Admission hyperglycemia as a prognostic indicator of outcome in major trauma patients at Bugando Medical Centre, Mwanza, Tanzania

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Abstract

Background: Admission hyperglycemia has been reported to be associated with poor outcomes among patients with major trauma. However, most of the available literature on this subject has been conducted in the developed world. This study aimed to determine the association between admission hyperglycemia and the outcome of major trauma patients admitted to Bugando Medical Centre.

Methods: This was a prospective cohort study, involving major trauma patients admitted to Bugando Medical Centre within 6 months from Sept 2017 to February 2018. The exposure was admission hyperglycemia (>11.1mmol/l) and non-exposure was normoglycemia (≤11.1mmol/l).

Results: A total of 217 patients (M: F ratio = 4.1: 1) were recruited. Their ages ranged from 4 to 97 years with a median age of 31 years. Out of 217 patients, 106 (48.8%) were hyperglycemic and the remaining 111(51.2%) were normoglycemic. The overall median days of the length of hospital stay (LOS) was 15 days. There was no statistically significant association between admission hyperglycemia and LOS (p =0.875). In this study, 73 patients died giving a mortality of 33.6%. Patients with admission hyperglycemia (>11.1mmol/l) had significantly higher mortality as compared to normoglycemic patients (≤11.1mmol/l) (p < 0.001).

Conclusion: This study found that admission hyperglycemia was statistically significantly associated with increased mortality among major trauma patients at Bugando Medical Centre. There is therefore a need to institute regular monitoring of blood sugar levels among these patients and give appropriate treatment to those found with elevated blood sugar levels.

Keywords: Admission hyperglycemia, prognostic indicator, major trauma outcome, Tanzania

Introduction

Trauma continues to be an enormous public health problem globally and contributes significantly to high morbidity, mortality, and long-term disabilities in the first four decades of life (Park, 2000; Hofman *et al.,* 2005). In low-income countries including Tanzania, trauma is increasing due to an increase in urbanization, motorization, civil violence, wars, and criminal activities (Museru & Leshabari, 2002; Bevan *et al.,* 2008; Chalya *et al.,* 2010). In these countries, major trauma remains a major cause of hospitalization and intensive care utilization and consumes a significant amount of the health care budget (Bevan *et al.,* 2008).   At Bugando Medical Centre, major trauma is the single most common

reason for trauma admission to the Intensive Care Unit (Chalya *et al.*, 2011), and it is associated with a substantial emotional, physical and financial burden on the community and hospital resources.

   All major trauma patients experience a hyper-metabolic response characterized by among other features massive protein catabolism and stress-induced hyperglycemia (Marik & Bellomo., 2013; Simsek*et al.,* 2014). Hyperglycemia, one of the two most prominent features of the hyper-metabolic response has been recognized as a common occurrence in trauma patients (Marik & Bellomo., 2013). The etiology of hyperglycemia in these patients is a multifactorial and complex cascade (Simsek *et al.,* 2014). A combination of several factors, including the presence of excessive counter-regulatory hormones such as glucagon, growth hormone, catecholamines, glucocorticoids, and cytokines such as IL-1, IL-6, and TNF-a plays an important role (Reinhold*et al.,* 1996). Additionally, insulin resistance and decreased insulin production have also been implicated (Rassias *et al.,* 1999). Previously, this hyperglycemia was perceived as a 'normal' response to major trauma; thus, the intervention was thought unnecessary (Black *et al.,* 1990). However, recent studies have established an association between hyperglycemia and poor outcome in patients with major trauma (Gore *et al*., 2002; Yendamuri *et al*., 2003; Simsek *et al.,* 2014; Torbati *et al.,* 2015). Early recognition and treatment of this profound metabolic change have been shown to improve clinical outcomes (Torbati *et al.,* 2015).

   Even though stress-induced hyperglycemia has been associated with an increase in morbidity and mortality among patients with major trauma (Simsek *et al.,* 2014; Torbati *et al.,* 2015), the available literature on stress-induced hyperglycemia post-trauma has been conducted in the developed world (Gore *et al*., 2002; Yendamuri *et al*., 2003; Sung *et al.,* 2011; Simsek *et al.,* 2014; Torbati *et al.,* 2015). This study is distinct from other reports in the literature, for its setting in a developing country with unique characteristics, challenges, and the largest burden of trauma. It is because of this knowledge gap the author decided to conduct this study to provide baseline data from our local setting. This study aimed to determine the association between admission hyperglycemia and the outcome of major trauma patients at Bugando Medical Centre, a tertiary care hospital in northwestern Tanzania.

