BLOOD SUGAR PATTERNS IN CRITICALLY ILL PATIENTS WITH TRAUMATIC BRAIN INJURY AT KENYATTA NATIONAL HOSPITAL.

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DECLARATION

I, **Dr. Abel Odhiambo Oduor**, hereby declare that this dissertation is my original work and it has not been presented before either in whole or part to this institution or any other institution elsewhere for academic qualification.

I further declare that all material cited in this report which are not my own have been duly acknowledged.

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DEDICATION.

To my family and especially my mother who continue to be my constant source of motivation. You are appreciated.

LIST OF ABBREVIATIONS AND ACRONYMS

ACTH- Adreno-CorticoTrophic Hormone

ADA -American Diabetes Association

ANLS -Astrocyte-neuron lactate shuttle

BBB- Blood Brain Barrier.

BTF- Brain Trauma Foundation.

CCU- Critical Care Unit.

CIT- Conventional Insulin Therapy.

CRH- Corticotrophin Releasing Hormone

CSF- Cerebrospinal Fluid.

CT- Computed Tomography

CVA- Cerebrovascular accident.

DH- Diabetic Hyperglycemia.

DM- Diabetes Mellitus.

EEG- Electroencephalogram

EVD- Extra-Ventricular Drain

FDA- Food and Drug Administration

GCS- Glasgow Coma Scale.

GLAST- Glutamate Aspartate Transporter

GLUT- Glucose transporter

GOS- Glasgow Outcome Scale.

ICH- Intracranial Hemorrhage.

ICU- Intensive Care Unit.

IIT- Intensive Insulin Therapy.

KNH- Kenyatta National Hospital.

MCT-

NALS-Neuron-astrocyte lactate shuttle

POE- Percentage of Excursion

REDCap- Research Electronic Data Capture.

RRA- Resuscitation Room A.

RRB- Resuscitation Room B.

SAH- Subarachnoid Hemorrhage.

SIH- Stress induced Hyperglycemia.

SIRS- Systemic Inflammatory Response Syndrome

TBI- Traumatic Brain Injury.

OPERATIONAL DEFINITIONS

Diabetes- HbA1c of 6.5% or more as defined by the American Diabetes Association. [1]

Hyperglycemia- Blood sugar ≥11.1mmol/l

Hypoglycemia- Blood Sugar ≤4mmol/l

Severe Hypoglycemia- Blood Sugar level ≤2.2 mmol/l

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ABSTRACT

Background: Traumatic Brain Injury (TBI) is a significant source of morbidity and mortality, contributing to a significant proportion of admissions to Critical Care Units (CCUs) internationally and in Kenya. Outcomes are largely poor and have a significant negative impact on the patient's life as well as on their families and the larger society itself. Severe cases of TBI are often admitted to CCUs where the mainstay of management is the prevention and hindering the development of secondary brain injury. Identification and management of recognized Secondary systemic insults has been shown to improve outcomes. Deranged blood sugar levels rank high among the most common of secondary systemic insults and is associated with poorer outcomes. The challenge herein arises from the heterogeneous nature of the clinical course of patients with TBI as well as the paucity of current evidence on the optimum blood sugar levels in these patients. Observation of patterns of blood sugar levels in patients with TBI is an essential baseline in the assessment of deranged blood sugar levels in patients with TBI.

Study Objective: To determine patterns of blood sugar levels for patients admitted at KNH Critical Care Units (CCUs) with traumatic brain injury.

Study Design: This was a prospective observational study.

Study Area and Setting: A single center study conducted in the Accident and Emergency and Critical care units at Kenyatta National Hospital.

Study Population: Critically ill patients with Traumatic Brain Injury (TBI) requiring admission at the Kenyatta National Hospital (KNH) Critical care units (CCU).

Methodology: The sampling technique employed was consecutive sampling technique. Patients that met the inclusion criteria were recruited on admission to the Critical care units.

Data collected included the study subjects' demographic data, CT scan diagnosis, Admission GCS and serial blood sugar levels. Blood sugar control methods were recorded during the study period as well. Data collection was done through a standardized glucometer and input into an electronic data collection tool (REDCap). Data was analysed using SPSS version 26. Descriptive statistics were used to describe the sociodemographic and clinical characteristics of patients. Categorical data was summarized as frequencies and percentages while continuous data as means and standard deviations or medians and interquartile ranges.

The blood sugar control methods used were tabulated using frequencies and percentages then compared with blood sugar levels of patients at different stages using the chi-square test of association. Admission and final blood sugar levels were compared for any differences using paired t-test/Wilcoxon signed-rank test.

