Outcomes of Major Trauma Patients Receiving Pre-Hospital Adrenaline for Haemodynamic Instability at Charlotte Maxeke Johannesburg Academic Hospital

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Abstract

Background: Trauma is a major cause of morbidity and mortality in South Africa, with more than five million people losing their lives worldwide per year due to major trauma. Current fluid resuscitation guidelines for shock are acceptable to most centres, but there is still debate on the role of vasopressor use, particularly in the pre-hospital setting. Therefore, the purpose of this study was to determine if pre-hospital adrenaline use in major trauma patients with hypotension results in higher in-hospital mortality in South Africa.

Results: Of the 8,210 priority 1 trauma patients seen at this Trauma Unit over a period of 72 months (from Jan 2011 to Dec 2016), only 460 met the study inclusion criteria of systolic blood pressure <90mmHg. Thirty-two (7%) of the 460 patients received pre-hospital adrenaline whilst 428 (93%) did not. The 24-hour mortality in patients receiving pre-hospital adrenaline was 37.5 % compared to 7.2% in the no pre-hospital adrenaline group. The 24-hour mortality of trauma patients who received pre-hospital adrenaline was 7.7 times (95% CI 3.4-17.2; p = 0.21) higher than that of patients not receiving pre-hospital adrenaline. The 30-day mortality rate was 37.5% for patients receiving adrenaline and 12.4% for patients not receiving pre-hospital adrenaline. The 30-day mortality of patients receiving pre-hospital adrenaline was 4.2 times (95% CI 2.0-9.1; p = 0.52) higher than in patients not receiving pre-hospital adrenaline.

Conclusion: Pre-hospital adrenaline use in hypotensive major trauma patients showed a statistically insignificant trend towards increased in-hospital mortality at 24 hours and at 30 days. Therefore, the role of selective use of pre-hospital adrenaline for hypotensive major trauma patients remains a challenge.

Keywords

Adrenaline Use; Hypotensive Resuscitation; Prehospital Care

Introduction

Approximately five million people lose their lives annually worldwide through major trauma of which almost 50% are young people between the ages of 15 to 44, with road accidents constituting the 2nd most common...
cause of these premature mortalities [1]. Statistics South Africa released a deaths report in 2017 on data from 1997 to 2015. Annual non-natural causes deaths ranged from 8.7% to 17% over this period of 20 years with young people of 15 - 49 years attributing 62.9% of such deaths, of which 77.3% were males [2].

Major trauma patients classified as Priority 1 (P1) patients, are individuals with immediately life threatening injuries [3], likely to develop organ dysfunction and haemodynamic instability [4] with shock and death often ensuing if no treatment action is taken [5,6]. Advanced Trauma Life Support (ATLS®) guidelines support the use of intravenous fluids for management of hypovolemia as the cornerstone of treating haemorrhagic shock [6-9]. Bouglé et al., and Coppola et al., likewise suggested that fluids are the first therapeutic measure for traumatic haemorrhagic shock [8,9]. The aim during initial resuscitation of major trauma patients is to achieve permissive hypotension i.e., blood pressure high enough to permit perfusion to vital organs, but low enough to prevent exsanguination [8-10].

Although studies demonstrated early use of fluids as the first strategy to be associated with better patient outcomes [7-11], it is sometimes inadequate to ensure tissue perfusion [11]. Furthermore, Haut et al., showed that prehospital intravenous fluids may be associated with higher mortality [12]. Adding to the controversy, in support of Haut et al., data from the Iraq war and other battle fronts suggested delayed fluid resuscitation as more beneficial [13-15]. If this is true, how can blood pressure and tissue perfusion be maintained? By early use of vasopressors? Beloncle et al., suggested that transient use of vasopressor agents may sustain life and maintain tissue perfusion in persistent hypotension [11]. Vasopressor agents such as noradrenaline and adrenaline reduce the radius of the arterial blood vessels, thereby facilitating tissue perfusion without the need for large fluid volume administration or transfusions [8,11].