Patients and Materials
Study design and setting
This was a prospective cohort study, involving major trauma patients admitted to Bugando Medical Centre (BMC) from September 2017 to February 2018. The study was conducted in the Emergency Department, ICU, surgical wards, and surgical outpatient clinic at BMC. It is a tertiary and Zonal hospital providing tertiary care and teaching hospital for the Catholic University of Health and Allied Sciences-Bugando Mwanza, Tanzania (CUHAS) and has a bed capacity of 960. It is located in Mwanza City, along the shores of Lake Victoria in north-western Tanzania. The hospital provides service to a population of approximately 16 million people from its neighboring regions in northwestern Tanzania. There is no trauma center or established advanced pre-hospital care in Mwanza City, as a result, all major trauma patients are referred to BMC for expertise management. At BMC, trauma patients are triaged at the Emergency department according to injury severity to identify critically injured patients who need rapid surgical intervention or specialized services.

Study population
The study included all major trauma patients (Kampala Trauma Score [KTS] II ≤ 6) of all age groups and gender who consented to the study during the study period. Patients who met the inclusion criteria were stratified into hyperglycemic>11.1mmol/l and normoglycemic 3.7- ≤ 11.1mmol/l. Patients who had hypoglycemia on admission, those who died before complete assessment, and those who had established diabetes mellitus on admission were excluded from the study to minimize the overlap between stress-induced hyperglycemia and diabetic hyperglycemia. The study also excluded all patients who were given DNS and dextrose before RBS measurement; identified by acquiring from an

escort nurse, or referral letter. The sample size for all patients enrolled in the study was calculated using the formula by Kirkwood and Sterne (2003). Convenience sampling for patients who met the inclusion criteria was enrolled until the sample size is reached.

Recruitment of patients

Recruitment of patients to participate in the study was done at the Emergency department. Patients were screened for inclusion criteria and those who met the inclusion criteria were enrolled in the study after signing informed consent to participate in the study. All recruited patients were resuscitated on admission according to advanced trauma life support. In all patients who were enrolled in the study, random blood sugar was taken on admission before resuscitation with intravenous fluid was done by the admitting surgical team. Random blood sugar was measured using coded glucose and recorded.

According to their admission RBS, all enrolled patients were divided into two groups: normoglycemic 3.7 - ≤ 11.1mmol/l and hyperglycemic ≥11.1mmol/l. The severity of the injury was determined using the Kampala trauma score II (KTS II) (Mutooro *et al.*, 2010). According to KTS II, severe injury consists of a KTS II ≤ 6. Depending on the type of injury, patients were treated either conservatively or by surgery. Patients were admitted to surgical wards or the intensive care unit to continue with treatment, serial blood glucose measuring/monitoring, and other investigations. Patients were followed up for 90 days during the follow-up period. The phone was used in some cases. Data collection from patients or their relatives was done using a structured questionnaire in both English and Swahili languages.

Statistical data analysis

Data collected were entered into a computer and analyzed using STATA version 13. The continuous variable was summarized using median with interquartile range whereas proportions and frequency tables were used to summarize categorical variables. To determine the association between admission hyperglycemia with mortality and length of hospital stay we determined the unadjusted and adjusted Odds ratios together with a 95% Confidence Interval using logistic regression analysis. Factors with a p-value less than 0.05 were considered statistically significant.

Results

Recruitment of major trauma patients

During the study period, a total of 245 major trauma patients were screened for eligibility of being enrolled in the study. Of these, 217 (88.6%) patients were recruited for the study whereas 29 (11.8%) were excluded due to various reasons. Of the 217 enrolled, 111 (51.2%) were having normoglycemia whereas 106 (48.9%) were hyperglycemic. Figure 1 below summarizes the number of major trauma patients at BMC.
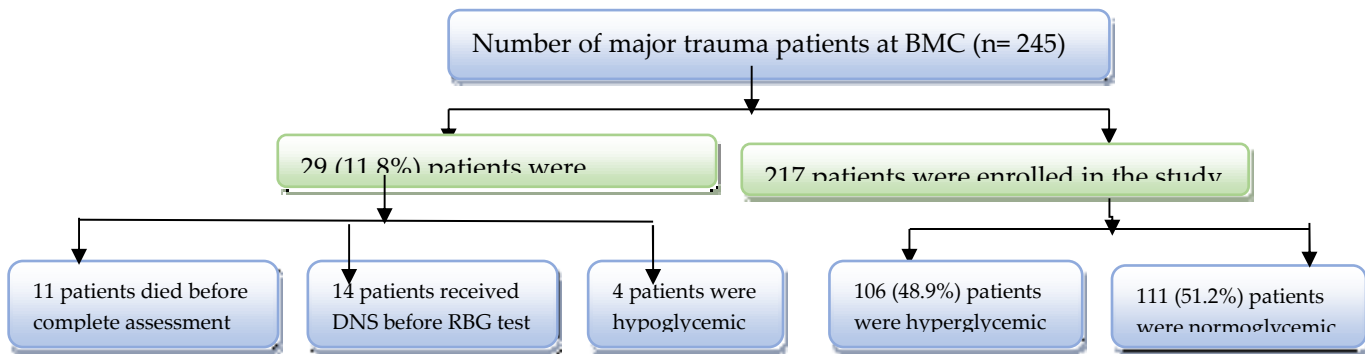
Figure 1: Flow chart showing recruitment of major trauma patients at BMC