Results: The study enrolled 66 subjects predominantly male (60) with a mean age of 35. Majority (53%) had severe TBI with subdural hematoma as the most common diagnosis at 39.4%. The proportion of patients within the hyperglycemic range on first reception to the hospital was at 9.1%. The daily mean blood sugar levels were between 7-8 mmol/l with the highest proportion of standard deviation occurring in the first 2 days of admission. Active blood sugar lowering with insulin was noted only on 8 incidences throughout the study period with no significant bearing on daily mean averages.

Conclusion: There exists varying prevalence of hyperglycemia in moderate to severe TBI. Significant glycemic variability occurs in the first 2 days of hospital stay. This study is the framework for which extended research into understanding glycemic derangement and control in patients with TBI is formed. Evidence from this study should aid in the design of a suitable glycemic control protocol for TBI patients in ICU settings in the region.

CHAPTER ONE: INTRODUCTION

1.1 BACKGROUND

Traumatic brain injury is broadly defined as an insult to the brain following external noxious stimuli that may be blunt or penetrative. It is further described as pathology that does not arise from congenital or degenerative etiology[2]. It occurs following various mechanisms with the leading mechanism resulting from road traffic accidents followed by assault[3].

TBI presents with varying degrees of injury with the widest acceptable means of scoring the degree of neurological injury being the Glasgow Coma Scale (GCS). This scale is used in grouping traumatic brain injuries based on the degree of severity: mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS of 8 or less). Cases classified as moderate to severe require admission for neurocritical care and possibly respiratory support through mechanical ventilation and cardiovascular support more so in cases with associated injuries including long bone fractures, thoracic and abdominal injuries. The clinical course of patients with TBI is variable and unpredictable at best posing a management challenge for clinicians. This is then followed by a diverse array of outcomes ranging from complete functional recovery, permanent disability and even death[4].

The approach to management of patients with TBI provides a particular challenge to hospital teams as a multidisciplinary approach is recommended. This involves the primary critical care practitioner, neurosurgical teams, nursing care, theatre personnel, radiology and nutritional teams in a coordinated effort to provide round the clock care.

Traumatic brain injury is biphasic in its progression and is described as occurring in primary versus secondary phases. Primary brain injury occurs as a direct result of anatomical damage

involving compression and shearing forces directly applied to the brain tissue[5]. However, there is very limited management or therapeutic options for the primary lesion. The initial lesion however; through a cascade of cellular events jeopardizes the surrounding neuronal tissue through local and systemic means in the next phase; secondary brain injury. This occurs in the following hours or days after the primary injury. Secondary brain injury can occur either cranially or in a systemic fashion. Cranial complications include; vasospasm, raised intracranial pressure, calcium ion toxicity and cerebral edema[6].

Secondary systemic insults have a negative connotation in the progression of secondary brain injury and are of particular interest as they represent potentially modifiable physiological risk factors that may give critical care practitioners the edge in obtaining improved outcomes. A retrospective study by Jeremitsky et al identified the impact of 11 secondary brain injury factors during the first 24 hours following traumatic brain injury. These include; hypotension, hypoxia, hypercapnia and hypocapnia, hyperglycemia, hypothermia and hyperthermia, metabolic acidosis, seizures, coagulopathy and intracranial hypertension. The study showed a mortality rate of up to 51 % associated with hyperglycemia[7].

The evolution of management of TBI is thus geared towards identification and prevention and management of secondary systemic insults. With respect to deranged blood sugar, consensus is still lacking. Peak and persistent hyperglycemia have been found to correlate with the severity of disease and as such serve as potential for use as prognostication markers in TBI[8].

The challenge in determining whether deranged blood sugar levels in critically ill patients with TBI warrants more attention from the critical care practitioners is based on the heterogeneity of the disease and lack of establishment of optimum blood sugar levels for this cohort. Establishing

the prevalence of deranged blood sugar levels in patients with TBI may go a long way in generation of treatment protocols and improved outcomes for this significant concern to society.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 The Brain and Glucose

The brain is predominantly dependent on glucose as a source of energy and ranks as the first in glucose consumption across all organs. Glucose uptake from extracellular fluid is mediated by the facilitated glucose transporter member 1; GLUT-1. This promotes glucose entry into cells such as astrocytes, oligodendria and microglia. Furthermore, another glucose specific transporter- GLUT-3 promotes entry into neuronal cells. Neurons and Astrocytes have the most glucose utilization capacity among the brain cells[9].