Some studies however suggested that the use of vasopressors in the trauma setting is associated with increased mortality [16,17]. For example, Collier et al., demonstrated that patients receiving vasopressors fared worse than patients not receiving vasopressors for refractory hypotension [16]. However, the vasopressor-exposed group may have fared worse as they had more severe injuries, and the mortality in the vasopressor-exposed group was expected to be close to 100% with or without vasopressor use [16]. Furthermore, Sperry et al., revealed that early vasopressor use was independently associated with a more than 80% risk of mortality (p = 0.013) [17].

In the South African prehospital setting, adrenaline bolus or intravenous infusions are used in the presence of advanced life support crews or emergency physicians [18,19]. Patients commenced on adrenaline before hospital admission are often the non-responders to fluid resuscitation or those with suspected cardiogenic or neurogenic shock [7,18,19].

Though there are arguments for and against early use of vasopressors in non-African population trauma patients, there is no such evidence from South Africa or the African continent. Furthermore, while there is uncertainty in the literature as to whether vasopressor use is associated with better outcomes in major trauma patients, there is also no data on prehospital adrenaline use in major trauma patients in South Africa.

Therefore, this study aimed to determine if prehospital adrenaline in major trauma patients with on-scene hypotension resulted in higher in-hospital mortality in the South African context.

Study Design and Methodology

Study design

This was a retrospective data collection study encompassing MediBank Resus Forms, operative record forms, clinical ward records and discharge summaries of major trauma patients presenting to the Trauma Unit at the Charlotte Maxeke Johannesburg Academic Hospital in South Africa.

Types of patients involved

Although a total of 8210 major trauma patients were treated during the study period of 72 months (Jan 2011 to Dec 2016), only 460 patients had a pre-hospital systolic blood pressure <90mmHg, no established hypertensive disease, a complete MediBank Resus Form and were older than 18 years. Patients with prehospital spontaneous cardiac arrest were excluded.

Types of data collected

Patient demographic characteristics including age, gender and race were collected. Patient physiological characteristics including Glasgow Coma Scale (GCS) upon arrival at the Trauma Unit, severity of trauma, evidence of hypothermia and acid-base status were recorded. Patient interventional characteristics including fluid resuscitation status, blood and blood product transfusion status, and whether operated were also collected. Data on whether a patient received prehospital adrenaline or not, and the 24 hour mortality and 30 day mortality were recorded.

Types of analysis used

Statistical analysis was done with assistance from the Steve Biko Biostatistics Centre, Faculty of Health Sciences, University of the Witwatersrand using the STATA V14 programme.
A p-value of < 0.05 was considered statistically significant. The null hypothesis was: prehospital adrenaline use in on-scene hypotensive major trauma patients is associated with a higher in-hospital mortality. Data on confounding factors were analysed by binomial regression analysis to eliminate these effects when determining the odds ratio between the adrenaline and the no adrenaline groups.

**Ethics approval and study permission**

Ethical approval was obtained from the Human Research Ethics Committee (HREC) (medical) of the University of the Witwatersrand with the clearance number: M160750. Permission to collect patient data and access MediBank Resus Forms and patient records was obtained from the Trauma Unit as well as from the hospital management.

**Results**

A total of 460 major trauma patients with a prehospital systolic blood pressure < 90mmHg and a complete MediBank Resus Form were included in the study.