Socio-demographic of the 217 major trauma patients

Among 217 major trauma patients included in the study, their ages at diagnosis ranged from 4 – 97 years with a median age of 31 [IQR 24 – 40] years. The age peak incidence was 21-40 years accounting for 61.8% of cases. One hundred and eighty (83.0%) were males and 37 (17.0%) were females with a male to female ratio of 4.7:1. The majority of patients, 141 (65.0%) were from urban areas and most of them, 143 (65.9%) were unemployed. Table 1 summarizes the socio-demographics of the 217 major trauma patients.

Table 1: Socio-demographic of the 217 major trauma patients

Patient particulars	Numbers (n)	Per cent (%)
Age group		
< 20	33	15.2
21 – 40	134	61.8
41 – 60	36	16.8
>61	14	6.5
Sex		
Male	180	83.0
Female	37	17.1
Residence		
Urban	141	65.0
Rural	76	35.0
Occupation		
Employed	74	34.1
Unemployed	143	65.9

*Injury characteristics in major trauma patients*

A road traffic accident was the most common cause of major trauma accounting for 64.5% of cases. The majority of patients, 109 (50.2%) sustained blunt injuries and 67.7% of cases had multiple injuries. Fractures were the most common type of injury occurring in 39.1% of cases. In most of the patients, 143 (65.9%) were unresponsive to pain during the initial assessment. Table 1 summarizes the injury characteristics of the major trauma patients.

Table 2: Injury characteristics of major trauma patients

Injury characteristics	Numbers (n)	Per cent (%)
Cause of injury		
Road traffic accident	140	64.5
Assault	58	26.7
Fall	10	4.6
Bullet injury	2	0.9
Others	7	3.2
Mechanism of injury		
Blunt injury	109	50.2
Penetrating injury	108	49.8
Anatomical site injured		
Head/neck	38	17.5
Thorax	13	6.0
Abdomen	12	5.5
Pelvis	2	0.9
Extremities	5	2.3
Multiple injuries	147	67.7
Type of injury		
Hematoma	37	17.6
Laceration	8	3.8
Cut wound	17	8.1
Penetrating wounds	66	31.4
Fractures	82	39.1
Level of consciousness		
Unresponsive to pain	143	65.9
Respond to pain	74	35.1

