter, we can determine how much emphasis we should place on prehospital corrective measures during training and continued education.
2. AIMS AND OBJECTIVES
This study primarily aims to establish the prevalence of prehospital hypotension and hypoxaemia in moderate to severe head injury in the Greater Johannesburg area, Gauteng, South Africa.

The Objectives of this study will be:
- To describe the demographic characteristics of patients with moderate to severe head injury.
- To determine the prevalence of hypotension in moderate to severe head injury.
- To determine the prevalence of hypoxaemia in moderate to severe head injury.

3. METHODOLOGY
a. Study design and methods
A retrospective cross-sectional descriptive (chart review) design will be used. Patient report forms will be obtained from ER24 and the prehospital patient care database of the University of Johannesburg (EMDATA) for the entire year of 2011. The EMDATA base covers all the cases seen by 1st to 4th years in their academic year, regardless of the service they worked with. This database will therefore be representative of cases which might not have been covered by ER24 (cases done by ER24 will be excluded from the EMDATA search). Adult (18 years and older) patients with suspected moderate to severe blunt traumatic brain injury (GCS ≤13) transported by ambulance or helicopter will be selected regardless of the level of care that they experienced prehospitaly.

The following variable will be extracted from the records: demographic characteristics such as age, gender, race, mechanism of injury, severity of TBI and concomitant injuries will be recorded. The prevalence of hypoxaemia (SpO₂ of 94% or less) and hypotension (SBP less than 90mmHg) will also be recorded. Initial prevalence is defined as a patient who presents with hypotension or hypoxaemia before intervention by the prehospital crews. Prehospital prevalence is defined as any episode of hypotension or hypoxaemia during the prehospital care and transport of the patient, regardless of intervention and excluding initial prevalence.

b. Data Management
Patient report forms (from ER24) are in written format, while patient care records (from EMDATA) are in electronic form. Written and electronic records will be captured in a password protected Excel spread sheet by two data capturers. The data will be consolidated and compared electronically. Should a field of a record be omitted, the entire record will be regarded as invalid and the specific record will be discarded. Disputes or discrepancies will be settled by the principal investigator, who will make a judgment on what is written on the data sheet - his answer will be the final and be accepted as such.
These Excel spreadsheets (and the electronic patient records) will be backed-up to two different external hard drives. These hard drives along with the original written records sheets will be locked away in a fire-proof safe. Only the primary researcher and the research supervisor will have access to data once it is locked away.

c. Limitations and Biases
The shortcomings of this study are listed:

- Recall bias might play a role in the accuracy of recall of the vital signs by the ambulance personnel. Recall bias might be minimised as prehospital providers are expected to complete their patient care records before shift handover.

- Measurement bias might play a role in the different instrumentation used by the ambulance personnel. A study (2010) performed in Johannesburg on a provincial service found that 37% sphygmomanometers were inaccurate within 3-10 mmHg.\(^1\) Pulse oximeters in the emergency setting are generally said to have a sensitivity of 92% and a specificity of 90%.\(^2\)

- The accuracy of the calculation of the initial GCS might also be dubious. This might include patients into the study that do not actually fit the criteria, or yet exclude others. A 2010 study among prehospital providers in Johannesburg found that 67% of the sample is able to accurately calculate the GCS scores of patients.\(^3\)

d. Sampling
Assuming that the population of Johannesburg is 3.6 million people\(^4\) and the incidence of TBI is 316 per 100 000,\(^3\) then the total cases are 11 376 per annum \((3\ 600\ 000 \div 100\ 000 \times 316)\). Of this population only 20% will fit the inclusion criteria (mild or moderate TBI), leaving the sampled population to be 2275 (20% of 11 376) in one year. A statistically significant sample would therefore be:

\[
\frac{N}{n} = 1 + N(e)^2
\]

\[
\frac{1137.5}{n} = 1 + 1137.5(0.05)^2
\]