| Demographic Characteristic | No Adrenaline Use (n = 428) | Adrenaline Use (n = 32) | 24 hour Mortality | 30 Day Mortality | p-Value |
|----------------------------|-----------------------------|-------------------------|-------------------|------------------|---------|
| Age                        |                             |                         |                   |                  |         |
| 18 – 25                    | 86 (20.1%)                  | 1 (3.1%)                | 0.55              | 0.55             |         |
| 25 – 44                    | 302 (70.6%)                 | 26 (81.3%)              | 0.51              | 0.51             |         |
| 45 – 65                    | 31 (7.2%)                   | 5 (15.6%)               | 0.06              | 0.06             |         |
| > 65                       | 9 (2.1%)                    | 0 (0%)                  | -                 | -                |         |
| Sex                        |                             |                         |                   |                  |         |
| Male                       | 382 (89.3%)                 | 30 (93.8%)               | 0.17              | 0.25             |         |
| Black                      | 405 (94.6%)                 | 30 (93.8%)               | 0.87              | 0.78             |         |
| Race                       |                             |                         |                   |                  |         |
| Black                      | 159 (37.1%)                 | 28 (87.5%)               | 0.99              | 0.99             |         |
| Blunt                      | 263 (61.4%)                 | 4 (12.5%)                | 0.68              | 0.68             |         |
| Penetrating                | 6 (1.4%)                    | 0 (0%)                  | -                 | -                |         |
| Burn                       | 39 (9.1%)                   | 0 (0.0%)                | 0.90              | 0.90             |         |
| Mode of Transport          |                             |                         |                   |                  |         |
| Private                    | 385 (90.0%)                 | 27 (84.4%)               | 0.50              | 0.50             |         |
| Ambulance                  | 111 (25.9%)                 | 0 (0.0%)                | 0.44              | 0.44             |         |
| Helicopter                 | 131 (30.6%)                 | 1 (3.1%)                | 0.85              | 0.85             |         |
| HLOE                       |                             |                         |                   |                  |         |
| BLS                        | 136 (31.8%)                 | 31 (96.9%)               | 0.17              | 0.17             |         |
| ILS                        | 6 (1.4%)                    | 0 (0.0%)                | 0.83              | 0.83             |         |
| ALS                        | 44 (10.3%)                  | 0 (0.0%)                | -                 | -                |         |

Table 1: Demographic characteristics of patients with numbers for each characteristic in terms of adrenaline, no adrenaline and p-values for that characteristic’s 24 hour and 30 day mortality.

HLOE: Highest Level of Education of initial responder; BLS: Basic Life Support; ILS: Intermediate life support; ALS: Advanced Life Support
Physiological characteristics

Patients in the prehospital adrenaline group had a higher incidence of hypothermia, acidosis, severe trauma and a Glasgow Coma Score (GCS) of less than 8 on arrival, compared to the patients in the no prehospital adrenaline group (Table 2).

Interventional characteristics

Patients in the prehospital adrenaline group had a higher fluid resuscitation status, blood and blood product transfusion status and intubation rate in comparison to patients in the no prehospital adrenaline group. Nearly an equal percentage of patients in both groups received operative care. None of the interventional patient characteristics influenced mortality (Table 3).

Mortality outcomes

The 24 hour and 30-day mortality rates in patients in the adrenaline and no adrenaline groups showed that patients in the adrenaline group had higher mortality rates at 24 hours and at 30 days, although neither is statistically significant (Table 4).

Data Analysis

Patients who received prehospital adrenaline had a 7.7 times (95% CI 3.4-17.2; p = 0.21) higher risk of 24-hour mortality than patients who did not receive prehospital adrenaline. Likewise, patients who received prehospital adrenaline had a 4.2 times (95% CI 2.0-9.1; p = 0.52) higher risk of a 30-day mortality than patients who did not receive prehospital adrenaline. Based on binomial regression analysis the relationship between prehospital adrenaline use and mortality was not statistically significant for either 24 hour or 30-day mortality. Except for hypothermia and severe acidosis, no other demographic, physiological and interventional factors recorded contributed significantly to the 24 hour and 30-day mortality. Further analysis of the confounding factors tested the relationships between acidosis, hypothermia, severe trauma and 24-hour mortality. A similar analysis was performed for 30-day mortality. This analysis was done to determine if such

| Physiological Characteristic | No Adrenaline Use (n = 428) | Adrenaline Use (n = 32) | p-Value |
|-----------------------------|----------------------------|------------------------|---------|
|                            | 24 hour Mortality          | 30 Day Mortality       |         |
| GCS <8 on Arrival           | 97 (22.7%)                 | 27 (84.4%)             | 0.18    | 0.13    |
| Severe Trauma [RTS < 4]     | 58 (13.6%)                 | 25 (78.1%)             | 0.14    | 0.11    |
| Hypothermic                 | 109 (25.5%)                | 15 (46.9%)             | 0.02    | 0.02    |
| Severe Acidosis             | 148 (34.6%)                | 19 (59.4%)             | <0.001  | <0.001  |

