# Prevalence of hypernatremia and outcome in adult burns patients admitted at Chris Hani Baragwanath Burns Unit

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine

**DECLARATION**

I Uamunovandu Tjinjeka declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (Surgery) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_______________________________ ____ day of ________________ 2018

***This report is written in the format for publication in the Burns and Trauma journal and has been submitted to the journal for consideration for publication***

## DEDICATION

This MMed is dedicated to my wife Vezerajo Tjinjeka and my two sons Unoviua and Undja Tjinjeka for their resolute support during this endeavor. I have been away from them for 6yrs in pursuit of my dreams and not a single day have they complained. I thank them for always believing in me.

**PRESENTATIONS**

The findings of this research were presented at the Bert Myburgh Research Forum, Department of Surgery, University of the Witwatersrand on the 28th of November 2018.

## ABSTRACT

**Background:** Hypernatremia is defined as serum sodium concentration exceeding 145 mmol/L. Studies show a relationship between hypernatremia and mortality in general. There is only one study to our knowledge that has investigated the effect of hypernatremia on mortality in burns patients. The European based study, had a small sample size, which could potentially have impacted on the results. This study aims to determine the prevalence of hypernatremia, its association to increased mortality and impact on patient's length of stay in burns patients, admitted to the Chris Hani Baragwanath Academic Hospital (CHBAH) adult burns unit in Johannesburg, South Africa.

**Methods**: A retrospective study of adult patients admitted to CHBAH burns unit from January 2014 to December 2015 with a total burned surface area of 15% and above was conducted. Logistic regression was used to determine the association between hypernatremia and mortality. For categorical and continuous variables, the Pearson Chi-squared test and Student t test were used for data analysis respectively. Statistical analysis was performed using STATA software version 15 and a p value of $< 0.05$ was considered statistically significant.

**Results:** The total admissions to the unit during the 2 years period was 486, with a mortality of 103. Of the 247 patients who met the criteria for the study, 64 (25.9%) patients had hypernatremia. Mortality was significantly higher in the hypernatremia group (39/64, 60.9%) compared to the non-hypernatremia group (40/183, 21.9%), p-value<0.001. Of the 48 individuals with available blood culture results, 26 (54.2%) were positive.. Blood culture positivity was higher in the hypernatremic group (21/34, 61.8%) compared to the non-hypernatremic group (5/14, 35.7%) P-value<0.001. The median hospital stay for patients who developed hypernatremia was 13.5 days compared to 15 days among non-hypernatremia group.

**Conclusions:** The findings show that approximately one in four patients meeting the study criteria were hypernatremic. A close link between hypernatremia, sepsis and a high mortality was shown, suggesting that hypernatremia can be used as a prognostic indicator in burns patients.

## ACKNOWLEDGEMENTS

My sincere gratitude goes to my two supervisors Prof. A. Muganza and Dr P. Fru for their immense contribution to this work. I thank them for being patient with me. Without their contribution this project would not have been possible. I also thank Mr. Joseph Ouma for statistical support.

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## ABBREVIATIONS

| | |
|---|---|
| ABSI | Abbreviated Burns Severity Index |
| BU | Burns Unit |
| CHBAH | Chris Hani Baragwanath Academic Hospital |
| HDU | High Dependency Unit |
| ICU | Intensive Care Unit |
| NHLS | National Health Laboratory Services |
| TBSA | Total Burned Surface Area |

## BACKGROUND

Hypernatremia is defined as serum sodium concentration of more than 145 mmol/L[1]. A hypernatremic state negatively affects many bodily functions and there is evidence that high serum sodium levels autonomously rises the risk of death in patients admitted to high dependency units (HDU) i.e. very sick patients [1]. Serum sodium level is closely controlled by water homeostasis and mediated by thirst, vasopressin and renal function in healthy individuals. Most commonly a hypernatremic state occurs as a result of two conditions, an addition of salt through administration of hypertonic fluids or a deficit of free water or both. The most common cause of In-hospital hypernatremia is iatrogenic and usually is a result of deficient or wrong fluid administration in the setting of increased free water loss [1,2]. The major defense against hypernatremia is thirst. Hypernatremia invariably occurs in conjunction with hyperosmolality.

High serum sodium levels and the attendant hyperosmolar state possess a myriad of physiologic consequences. One of the well-known ramifications of high serum sodium levels is the compromise on the nervous system. The evolution of hypernatremia and hypertonicity results in a movement of electrolyte free water from within the cells to the outside environment. This occurrence leads to neuronal cell shrinkage, which can lead to blood vessels rupture and strokes with irreversible brain damage [3].

Muscle weakness and cramps can also result which may lead to prolonged ventilation and therefore further exacerbate the problem due to increased free water intake. Hypernatremia and hyperosmolality are associated with a hyperglycemic state which in itself is linked to a heightened mortality in the very sick. The induction of hyperosmolality results in a derangement in glucose use and glucagon dependent glucose release [4].