\[
n = 340\ per\ annum.\ A\ quota\ sampling\ technique\ will\ be\ utilised.
\]
e. Data Analysis
A descriptive analysis method will be used to present categorical data. Means, medians and interquartile ranges will be calculated for numerical data using a 95% confidence interval and the 2010 version of Microsoft Excel. A percentage of patients with hypoxic episodes, hypotension and other injuries will also be presented. The prevalence of these will be calculated. Finally, the average vital signs (blood pressure, saturation levels, heart rate and GCS) will be calculated and presented. These numerical data will be presented according to the demographics of patients as well as level of care. The data will be subjected to a Chi square test in order to determine variance between prevalence among different demographic characteristics (age, gender, race, and mechanism of injury), level of care (basic, intermediate, advanced life support or emergency care practitioner) and the presence of other injuries (long bone fractures, suspected occult haemorrhage, external haemorrhage, chest injuries).

4. ETHICAL CONSIDERATIONS
a. Permission to access patient records
After approval by the University of Cape Town Departmental Research Committee and ethical approval, permission will be obtained from ER24 and University of Johannesburg for access to the patient records.

Permission to have access to the records will be obtained by hand-delivering the letter requesting permission (Appendix A) to the relevant parties along with the ethics certificate and the approved proposal. Written permission will then be obtained and data collection will commence.

b. Consent
Application will be made for a waiver of consent as this is a retrospective record review. Patients and the treating practitioners will remain anonymous and strict confidentiality of all data will be ensured (see data management). Identifiable data will therefore not be disclosed.
5. WORK PLAN

a. Budget

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6. DISSEMINATION OF FINDINGS

Results will be written up in a full dissertation document which will be bound and placed on disc and made available to the Department of Emergency Medicine. Results will be published in an appropriate peer-reviewed journal.
7. REFERENCES


8. APPENDICES

c. Appendix A: Letter for Permission

Good day,

I am a Masters student in the program Emergency Medicine at the University of Cape Town (UCT). As part of this program, I am required to complete a thesis within the sphere of emergency medicine. I am conducting a descriptive, retrospective patient record review study on the prevalence of hypotension and hypoxaemia in the prehospital setting of patients with moderate to severe traumatic brain injury. Demographic data these patients in the Greater Johannesburg area will also be collected. The prehospital phase is critical in the prevention of secondary brain injury, and is therefore pivotal in the eventual morbidity/mortality of these patients, and determining the prevalence of these factors (known to impact negatively on outcome) is therefore essential to provide a foundation for further research.

This study will involve looking at all the patients with moderate to severe head injury (GCS ≤13) in the year of 2010 seen in Johannesburg by your institution. The patient report forms (or care records) will be reviewed for any episodes of hypotension or hypoxaemia. Data will then be analysed and written up.

Ethical approval of this study was granted by the Emergency Medicine Departmental Research Committee of University of Cape Town, and later confirmed by the Research Ethics committee of this University. The ethics certificate and approved research protocol are attached.

Before initiating this study, I will require a letter granting me permission to have access to the patient records. This study WILL NOT identify any of your staff or the patients themselves and will purely be descriptive. Please could you get back to me in this regard as soon as possible. If there is other relevant people that I would need to contact in order to obtain permission, could you please be so kind to forward me their details.

Regards,

Willem Stassen
stassen88@gmail.com
0765022187
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**Prevalence of Hypotension and Hypoxaemia – STSWIL001**
3. NONDISCLOSURE AGREEMENTS OF DATA CAPTURERS

THE PREVALENCE OF HYPOTENSION AND HYPOXAEMIA IN THE
PREHOSPITAL SETTING OF TRAUMATIC BRAIN INJURY IN JOHANNESBURG,
GAUTENG

UCT MASTERS STUDY

NONDISCLOSURE AGREEMENT

I \textbf{T.L. KRIEL} \underline{\hspace{5cm}} have agreed to capture raw data in the
above-mentioned study. I have not been given any compensation for this service. I
have captured the data to the best of my knowledge and believe my capturing to be
a true reflection of the patient records.