Table 2: Physiological characteristics of patients with numbers for each characteristic in terms of adrenaline, no adrenaline and p-values for that characteristic’s 24 hour and 30-day mortality. GCS: Glasgow Coma Score; RTS: Revised Trauma Score

| Intervenational Characteristic | No Adrenaline Use (n = 428) | Adrenaline Use (n = 32) | p-Value |
|-------------------------------|----------------------------|------------------------|---------|
|                               | 24 hour Mortality          | 30 Day Mortality       |         |
| Fluid Resuscitated           | 278 (65.0%)                | 32 (100%)              | 0.62    | 0.19    |
| Blood and blood products transfusion | 104 (24.4%) | 24 (75.0%)             | 0.07    | 0.34    |
| Intubated                     | 76 (17.8%)                 | 26 (81.3%)             | 0.14    | 0.08    |
| Operated                      | 133 (31.1%)                | 10 (31.3%)             | 0.26    | 0.66    |

Table 3: Intervenational characteristics of patients with numbers for each characteristic in terms of adrenaline, no adrenaline and p-values for that characteristic’s 24 hour and 30-day mortality.

| Primary Outcome | No Adrenaline Use (n = 428) | Adrenaline Use (n = 32) | p-Value |
|-----------------|----------------------------|------------------------|---------|
| 24 Hour Mortality | 31 (7.2%)               | 12 (37.5%)             | 0.21    |
| 30 Day Mortality | 53 (12.4%)               | 12 (37.5%)             | 0.52    |

Table 4: Primary outcome (24 hours and 30-day mortality) in the adrenaline and no adrenaline groups.
relationships could possibly explain the outcomes achieved.

Hypothermic patients had a 4.5 times (95% CI 2.3-8.5; p = 0.02) higher risk of 24-hour mortality. Severely acidic patients had an 8.1 times (95% CI 3.7-17.3; p < 0.001) higher risk of 24-hour mortality and severe trauma patients had a 9.7 times (95% CI 4.9-18.9; p = 0.14) higher risk of 24-hour mortality. Analysis also showed that hypothermic patients had a 3.2 times (95% CI 1.9-5.5; p = 0.02) higher risk of 30-day mortality. Severely acidic patients had a 5 times (95% CI 2.9-8.9; p < 0.001) higher risk of 30-day mortality and patients with severe trauma had a 8.4 times (95% CI 4.7-15.0; p = 0.11) higher risk of 30 day mortality. Patients who received prehospital adrenaline had a 2.6 times (95% CI 1.2-5.3; p = 0.01) higher risk to be hypothermic and a 2.8 times (95% CI 1.3 -5.8; p = 0.007) higher risk to be severely acidic. These patients also were 22.7 times (95% CI 9.4-55.1; p < 0.001) more likely to be severe trauma patients.

### Discussion

The study shows that young black male subjects are the most common victims of major trauma. This is in keeping with the rest of the world where trauma is predominantly a disease of young men less than 50 years of age [2,20,21]. Local studies consistently show that more than 70% of trauma subjects are indeed men [22-28].

Penetrating trauma is the most common mechanism of trauma and is in keeping with the unique mechanism of the trauma profile seen in South Africa [5,21]. Major trauma centres overseas: (University Medical Center Utrecht (UMCU), John Hunter Hospital (JHH) and Harborview Medical Center (HMC)) have shown that blunt trauma is the commonest mechanism of injury in the developed world. These aforementioned centres reported blunt trauma incidences of 93.1%, 94.8% and 86.6% respectively and less than 15% for penetrating trauma [21]. The high prevalence of penetrating trauma in the local trauma unit is related to the high incidence of interpersonal violence recorded in South Africa [28]. This pattern of trauma arose due to changes in the South African political landscape in the 1980s and is yet to diminish to the levels seen in other parts of the world [2,25].

Major trauma (P1) patients require prompt and dedicated care [3,5,26]. These severely injured patients are prone to high morbidity and/or mortality if not managed early and appropriately [3,5,26]. Importantly, 27% of the patients were hypothermic and 36% were severely acidic. This means that about a third of the patients had components of the lethal triad of trauma [6,7]. It was therefore important to evaluate major trauma patients at this large hospital.