Hyperosmolality induces pro-inflammatory cytokine release [5] which can lead to multi-organ dysfunction and organ failure, also hypercoagulability may result to deep venous thrombosis and pulmonary embolus. Hypernatremia can cause left ventricular dysfunction with impaired tissue perfusion. Elevated serum sodium levels may also cause rhabdomyolysis with subsequent renal failure.

The prevalence of hypernatremia and the outcome in the general critically ill population has been widely studied. O'Donogue et al (2009) found an incidence of Intensive Care Unit (ICU) acquired hypernatremia of 7.7% with an associated in-hospital mortality of 33.5% [6]. Medical admissions had a heightened risk of hypernatremia compared to surgical patients. Lindner et al in their 2007 study of 981 ICU patients demonstrated that hypernatremia independently increased in-hospital mortality and duration of admission to ICU [7]. In the study, the prevalence of hypernatremia was found to be 9% with a mortality of 39 %.

Kuroda et al**(**1997) demonstrated that hypernatremia in burns is associated with evolution of a burn wound from superficial to a deeper wound which may lead to the need of surgical intervention like debridement and skin grafts as well as prolonged hospital stay and increased risk of nosocomial infections [8]. This progressive tissue necrosis may be due to poor perfusion of the zone of stasis as a result of intravascular volume depletion. Harada et al (1998), provided evidence that hypernatremia, an osmotic injury, is associated with progressive burn wound necrosis by comparing the number of hair follicle cells in a burn wound in rats with hypernatremia to the control group [9]. The number of hair follicles in the hypernatremic group was significantly reduced as compared to the normonatremic group (30% vs. 88%). Hair follicle cells are responsible for regeneration of new skin cells after a burn injury.

There are very few studies to date on hypernatremia and its sequelae in burns. In 2002, Ebrahim et al investigated the relationship between hypernatremia and the development of sepsis in burns ICU patients [10]. Hypernatremic subjects displayed a typical pattern of sepsis with prompt onset, recurrent episodes, with multiple organisms involved requiring more than one antibiotic for treatment. The duration of sepsis was protracted with a higher mortality rate. The close association between the onset of hypernatremia and the onset of septicemia noted in this study suggest that hypernatremia can be used as a marker of septicemia in burns patients. In a retrospective study by Namdar et al (2010), to determine the incidence of hypernatremia and survival in 40 subjects with a total burned surface area (TBSA) >10%, the authors concluded that burn injury subjects who develop hypernatremia while in the hospital have an increased risk of death [11].

In summary, studies show a relationship between hypernatremia and mortality in general. A similar trend was observed in burns patients at the CHBAH burns unit. Apart from the study by Namdar et al. (2010) investigating the effect of hypernatremia on mortality in burns, we are not aware of similar studies elsewhere. This is in contrast to the numerous studies on ICU patients in general. The problem with the said study was the small sample size of 40 participants only, which could have influenced the outcome. Here, we performed a similar study and expanded on the sample size in a high-volume burns unit to determine prevalence, length of hospital stay and mortality. Furthermore, the relationship between hypernatremia and sepsis in the burns patients was also determined.

## METHODS

This was a retrospective study examining biochemistry and blood culture results of burns patients admitted at the Chris Hani Baragwanath Academic Hospital Burns Unit to extract those with hypernatremia and sepsis. Ethical clearance to perform the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) (Medical Ethic number M180235) on the 11$^{th}$ of July 2018. A population of hypernatremic burns patients from

January 2014 to December 2015 was examined. Hypernatremia was defined as serum sodium levels of more than 145 mmol/l. All patients admitted at CHBAH burns unit with 15% TBSA burns and above within the study period were included. Out of the 486 admissions in the unit during this time, a total of 247 patients met the study criteria. This sample size was sufficiently powered at ≥ 95% confidence interval when assuming a 50% prevalence given that at 95%, n=215. To facilitate comparison, variables such as age, gender, TBSA, cause of burns, ventilation, hospital stay, presence of sepsis and death were extracted from the admission book between January 2014 to December 2015.

**Data Analysis**

Data obtained from the burns admission records and the National Health Laboratory Service (NHLS) was captured in a spreadsheet using Microsoft Excel and the statistical analysis was done using STATA software version 15. Continuous data such as age and %TBSA was analyzed using T-test while categorical data such as cause of burns was analyzed using Chi-squared test. Univariate, bivariate and multivariate logistic regression analysis were performed. For the bivariate analysis, chi square test and t-test were used to assess the association between hypernatremia and the categorical or continuous variables respectively.