I realise that the data that I captured is sensitive and confidential. I agree to not
divulge any of the information that I have viewed to any parties unless required to do
so by law.

[Signatures]

Signed \hspace{1cm} \hspace{1cm} Principal Investigator
I have agreed to capture raw data in the above-mentioned study. I have not been given any compensation for this service. I have captured the data to the best of my knowledge and believe my capturing to be a true reflection of the patient records.

I realise that the data that I captured is sensitive and confidential. I agree to not divulge any of the information that I have viewed to any parties unless required to do so by law.

Signed

Principal Investigator
4. INSTITUTIONAL CONSENT

Good day Mr Stassen

We have pleasure in confirming that your research proposal has been accepted and approved by the committee. We confirm that you have access to documentation as requested in your proposal.

We look forward to a long and mutually beneficial relationship going forward and await the final document.

Kindest regards

[Signature]

Jill Lithgow
Education, Training and Development Manager
ER24 EMS
Manor 4, Cambridge Manor, Cnr Witskoppen & Stonehaven, Paulshof
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Website: www.er24.co.za
GPS: S 26° 02’ 08” / E 028° 03’ 09”
Access to EMDa
da

Lambert, Craig <clambert@uj.ac.za>
To: "stassen88@gmail.com", "stein@uj.ac.za"

Dear Mr Stassen

The Department has considered your request and have agreed to make our data available for your research study.

Please go ahead and contact Mr Stein regarding the logistical arrangements.

I wish you all the best with your projects and trust you will share with us a copy of the final dissertation.

regards

C Lambert
Head: Department of Emergency Medical Care & Podiatry
FACULTY OF HEALTH SCIENCES
+27 11 559 6257
clambert@uj.ac.za

-----Original Message-----
From: Willem Stassen <stassen88@gmail.com>
Sent: Tuesday, April 24, 2012 9:49 AM
To: Lambert, Craig; Stein, Chris
Subject: Access to EMDa
5. SURGICAL DRC-APPROVAL

8th February 2012

Willem Stassen
Department of Surgery
Division of Emergency Medicine
Groote Schuur Hospital
University of Cape Town

Dear Mr Stassen

RE: PROJECT 2012/016

PROJECT TITLE: The prevalence of hypotension and hypoxaemia in the prehospital setting of traumatic brain injury in Johannesburg, Gauteng

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely,

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE
6. ETHICAL APPROVAL

TO MR W STASSON,

DEAR MR STASSON,

PROJECT TITLE: THE PREVALENCE OF HYPOTENSION AND HYPOXAEAMIA IN THE PREHOSPITAL SETTING OF TRAUMATIC BRAIN INJURY IN ADULTS WITH BRIEF CONSCIOUSNESS

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

Approval is granted until 28 March 2013. Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS010).

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely,

[Signature]

PROFESSOR MARC BLOKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

This serves to confirm that the University of Cape Town Human Research Ethics Committee concurs with the Ethical Standards of Clinical Research as set out in the guidelines of the National Research Council (NRC-SA), Food and Drug Administration (FDA-US), International Convention on Harmonisation Good Clinical Practice (ICH-GCP) and Declaration of Helsinki 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.
7. ACKNOWLEDGEMENTS

I would like to acknowledge the following individuals for their assistance in the completion of this research project.

- Dr. Tyson Welzel for his technical expertise as research supervisor.
- Dr. Heike Geduld for her advice on the research scope and research design.
- Dr. Robyn Holgate and Mrs Jill Lithgow for their prompt feedback and permission to obtain records from ER24.
- Mr Jester Ogle for his assistance in obtaining the records through ICD10-code searching.
- Mrs Liesl van der Nett for her assistance in gaining access to the helicopter case sheets.
- Mr Chris Stein for his assistance in obtaining the records through EMData.
- Mr Theodore Kriel and Mr Bruce Culley for capturing the data free of charge.
- Dr. Justin Harvey for his advice on statistical analysis.
- Prof. Rhena Delport for her advice on statistical analysis.