This study shows that the 24 hour and 30 day mortalities in patients receiving prehospital adrenaline is the same (37.5%), compared to the 7.2% and 12.4% in patients not receiving prehospital adrenaline. Higher mortality observed in patients receiving prehospital adrenaline is in keeping with the study by Sperry et al., which demonstrated a 34.5% mortality rate in subjects receiving early vasopressors and an 8.9% mortality rate in subjects not receiving early vasopressors [17]. Although Sperry et al., demonstrated a statistically significant result [17], the same comparison in the current study does not reach statistical significance. These are interesting findings as they statistically purport that use of prehospital adrenaline has no influence on mortality, which is in contrast to Collier et al., and Sperry et al., [16,17]. Although not statistically significant, the results are clinically significant. The study impresses on a trend towards increased mortality in hypotensive trauma subjects who received prehospital adrenaline. The increased likelihood of mortality in hypotensive trauma patients receiving prehospital adrenaline may be because prehospital adrenaline use is possibly an indicator of the severity of trauma. The prehospital adrenaline group has higher proportions (78% versus 13%) of patients with Revised Trauma Scores < 4. Additional analysis shows that patients who received prehospital adrenaline were 22.7 times (95% CI 9.1 - 55, p < 0.001) more likely to have had severe trauma. Furthermore, the participants in the adrenaline group had a higher proportion of participants with GCS < 8, receiving intubations, fluid resuscitations and blood products. These patients were therefore critically ill. Despite this, 62.5% of the patients who received adrenaline survived beyond 30 days. This is an important clinical outcome as it goes against what is commonly believed in trauma that adrenaline use in trauma equals mortality.

Additionally, other confounders that may contribute to the high mortality rate seen in major trauma patients who received prehospital adrenaline include hypothermia and severe acidosis. The study shows that there is a statistically significant relationship between hypothermia and severe acidosis with both 24 hour and 30 day mortality. This finding is consistent with trauma literature in which hypothermia and acidosis are quoted as major contributors to mortality in major trauma patients [6,7]. The various other demographic, physiological and interventional confounding analysed by binomial regression analysis did not indicate any influence on mortality.

### Limitations and Strengths of the Study

Due to the retrospective nature of the study it was open to selection and clinician bias. Selection bias resulted from having only one researcher collecting the data whilst clinician bias was a consequence of health care provider training. Health care
workers were more likely to administer prehospital adrenaline to patients they deemed more seriously injured.

Another concern with the study design is with the use of the Revised Trauma Score (RTS) as the only measure of severity of trauma. RTS predicts mortality by assessing the patient’s physiological parameters whilst the Injury Severity Score (ISS) assess the extent of anatomical injury to predict mortality [29]. Though the literature is divided on which score is more accurate [29,30], it would have been advantageous to obtain an ISS as well. This additional information could have allowed better relation of severity of trauma to mortality. Akhavan et al., showed that the ISS scoring system was superior to the RTS scoring system in predicting mortality whilst Soni et al., showed that the RTS was a better predictor for in-hospital mortality than the ISS, although this was in paediatric populations [29,30]. In this study, the final ISS was more challenging to obtain than the RTS, as some of the subject’s records did not contain all the anatomical injury information required to enable the calculation of ISS scores.

Furthermore, the only vasopressor used in this study was adrenaline. Adrenaline was used as it is the most accessible of the various vasopressor subtypes. Though Sperry et al., indicated that it probably does not matter which vasopressor is used, this still needs to be evaluated in our context. As such it remains uncertain what the influence of other vasopressors would be on P1 patient mortality. It is also important that the exact dose of adrenaline was also not included in this study due to the nature of care in the prehospital setting. Pre-hospital services titrate adrenalin without use of pumps making it difficult to give actual specific doses. This may have had an impact on the interpretation of the results.

The strength of this study is the fact that although it is a retrospective study, it represents the first of its kind to investigate the effect of prehospital adrenaline on mortality of P1 patients in Africa. As such it creates a framework or platform to encourage subsequent research on this topic in the future.

Conclusion

This study showed a statistical insignificant trend towards increased in-hospital 24 hours (p = 0.21) and 30 days (p = 0.52) mortalities in hypotensive major trauma patients receiving prehospital adrenaline, in contrast to Collier et al., [16] and Sperry et al., [17]. Although pre-hospital adrenaline use is practiced in our setting, prospective trials are required to offer clarity on safe use of prehospital adrenaline in major trauma hypotensive patients.

Conflict of Interest

All authors declare no conflicts of interest in this article.

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