## RESULTS

Only individuals with complete information for the variables at each stage of analysis were included. The total admissions to the unit during the two years period was 486, with a mortality of 103. Out of 486 admissions**,** 247 met the inclusion criteria for the study. Figure 1 is a flow diagram summarizing mortality and recruited participants for both the hypernatremic and non hypernatremic groups.

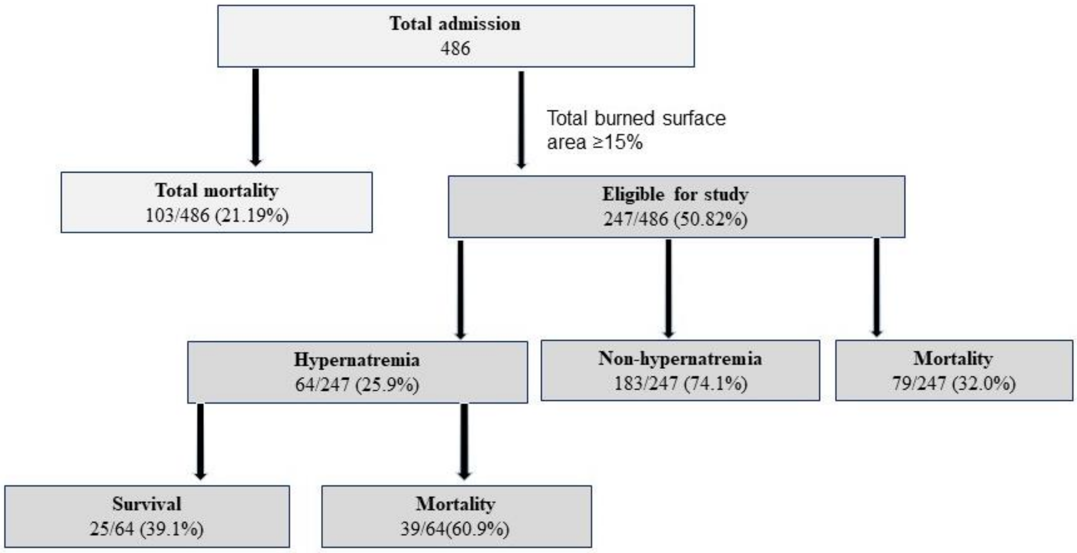


**Figure 1:** Flow diagram showing participant sampling.

**Patient Characteristics**

Table 1 presents uni-variate analysis of demographics and selected clinical characteristics of the study participants. Records for the 247 patients admitted to the burns unit, Chris Hani Baragwanath Academic Hospital were extracted from patients' files. Of those included in the study, 66% were male and the mean age was 34.7±13.6 years (Male, 33.4 vs Female, 37.2). The median stay in hospital was 14.5 days (IQR: 7-29). The median TBSA due to burn was 25% and more than two thirds of the burns (173/227) were due to flame while only 14 (6.2%) patients experienced burns due to other causes. Mechanical ventilation was required in about 40% of the patients.

**Table 1:** Demographic and clinical characteristics of the patients in this study

| **Variable** | **N=247 (%)** |
|---|---|
| **Gender**[1] | |
| Male | 161 (65.7) |
| Female | 84 (34.3) |
| **Age**[2] | |
| Mean (SD) | 34.7 (13.6) |
| Median (IQR) | 32 (25-42) |
| **Hospital stay (days)**[3] | |
| Mean (SD) | 22.9 (22.2) |
| Median (IQR) | 14 (7-29) |
| **TBSA** | |
| Mean (SD) | 28.2 (12.8) |
| Median (IQR) | 25.0 (18.0-35.0) |
| **Mortality** | |
| No | 168 (68.0) |
| Yes | 79 (32.0) |
| **Cause of Burn**[4] | |
| Flame | 173 (76.2) |
| Hot water | 40 (17.6) |
| Other | 14 (6.2) |
| **Mechanical Ventilation done**[5] | |
| No | 146 (60.8) |
| Yes | 94 (39.2) |

[1]*Excludes 2 individuals who had no information on Gender,*
[2]*Excludes 5 individuals who had no information on age,*
[3]*Excludes 20 individuals who had no information on Hospital stay*
[4]*Excludes 20 individuals who had no information cause of burn*
[5]*Excludes 7 individuals who had no information on mechanical ventilation*.

Table 2 presents the summary results of the key outcome, hypernatremia. For this study, hypernatremia status was derived from serum sodium level measurements . Patients were considered hypernatremic if their serum sodium level was more than 145 mmol/l. Overall, 64/247 (25.9%) patients had hypernatremia. The median serum sodium level among the hypernatremia group was 152.8±5.2 mmol/l, with a range of 146 mmol/l to 172 mmol/l while the median serum sodium level among the non-hypernatremia group was 139.2±3.6 mmol/l with a range of 128 mmol/l to 145 mmol/l.