The exact fate of glucose once glucose uptake has occurred is as of yet undetermined due to technological limitation limiting the ability to quantify in vivo metabolic activity. Several theories have been put up to that effect, to account for movement of lactate between neurons and astrocytes. This is postulated to occur between shuttling systems termed as the Astrocyte-neuron lactate shuttle (ANLS) and the Neuron-astrocyte lactate shuttle (NALS)[10]. The ANLS theory proposes that glucose uptake occurs in astrocytes and metabolized to lactate which is extruded from the astrocytes for neuronal uptake to be utilized as fuel through monocarboxylate transporters (MCTs). On the other hand; the NALS model suggests that glucose uptake is through the GLUT-3 into neuronal cells which is metabolized into lactate for transport into astrocytes.

There's evidence to show a curious neuronal preference for lactate in conditions where both glucose and lactate are present. Neurons and Astrocytes thus have a strong demand for glucose and lactate as energy sources and are rather intolerant to deficient supply and this forms the basis

of various central neurological pathophysiology underlining the importance of determining the interaction between brain glucose metabolism with cerebral diseases particularly; Traumatic brain Injury[11].

2.2 Burden of Traumatic Brain Injury

Traumatic Brain Injury is a significant matter of public health interest, with rising mortality rates accounting for up to 30% of injury related deaths and disability. Internationally, surveys of trauma registries indicate TBI is estimated to be the cause of collectively 4.5 million deaths a year. In terms of morbidity; TBI is estimated to result in 8.1 million years lived with disability and mortality. This translates to raised costs of treatment and rehabilitation that befalls public health systems. Due to the primary population affected and its long-term consequences- it results in significant loss of workforce population with reaching economic effects from the loss of house bread-winner to drop in a country's Gross Domestic Product[12]. It was initially projected that by the year 2020 road traffic accidents would be a major cause of TBI, becoming the leading cause of mortality and even rank as 3rd in terms of leading cause of Disability adjusted life years earning the appellation 'the silent epidemic'.

There's a disproportionate occurrence of TBI related deaths occurring in low- to middle income generating countries with up to 90% case specific mortality rates occurring in these regions. This is multifactorial ranging; from ineffective implementation of preventative policies such as mandatory protection and speed limit enforcement, delayed presentation to health facilities and a large proportion of under-reported cases[13].

Locally, it is estimated that up to 3000 Kenyans die annually as a result of Road traffic accidents with similar implications on economic burden as witnessed internationally. A large proportion is estimated to be attributed to motorcycles and mainly affecting young adult males[14].

Kenyatta National Hospital is the largest referral hospital in East and Central Africa and as per its status will receive the bulk of severe cases of TBI both locally and occasionally regionally due to the infrastructure and available skilled manpower. To that respect, the main Critical care unit handles the bulk of the critical cases of TBI following the number of referrals. The observed average monthly admission rate is 22 patients accounting for 29.4% as a proportion of average monthly admissions. In light of this data; TBI represents a serious concern in the local setting and more could be done to improve outcomes from a clinical perspective.

2.3 Pathophysiology of hyperglycemia in TBI.

2.3.1 Stress Response

There are multiple theories to explain high blood sugar levels that sometimes follow brain injury. The one that is widely researched is stress induced hyperglycemia. It postulates that hyperglycemia in TBI occurs as a result of sympatho-medullary activation following the injury. Several studies have investigated the cause of hyperglycemia in the background of traumatic brain injury. Clifton et al demonstrated in a prospective observational study that plasma norepinephrine levels were found to be consistently elevated in a large proportion of polytrauma patients but notably in those with head injury as the primary illness. Norepinephrine levels were found to be directly proportional to the severity of neurological injury. This sympathetic stimulation results in hypermetabolism and cardiovascular changes and might imply the consequential glycemic levels[15].

Bosarge et al examined the effects of stress-induced hyperglycemia versus diabetic hyperglycemia on patients with TBI. This single center study involved dichotomization of patients into 2 categories; stress induced hyperglycemia and diabetic hyperglycemia. Mortality in patients with Stress induced hyperglycemia (SIH) was nearly 50% higher than the diabetic group

with no significant association between the diabetic group and hyperglycemia[16]. This may be because diabetics experience a long-term cellular adaptation to raised blood sugar levels thus the hypothesis that the presence of diabetic hyperglycemia in the background of TBI has less negative impact[17].