Treatment modalities and Outcomes

Among the 217 patients enrolled in the study, 151 (69.6%) were treated surgically and the remaining 66 (30.4%) had non-surgical treatment. Out of the 217 major trauma patients, 66 developed complications giving a complication rate of 36.5%. Of these, pressure sores were the most common complication accounting for 42.4% of cases (Figure 2). The overall median days of the length of hospital stay (LOS) was 15 days. Of the 217 patients with major trauma, 144 (66.4%) stayed longer (>14 days) in the hospital and the remaining 73 (33.6%) had short LOS (≤ 14 days).In this study, 73 patients died in-hospital giving a mortality rate of 33.6%.
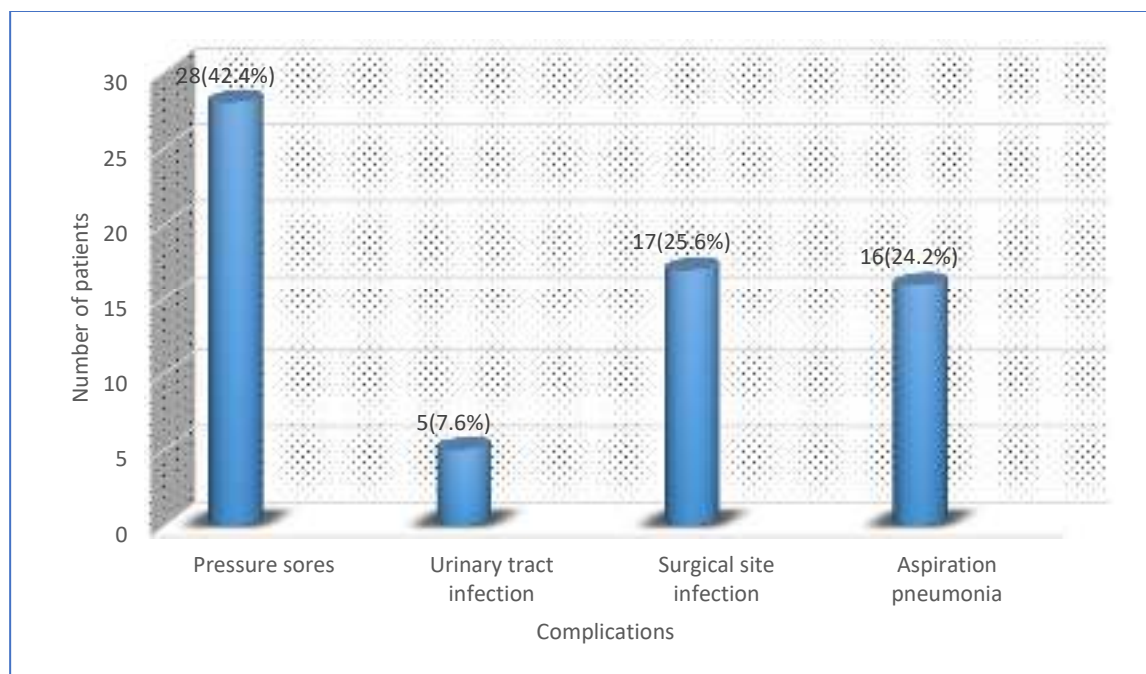
Figure 2: Complications among major trauma patients at BMC

Association between admission hyperglycemia and length of hospital stay among major trauma patients

There was no statistically significant association between admission hyperglycemia and length of hospital stay (p = 0.875) as shown in Table 3 below.

Table 3: Association between admission hyperglycemia and length of hospital stay among major trauma patients

Patients' characteristics	Length of hospital stay		Un-adjusted		Adjusted	
	Long	Short	OR[95%]	p-value	OR[95%]	p-value
	n (%)	n (%)				
	Median [IQR]	Median [IQR]				
Level of blood glucose (mmol/l)						
≤ 11.1	74 (51.4)	37 (50.7)	1.0			
> 11.1	70 (48.6)	36 (49.3)	1.0[0.6 – 1.7]	0.922	1.0 [0.6-1.9]	0.875

Adjusted for age, sex, type of injury, and level of consciousness

Association between admission hyperglycemia and mortality among major trauma patients

Admission hyperglycemia had an increased mortality rate compared with patients with normal admission hyperglycemia (50.9% versus 17.1%).To control the possibility of the confounding effect of other variables on the effect of hyperglycemia on mortality, age, sex, type of injury, and level of consciousness were adjusted for hyperglycemia. There was a strong association between admission hyperglycemia and mortality rate (*p< 0.001*). Table 4 below summarizes the association between the admission of hyperglycemia and the mortality rate among major trauma patients.

Table 4: Association of admission hyperglycemia and mortality among major trauma patients

Patient Characteristics	Death		Un-adjusted		Adjusted	
	Yes	No				
	n (%)	n (%)	OR[95% CI]	p-value	OR [95% CI]	p-value
Level of blood glucose (mmol/l)						
≤ 11.1	19(17.1)	92 (82.9)	1.0			
> 11.1	54 (50.9)	52 (49.1)	5.0 [2.7 – 9.4]	0.001	5.7[3.0 – 11.3]	< 0.001

Adjusted for age, sex, type of injury, and level of consciousness

Discussion

In this study, most of the trauma patients were young adults and showed a male preponderance. This finding is similar to the previous studies reported by others (Otieno *et al.*, 2004; Solagbaru *et al.*, 2006Chalya *et al.*, 2013). This male preponderance among young adult trauma patients may be attributed to the fact that males and young adults are more mobile looking for daily earnings to support their life as compared to females, and therefore exposes themselves to road-traffic accidents. In keeping with what was observed by Solagbaru *et al*(2006) in Nigeria, this study also found that the majority of trauma patients were unemployed. This observation could be attributed to the fact that unemployed people move around a lot more than formally employed ones and hence predisposes them to road traffic accidents. These movements may include selling goods for petty trading which make them move from one place to another.