**Table 2:** Prevalence of hypernatremia and other outcomes after diagnosis

| **Total admission over 2 years** | | | **486** |
|---|---|---|---|
| **Variable** | **Yes, n (%)** | **No, n (%)** | **Total** |
| Hypernatremia | **64 (25.9)** | **183 (74.1)** | **247** |
| **Serum Sodium level** (mmol/l) | | | |
| Mean (SD) | 152.8 (5.2) | 139.2 (3.6) | 142.7 (7.3) |
| Median (Min-Max) | 153 (146-172) | 139 (128-145) | 142.7 (128-172) |
| **Mortality** | | | |
| No | 25 (39.1) | 143 (78.1) | 168 (68.0) |
| Yes | 39 (60.9) | 40 (21.9) | 79 (32.0) |
| **Blood culture results** [1] | | | |
| Negative | 13 (38.2) | 9 (64.3) | 22 (45.8) |
| Positive | 21 (61.8) | 5 (35.7) | 26 (54.2) |

[1-] *Blood cultures were available only for 48 patients*

### Culture results and hypernatremia

Of the 48 individuals who had blood culture results, 54.2%(26/48) had a positive blood result. Blood culture positivity was higher in the hypernatremia group (21/34, 61.8%) compared to the non-hypernatremia group (5/14, 35.7%).

### Mortality

Of the total number of individuals included in the analysis, 79 (32%) died. Mortality was significantly higher in the hypernatremia group (39, 60.9%) compared to the non-hypernatremia group (40, 21.9%), p-value<0.001.

### Prevalence of hypernatremia

Table 3 presents prevalence of hypernatremia by demographic and selected clinical characteristics of the patients included in the study. Overall, the prevalence of hypernatremia was 26% among the study participants. Prevalence was slightly higher among females (27.4%) compared to males (25.5%). Individuals who developed hypernatremia were slightly older compared to those who did not develop hypernatremia (average age 36.4 years vs 34.1 years).

The median hospital stay for patients who developed hypernatremia was 13.5 days compared to 15 days among non-hypernatremia group (p=0.872). The differences in hypernatremia prevalence by age, gender and duration of hospital stay were however not statistically significant.

**Table 3:** Prevalence of Hypernatremia

| **Variable** | **Yes, n (%)** | **No n (%)** | **P-value** |
|---|---|---|---|
| Hypernatremia | **64 (25.9)** | **183 (74.1)** | |
| **Gender**[1] | | | |
| Male | 41 (25.5) | 120 (74.5) | |
| Female | 23 (27.4) | 61 (72.6) | 0.746 |
| **Age**[2] | | | |
| Mean (SD) | 36.4 (15.1) | 34.1 (13.0) | |
| Median (IQR) | 33 (24-47) | 32 (26-41) | 0.246 |
| **Hospital stay**[3] | | | |
| Mean (SD) | 23.4 (21.4) | 22.8 (22.5) | |
| Median (IQR) | 13.5 (10-29) | 15 (7-30) | 0.872 |
| **TBSA** | | | |
| Mean (SD) | 32.7 (13.6) | 26.6 (12.2) | 0.001 |
| Median (IQR) | 31 (21.5-43.0) | 23.0 (18.0-30.0) | |
| **Cause of Burn**[4] | | | |
| Flame | 51 (29.5) | 122 (70.5) | |
| Hot water | 4 (10.0) | 36 (90.0) | 0.030 |
| Other | 5 (35.7) | 9 (64.3) | |
| **Mechanical Ventilation done**[5] | | | |
| No | 18 (12.3) | 128 (87.7) | |
| Yes | 45 (47.9) | 49 (52.1) | <0.001 |

[1] *Excludes 2 individuals who had no information on Gender,*
[2] *Excludes 5 individuals who had no information on age,*
[3] *Excludes 20 individuals who had no information on Hospital stay*
[4] *Excludes 20 individuals who had no information cause of burn*
[5] *Excludes 7 individuals who had no information on mechanical ventilation.*

Hypernatremia patients had a significantly higher average TBSA of 32.7 % compared to 26.6 % TBSA in the non-hypernatremia patients (p=0.001). The prevalence of hypernatremia was lowest among individuals who had hot water burn (10%) and highest among those who experienced a burn due to other causes (35.7%). Of those who were on mechanical ventilation, 45 (48%) had hypernatremia, compared to only 18 (12.3%) of those who were not on mechanical ventilation(p<0.001).