Other studies correlating catecholamine surge and raised levels of insulin counter-regulatory hormones are associated with the dysglycemia seen in traumatic brain injury[18]. The hypothalamo-pituitary-adrenal axis activation after brain injury leads to increased circulating levels of not just catecholamines but glucagon, cortisol and growth hormone levels. This in turn enhances glycogenolysis and produces a hypercatabolic state that leads to spikes in blood sugar levels.

Catecholamine surge reduces insulin production coupled with raised glucagon production through its effect on the pancreatic alpha cells further hampering the body's main mechanisms for blood sugar regulation[18].

This theory is further supported by Bessey et al in a randomized crossover study investigating the effects of stress hormones produced during injury periods[19]. The study subjects were determined to be free of pathology through standard laboratory tests. A triple hormone infusion (glucagon, catecholamines, and cortisol) administered over a 4-day period was found to cause hyperglycemia similar to that observed in mild to moderate stress. A single hormone infusion of either catecholamines, glucagon, or cortisol alone did not cause hyperglycemia. This finding thus suggests a synergistic hormonal effect after injury.

Finally, Insulin resistance is another known mechanism in SIH that affects glucose metabolism. Strommer et al conducted animal experimental models in mice that observed raised

corticosterone levels following small bowel resection. The resultant rise in blood sugar was associated with skeletal muscle resistance to glucose uptake and glucose-induced hindered insulin production from the pancreas. Interleukin-6 is thought to be responsible for this finding[20]. Together with stress hormones it is postulated to have the secondary effect of impaired peripheral glucose uptake either through hindered receptor expression or inhibition of intermediaries with key roles in glucose uptake[21].

2.3.2 Inflammatory Response

The primary lesion in TBI triggers a systemic inflammatory response syndrome (SIRS) that triggers a number mechanisms resulting in hyperglycemia. Several cytokines have been identified as instigators to this process most notably; IL-1, IL-6, TNF-α and CD11d. Previous studies have shown that TNF-α downregulates adipocyte specific genes by 2-fold including that of GLUT-4, as well as a 3-fold upregulation of preadipocyte specific genes with a net effect of hyperglycemia in the background of insulin resistance[22].

McClain et al investigated the role of release of interleukin 1 as the main cytokine mediating the acute phase response. In this experimental study, it was observed that there was significant IL-1 activity detected in ventricular fluid that correlated with the metabolic response- with outcomes such as fever, hypozincemia and increased C-Reactive protein levels in contrast to negligible levels obtained from cerebrospinal fluid. This added credence to the role of the inflammatory response in the overall contribution to secondary brain injury[23].

This general inflammatory response triggers activation of the pituitary-adrenal axis through increased circulating levels of corticotrophin releasing hormone (CRH) as a result of the inflammatory response involving the cytokines; IL-1, IL-6 and TNF-α. Adrenocorticotrophic Hormone (ACTH) is subsequently released from the anterior pituitary eventually resulting in

hyperglycemia. Nitric oxide- an important participant in physiological and pathophysiological processes alike has been implicated in contributory role towards the release of corticosterone from the adrenal cortex[24].

2.3.3 Pituitary and Hypothalamic Dysfunction

The pituitary's role in glucose homeostasis through its actions in increased insulin sensitivity and modulatory effect on hepatic gluconeogenesis is well documented. Recent data indicates that pituitary and hypothalamic insult occurs in patients with TBI and is associated with worse outcomes- as has been evidenced by increased ICU and hospital length of stay, increased infection rates and mortality rates[25].

The incidence of hypopituitarism was the subject of a study involving microscopic evaluation of 42 patients that died after involvement in road traffic accidents. This found pituitary necrosis in up to 50% of the 42 study subjects who survived after 1 day following the accident. This was the first study of its nature that gave credence to consideration of hypopituitarism as part of complications following TBI[26].

These resultant neuroendocrine disorders are potential cause of impaired blood sugar regulation. Most notably, the deficiency of gonadotrophic and growth hormones has been identified to be commonly occurring in TBI and have ramifications in the sense of blood sugar dysregulation[27]. These processes occurring simultaneously to contribute to dysglycemia in patients with underlying TBI.

2.3.4 Diabetes Mellitus

Diabetes in TBI has been identified as a possible independent predictor of poor outcomes. This follows studies indicating higher mortality rates of up to 14% in diabetic patients who sustained

severe traumatic brain injury vs 8.2% in those without[27]. This was however difficult to effectively establish an exact relationship due to the heterogeneity of the disease as well as inadequate patient numbers to effectively generate a statistical relationship. The suggestion is that the relative insulin insufficiency possibly contributes to the observed increase in mortality between the two groups all things considered. Similar results were observed in a study that found a 17.1% mortality rate in patients with TBI with DM in the background than patients without DM[28].