The length of hospital stay has been reported to be an important measure of morbidity among trauma patients (Chalya *et al.*, 2010). Prolonged hospitalization is associated with an unacceptable burden on resources for health and undermines the productive capacity of the population through time lost during hospitalization and disability (Krug *et al.*, 2000). Prolonged LOS in our study is attributable to the presence of multiple injuries that recovered slowly example severe head injuries and a large number of patients with long bone fractures most of which are open and of the crushed type which took time to heal.

Among trauma patients, the association of outcome with hyperglycemia has been studied extensively in major trauma patients, in whom it portends a poorer prognosis (Gore *et al.*, 2002; Yendamuri *et al.*, 2003; Simsek *et al.,* 2014; Torbati *et al.,* 2015). This finding is attributed to the fact that trauma patients present with a hypermetabolic response to injury that is driven by an increase in the activity of the hypothalamus and sympathetic nervous system that leads to an increased release of ACTH, catecholamine, and glucagon. Stress carbohydrate metabolism in these patients is characterized by increased glycogenolysis and gluconeogenesis with an increased glucagon/insulin ratio (Chernow *et al.*, 1982; Black *et al.,* 1990; Simsek *et al.,* 2014). These acute changes lead to hyperglycemia.

Previous studies have shown that both insulin and glucose can affect the systemic inflammatory response (Reinhold *et al.,* 1996; Rassias *et al.,* 1999). It has been found that high plasma glucose concentrations impair immune function by altering cytokine production from macrophages, diminishing lymphocyte proliferation, and depressing intracellular bacterial activity of leukocytes (Sung *et al.,* 2011). A reduction in chemotaxis, adherence to vascular endothelium, phagocytosis, and cell-mediated immunity has also been described (Reinhold *et al.,* 1996) the concentrations above 11.1mmol/l (200 mg/dl) have been shown to glycosylate immunoglobulin causing a significant reduction in opsonic activity (Mowlavi *et al.,* 2000). As a result, the presence of elevated blood glucose impedes normal host defenses against infection and impairs normal inflammatory responses (Reinhold *et al.,*

1996). Response several cytokines are released, including TNF-α, and IL-6.TNF contributes to insulin resistance and hyperglycemia secondly, inflammatory responses increase the level of corticotrophin-releasing hormone (CRH) and stimulate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which induce elevated levels of blood glucose (Reinhold *et al.,* 1996).

Several studies have demonstrated that admission hyperglycemiais an independent predictor of hospital length of stay among trauma patients (Bochicchio *et al.,* 2005; Mecott *et al.,*2010; Marik & Bellomo., 2013). However, in our study, there was no statistically significant association between admission hyperglycemia and prolonged hospital stay. This finding is similar to a previous study which was done in Taiwan by Cheng *et al* (2017) which demonstrated no association between admission hyperglycemia and length of hospital stay. This observation could be attributed to the fact that most major trauma patients who died had a short hospital stay.

The association between admission hyperglycemia and mortality among major trauma patients has been largely studied (Black *et al.,* 1990; Reinhold *et al.,* 1996; Gore*et al.,* 2001; Laird *et al.,* 2004; Bochicchio *et al.,*2005; Bosarge*et al.,* 2015). In agreement with other studies, this study has demonstrated a strong association between admission hyperglycemia and mortality (Black *et al.,* 1990; Reinhold *et al.,* 1996). Patients who died had significantly higher admission blood glucose levels than those who survived. This association provides another variable apart from hypoxia, bleeding, and hypotension that can be easily obtained early in the clinical course of traumatic patients that may allow the ability to triage these patients appropriately and optimize resources available for early intervention to minimize mortality caused by transient hyperglycemia. Failure to determine HbA$_{1c}$ levels to exclude the confounding effects of preexisting diabetes mellitus in patients with major trauma was the major limitation of this study. However, despite this limitation, the study has provided local data that can be utilized in the establishment of management guidelines for patients with major trauma having transient hyperglycemia.

In conclusion, this study has demonstrated a strong association between admission hyperglycemia and mortality in patients with major trauma at BMC. Therefore, there is a need to institute regular monitoring of blood sugar levels among these patients and give appropriate treatment for those found with hyperglycemia. A further larger study should be done which will include an HbA$_{1c}$ test to exclude the confounding effects of preexisting diabetes mellitus in patients with major trauma.

Ethical consideration: Ethical approval to conduct the study was obtained from the Joint CUHAS-BMC Research, Ethics and Review Committee (CREC /239/ 2017). Permission to conduct the study was obtained from the BMC administration. Informed written consent was sought from each patient before being enrolled in the study. The patients were assured of confidentiality and their right to withdraw from the study. The study did not interfere with the decision of the attending doctor. In patients aged below 18years consent was sought from guardians or parents.

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