Multivariate logistic regression analysis was conducted to determine the association of hypernatremia and the demographic and selected clinical characteristics of the patients as shown in Table 4. The results show a significantly higher likelihood of hypernatremia among individuals on mechanical ventilation compared to those not on mechanical ventilation at 5% level of significance (AOR, 7. 63; 95% CI 3.35-17.38). There was also a significantly higher likelihood of hypernatremia among patients with burns due to other causes compared to burns due to Flame (AOR, 4.98; 95% CI, 1.23-20.17) at 5% level of significance. The likelihood of hypernatremia was also observed to significantly increase with increasing age at 10% level of significance. The adjusted analysis further shows no statistically significant difference in the prevalence of hypernatremia by gender, total average burn surface area and burns due to hot water compared to burns due to flame. There was significant association observed between hypernatremia and Serum sodium level (P<0.001), death (P<0.001) and Blood culture results (P<0.001) shown in Table 5.

**Table 4:** Factors associated with hypernatremia

| Variable | COR* (95% CI) | AOR (95% CI) | P-value |
|---|---|---|---|
| **Gender** | | | |
| Female | | | |
| Male | 0.91 (0.499, 1.65) | 1.34 (0.65-2.79) | 0.488 |
| **Age** (Mean, SD) | 1.01 (0.99.4-1.03) | 1.03 (1.00, 1.06) | 0.088 |
| **TBSA** (Mean, SD) | 1.04 (1.01-1.06) | 1.01 (0.99-1.04) | 0.349 |
| **Cause of burn** | | | |
| Flame | | | |
| Hot water | 0.27 (0.09-0.79) | 0.78 (0.20-3.08) | 0.726 |
| Other | 1.33 (0.42-4.16) | 4.98 (1.23, 20.17) | 0.027 |
| **Mechanical ventilation done** | | | |
| No | | | |
| Yes | 6.53 (3.45-12.36) | 7.63 (3.35-17.38) | <0.001 |

**COR-Crude Odds Ratio, AOR – Adjusted Odds Ratio*

| **Table 5:** Association between hypernatremia and other outcomes | | | |
|---|---|---|---|
| **Variable** | **Yes, n (%)** | **No, n (%)** | **P value** |
| Hypernatremia | **64 (25.9)** | **183 (74.1)** | |
| **Serum Sodium level (**mmol/l) | | | |
| Mean (SD) | 152.8 (5.2) | 139.2 (3.6) | <0.001 |
| **Died** | | | |
| No | 25 (39.1) | 143 (78.1) | <0.001 |
| Yes | 39 (60.9) | 40 (21.9) | |
| **Blood culture results** [1] | | | |
| Negative | 13 (38.2) | 9 (64.3) | <0.001 |
| Positive | 21 (61.8) | 5 (35.7) | |

[1-] *Blood cultures were available only for 48 patients*

## DISCUSSION

The grounds of this study were to determine the prevalence of hypernatremia and its consequences in burns patients. Hypernatremia is associated with multitudes of physiologic derangements such as muscle weakness, hypercoagulable states and multiorgan dysfunction, which can lead to increased mortality. The prevalence of hypernatremia in this study was 25.9%. The serum sodium levels in the hypernatremic group ranged from 146 mmol/l to 172 mmol/l with a median of 153 mmol/l. A majority of the patients were male (65.7%) and mean age was 34.7 yrs. Flame burns was the most common form of burns and the average TBSA was 28.2%. Only 39.2% of the patients were ventilated. A hypernatremia prevalence of 25.9% in burns patients was much higher than the prevalence of hypernatremia in the general ICU patients which ranges between 7.7% to 9% [6,7]. This phenomenon may be due to an increased insensible water loss associated with loss of the protective skin barrier in burns patients.

This study demonstrated a mortality rate of 60.9% in the hypernatremic group versus 21.9% in the non hypernatremic group. The difference in mortality between the two groups was significant with a P-value<0.001. According to the literature the mortality associated with hypernatremia in the general population ranges between 33.5% to 39%, although high, it is much less than in this study. Namdar et al (2010), in a study similar to this demonstrated a mortality of 20% amongst hypernatremic patients [11]. Their results are three times less than what we found. We believe this is an underestimation stemming from the small study population (40 patients) and a low TBSA (10%).

In this study, 61.8% of patients with hypernatremia had positive blood culture results (sepsis) compared to only 35.7% in the non-hypernatremic group. An increased mortality rate in burns patients is mainly attributed to sepsis and subsequent multiorgan failure. Patients with burns are at a much higher risk of infection and hypernatremia both due to loss of the protective skin barrier. This explains why hypernatremia is closely associated with sepsis. A larger TBSA will put the patient at a much higher risk to acquire the aforementioned conditions. The median hospital stay for patients who developed hypernatremia was 13.5 days compared to 15 days among non-hypernatremia group. The duration of hospital stay was not significantly different between hypernatremia and the non-hypernatremia groups, (p-value=0.872). Though we expected patients with hypernatremia to stay longer in the hospital the study shows the opposite. A shorter hospital stay in this patient group could be because most of the patients succumbed early due to the severity of the burns compared to the non hypernatremic group.

The diagnosis of sepsis in burns can be difficult. The usual indicators of sepsis such as fever may not be apparent, white cell count and c- reactive protein levels are unreliable and the clinician solely relies on blood cultures for diagnosis. We believe that a simple screening tool for sepsis like the determination of sodium levels can be quite handy for clinicians involved in the management of burns patients especially in resource limited settings. In the presence of hypernatremia in critical patients we recommend blood cultures and initiation of empiric antibiotics while awaiting blood culture results for escalation or de-escalation.

However retrospective studies are fraught with confounding factors by nature therefore one cannot make firm conclusions based on this type of studies. In this study there was a problem of missing data in some of the records requiring that those cases be excluded resulting in a reduction in the numbers analysed in some cases. A more controlled follow up prospective study is planned. The prospective study will also explore the timing of the onset of hypernatremia in relation to sepsis. It will also be interesting to demonstrate if the type of fluids used during resuscitation have an effect on the development of hypernatremia.

## CONCLUSION

The prevalence of hypernatremia was 26%(64/247). Mortality was significantly higher in the hypernatremia group (39, 60.9%). We found a close relationship between the development of sepsis and hypernatremia. This study suggest that hypernatremia can be used as an indicator for sepsis. We also concluded that hypernatremia can be used as a predictor of mortality/prognosis.

## DISCLOSURES


### Acknowledgements

The authors would like to thank Mr Joseph Ouma for statistical support.

### Funding

No funding was required for this study


### Authors contributions

UT, PF and AM contributed to the design of the study. AM contributed to the conceptualization of the study. UT acquired the data and wrote the first draft with contribution from PF. UT, PF, AM contributed to the analysis, interpretation and revision of the manuscript. PF revised the manuscript critically for important intellectual content. PF and AM supervised the project. All authors approved of the final version.

## Ethics approval

This study was approved by the human research ethics committee of the University of the Witwatersrand, study number M180235.

## Consent for publication

Not applicable

## Competing interest

The authors declare that they have no competing interest.

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**APPENDIXES**

**Appendix 1:** Ethics Clearnance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Uamunovandu Tjinjeka

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**

**CLEARANCE CERTIFICATE NO. M180235**

| | |
|---|---|
| **NAME:** **(Principal Investigator)** | Dr Uamunovandu Tjinjeka |
| **DEPARTMENT:** | Plastic Surgery<br>Chris Hani Baragwanath Academic Hospital<br>National Health Laboratory Service (NHLS) |
| **PROJECT TITLE:** | Prevalence of hypernatremia and outcome in adult burns patients admitted at Chris Hani Baragwanath Burns Unit |
| **DATE CONSIDERED:** | 23/02/2018 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof Muganza and Dr Fru-Fonteh |
| **APPROVED BY:** | Professor CB Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 11/07/2018 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature　　　　Date 13.7.18

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

**Appendix 2**: Turniitin report.

**Appendix 3**: Study Protocol

**NB: Not to be assessed but to served as background for the planned work since the report has been streamlined in the form of a publication.**

# Prevalence of hypernatremia and outcome in adult burns patients admitted at Chris Hani Baragwanath Burns Unit

**MMed Candidate**: Dr U Tjinjeka

**Student Number**: 1262294

## Supervisors

Dr Muganza

MD, FRCS, FCS (SA)

Dr Fonteh

PhD

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**INTRODUCTION/BACKGROUND**

Hypernatremia is defined as serum sodium concentration exceeding 145mmol/L[1]. Hypernatremia has detrimental effects on various physiologic functions and was shown to be an independent risk factor for increased mortality in critically ill patients [1]. Serum sodium level is closely controlled by water homeostasis and mediated by thirst, vasopressin and renal function in healthy individuals. Hypernatremia can only develop as a result of either a gain of sodium or a loss of free water or a combination of both. The most common cause of in hospital hypernatremia is iatrogenic and usually is as a result of inadequate or inappropriate fluid prescription in the setting of increased water loss [1, 2]. The major defense against hypernatremia is thirst. Hypernatremia is always associated with hyperosmolality. The serum osmolality is regulated within narrow ranges, a slight elevation in serum osmolality leads to the secretion of antidiuretic hormone by the pituitary gland leading to increased water retention.

Hypernatremia and the associated hyperosmolar state have a multitude of effects on bodily function. One of the well-known consequences of hypernatremia is on the neurologic function. The development of hypernatremia and hyperosmolality leads to a shift of free water from the intracellular to the extracellular space. This shift leads to brain cell shrinkage, which can lead to vascular rupture and cerebral infarcts with permanent neurologic deficit in severe cases [3].

Muscle weakness and cramps can also result which may lead to prolonged ventilation and therefore further exacerbate the problem due to decreased free water intake. Hypernatremia and hyperosmolality are associated with a hyperglycemic state which in itself is linked with increased mortality in critically ill patients. *In vitro* studies have demonstrated that the induction of hyperosmolality leads to an impairment in glucose utilization and glucagon dependent glucose release [4]. In healthy volunteers, it has been shown that the slight increase in serum osmolality from 280 to 302mosm/kg was associated with a severe impairment in --insulin-mediated glucose metabolism thus leading to the development of hyperglycemia.

Hyperosmolality induces pro-inflammatory cytokine release [5] which can lead to multi-organ dysfunction and organ failure, also hypercoagulability may result with deep venous thrombosis and pulmonary embolus. Hypernatremia can cause left ventricular dysfunction with impaired tissue perfusion. Elevated serum sodium levels may also cause rhabdomyolysis with subsequent renal failure.

The prevalence of hypernatremia and the outcome in the general critically ill population has been widely studied. O'Donogue et al [6] found an incidence of Intensive Care Unit ( ICU) acquired hypernatremia of 7.7% with an associated in-hospital mortality of 33.5%. They also found an incremental increase in mortality associated with a magnitude of sodium elevation as defined by sodium group. Patients admitted for medical reasons were at increased risk of hypernatremia as compared to surgical patients. These results demonstrated that the risk of hypernatremia varies amongst and within diagnostic categories and broad patient subgroups. Lindner at al [7] in their study of 981 ICU patients demonstrated that hypernatremia is an independent risk factor for 28-day hospital mortality and is associated with increased length of stay in ICU. In this study, the prevalence of hypernatremia was found to be 9% with a mortality of 39%. Close to 80% of episodes of hypernatremia developed during the ICU stay which were not present on admission to ICU. The mean length of hospital stay in patients without hypernatremia was found to be 8 days versus 20 days in the hypernatremic group. This is more than double the duration of the normonatremic group.

Kuroda at al [8] in 1997 published their study where they evaluated the influence of hypernatremia on progressive burn wound necrosis. This study was done on rats. Contact burn injury was induced with a metal plate and the rats were divided into two groups. In one group, hypernatremia was induced by hypernatremic saline infusion while the control group was infused with a hyponatraemic solution. The level of neutrophil infiltration into the burn wound was used to determine the depth of tissue necrosis (demarcating border between viable and necrotic tissues). The demarcating borderline in rats with hypernatremia was found to be significantly deeper than that of rats with normonatremia. This study shows that hypernatremia in burns is associated with evolution of a burn wound from superficial to a deeper wound which may lead to the need of surgical intervention like debridement and skin grafts as well as prolonged hospital stay and increased risk of acquiring hospital infections. This progressive tissue necrosis maybe due to poor perfusion of the zone of stasis as a result of intravascular volume depletion associated with hypernatremic states. In a similar study on rats, Harada at al [9], in 1998, provided evidence that hypernatremia, an osmotic injury, is associated with progressive burn wound necrosis by comparing the number of hair follicle cells in a burn wound in rats with hypernatremia to the control group. The number of hair follicles in the hypernatremic group was significantly reduced as compared to the normonatremic group (30% vs. 88%), so hypernatremia was associated with a significant apoptosis of hair follicle cells. Hair follicle cells a responsible for regeneration of new skin cells after a burn injury. If hair follicles and their cells are well preserved, the burn wound heals spontaneously in 2 weeks and hair is preserved. If not, the wound remains deeper and skin graft operations are frequently needed and hair never re-grows.

There are very few studies to date on hypernatremia and its sequelae in burns. In 2002, Mohammed at al [10] published a retrospective study to investigate the relationship between sepsis and the development of hypernatremia in the burns intensive care unit. In their study population of 105 septicemic patients in the burns intensive care unit only 36 (34%) developed hypernatremia. In this study hypernatremia was defined as serum sodium of more than 150mmol/l. In the hypernatremic group 83.3 % ( 30 out of 36) patients died while only 24.6 % ( 17 out of 69) in the non-hypernatremic group died. Hypernatremia occurred in older age group and predominantly amongst female septicemic patients. The average Total Body Surface Area (TBSA) of 61% in hypernatremia patients was significantly higher compared to the 48% in the non-hypernatremia group. Twenty patients (55.6%) in the hypernatremia group had inhalation injury while only 13 patients (18.8%) in the non-hypernatremic had it. Therefore, septicemic patients who developed hypernatremia were found to have a higher incidence of inhalation injury and larger burn area (TBSA) signifying a greater free water losses in the face of increasing fluid requirement. At the time of development of hypernatremia, 27 of patients (75%) were on mechanical ventilation while in the non-hypernatremic group 13 patients needed mechanical ventilation. Patients who developed hypernatremia showed a characteristic pattern of septicemia: early onset, multiple episodes, polymicrobial, need for multiple antibiotics, longer duration, and a higher mortality, indicating a more severe sepsis. The average duration of hypernatremia in these patients was 5.5+/-3.5 days. Sepsis developed early in the Hypernatremia group (9.3 +/- 6.1 days) compared to 12.4+/-11.1 days post admissions in the non-hypernatremic group. The close association between the onset of Hypernatremia and the onset of septicemia noted in this study suggest that hypernatremia can be used as a marker of septicemia in burn patients. Interestingly patients who were treated with early wound excision were less prone to develop hypernatremia when compared to those who did not undergo early wound excision.

Thomas at al [11], in a retrospective study for the incidence of hypernatremia and survival in 40 patients with a total burned surface area (TBSA) >10% found a mortality of 20% in the hypernatremic patients (3 patients out of 15 died). In this study hypernatremia was defined as serum sodium levels of greater than 146 mmol/l. Two patients died in a septic state due to pneumonia while one patient died in a multi-organ failure state. There were no mortalities in the normonatremic patients. Hypernatremia occurred on day 5 +/-1.4 days. There were no significant differences in terms of age, sex, TBSA, Abbreviated Burn Severity Index (ABSI)-Score, partial or full thickness body surface area and fluid resuscitation within the first 24 hours in both groups. Fourteen patients out of fifteen in the hypernatremic group required mechanical ventilation while none of the patient in the normonatremic group required ventilation. A significant association of mechanical ventilation and incidence of hypernatremia was found. The conclusion from this study was that burned patients with an in-hospital acquired hypernatremia have an increased risk of mortality. 20% mortality however, is lower than the hypernatremic associated mortality in the general critically ill population which ranges from 38% to 66%. This significant difference may be due to a smaller study population in this study.

In summary, studies show a relationship between hypernatremia and mortality in general. We have observed a similar trend in burned patients in our practice. To date, we are only aware of one study investigating the effect of Hypernatremia on mortality in burns compared to numerous studies in ICU in general. The problem with the said study was the small sample size and therefore this might have impacted on the results. We aim to perform a similar study and expand on the sample size in a high volume hospital as well as determining if there is a relationship between hypernatremia and sepsis in the burns patients.

## Study objectives

### Primary objective

To determine the prevalence of hypernatremia in burns patients admitted to CHBAH burns unit from January 2013 to December 2015

### Secondary objectives

1. To determine the association between hypernatremia and sepsis in burns patients
2. Compare the duration of hospital stay of hypernatremic patients to the normonatremic group
3. To determine if hypernatremia in the burns patients is associated with an increased mortality

## Methods

This is a retrospective study which will examine chemistry and blood culture results of burns patients admitted at Chris Hani Baragwanath Academic Hospital Burns Unit to examine those with hypernatremia and sepsis. The study aims to examine a population of 100 hypernatremia burns patients from January 2013 to December 2015, that is, over a 3 year period. In this study, hypernatremia will be defined as serum sodium levels of more than 145mmol/l. All patients admitted at CHBAH burns unit with 15% TBSA burns and above within the study period will be included. To facilitate comparison, variables such age, gender, TBSA, cause of burns, ventilation, hospital stay, presence of sepsis and death will be extracted from the admission book.

**Data Analysis**

Data obtained from the burns admission book and NHLS will be captured in a spreadsheet using EXCEL and the statistical analysis will be done using STATISTICA. Continuous data such age and %TBSA will be analyzed using T-test while categorical data such as age and cause of burns will be analyzed using Chi-test.

**Ethics Approval**

Ethics approval for this study will be sort for by August 2016. A submission in this regard will be made with the Human Research Ethics Committee of the University of the Witwatersrand. Others submissions will be made to the hospital manager and the NHLS manager for permission to access patient's files and blood results respectively.

**Problems**

Like with any retrospective study, some data required may be missing from the records.

**Funding**

There will be minimal financial implications.

**Timing**

| | May 2016 | June 2016 | July 2016 | Aug 2016 | Sept 2016 | Oct 2016 | Nov 2016 | Dec 2016 | Jan 2017 | Feb 2017 |
|---|---|---|---|---|---|---|---|---|---|---|
| Literature review | | | | | | | | | | |
| Preparing protocol | | | | | | | | | | |
| Protocol assessment | | | | | | | | | | |
| Ethics application | | | | | | | | | | |
| Data collection | | | | | | | | | | |
| Data analysis | | | | | | | | | | |
| Writing up | | | | | | | | | | |

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**Appendix 1**

**Data Collection Sheet**

| | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** |
|---|---|---|---|---|
| 1.Age | | | | |
| 2.Gender | | | | |
| 3.TBSA | | | | |
| 4.Cause of burn | | | | |
| 5.Serum sodium level | | | | |
| 6.Date of Admission | | | | |
| 7.Date of discharge | | | | |
| 8.Blood culture results | | | | |
| 9.Hospital stay | | | | |
| 10.Mechanical ventilation | | | | |