Undiagnosed Diabetes mellitus also poses a significant threat to these patients, more so in the elderly as symptomatology may be exacerbated in TBI yet at the same time masked as the presentation is variable in its clinical course. These patients with underlying insulin resistance as in type 2 DM have characteristically unregulated blood sugar levels coupled with the resultant metabolic disturbance that further deteriorates the patients' overall condition.

2.3.5 Iatrogenic Factors

Various treatment strategies have also been implicated in unbalanced blood sugar levels in patients with TBI. This includes but not limited to; exposure to anesthesia and surgery, use of glucose containing solutions or high-or-low caloric nutrition (more so for TBI patients whose feeding is at the discretion of healthcare practitioners) and use of insulin strategies as well as psychological stressors following admission to critical care units[29].

2.4 The effects of blood sugar control on brain activity in TBI.

2.4.1 Oxidative Stress

The exact nature to which hyperglycemia causes neurological injury remains unknown. Several theories have been put forward trying to account for this phenomenon. One of these is the Brownlee theory which postulated that the excess substrate (in the form of increased blood

sugar) increases intracellular oxidative stress which in turn leads to activation of metabolic pathways of various enzymatic elements of glucose metabolism that are said to bring about neuronal damage[30]. With the background of oxidative stress this leads to generation of toxic end-products at various sections of the pathways for instance: hexosamines, protein C activators, polysols and even advanced glycation end products. These mechanisms ultimately result in the activation of Reactive Oxygen Species (ROS) while indirectly leading to an increase in circulating inflammatory cytokines as well as suppressed immune functions. Retrospectively, the maintenance of an extracellular euglycemic environment as well as the inhibition of ROS has been shown to possibly restore metabolic and vascular perturbations with blockage of neuronal damage although this has been done in the context of diabetes and it is unclear whether the same applies to stress induced hyperglycemia.

2.4.2 Lactic Acidosis

A systematic review by Prakash alluded to the presence of lactic acidosis as another mechanism by which neuronal damage occurs in the presence of hyperglycemia[31]. It's been demonstrated that in areas of focal ischemia as is bound to occur in traumatic brain injury, the abundance of glucose as a substrate in oxygen scarce situations leads to anaerobic metabolism hence generation of large amounts of lactate. This leads to intracellular lactic acidosis. A study by Kraig et al determined the critical pH to be a value of 5.3. This was evidenced by a cascade of events involving intracellular influxes of calcium, initiation of lipolysis and generation of cytotoxic fatty acids and glutamates consequently led to neuronal destruction[32]. Indeed, it is the same animal experimental study that identified similarities in the pattern of neuronal tissue necrosis in cerebral lactic acidosis as was appreciated in brain infarction.

2.4.3 Electrolyte Disturbances.

Primary neuronal injury leads to impaired cellular metabolism and lactic production at large. This has been shown to result in intracellular accumulation of glutamate and Free Fatty acids. Glutamate has a primary role as an excitatory neurotransmitter in the neurons. Unregulated glutamate activity following its accumulation brings about a process aptly named glutamate-mediated excito-toxicity. This occurs due to glutamate mediated intracellular influx of sodium and calcium ions that bring about the neuronal cells demise after calcium induced caspase activation[3334]. Astrocytes bear a defensive role thus neurons are the initial focus of this mechanism of injury. However, it has been noted that in the subsequent stages of the injury; with increasing extra-cellular glutamate levels, astrocytic expression of glutamate transporters; Glutamate transporter 1 (GLT-1) and Glutamate-aspartate transporter (GLAST) reduces which means that astrocyte damage occurs at this point[35]. The process is thought to be made worse secondary to the intracellular accumulation of sodium which reverse the transport of glutamate. Glutamate extrusion from the astrocytes happens at this point in a paradoxical fashion which means that the astrocytes become part of the pathology.

Lactic acidosis from hyperglycemia additionally impairs the Na+-K+ ATPase pump through its hindrance of ATP production consequently resulting in increased extracellular sodium levels. This exerts more osmotic pressure leading to cellular edema, raised intracranial pressure and in extreme conditions; cerebral herniation[36].

2.4.4 Inflammation

Neuroinflammation has been identified as a significant part of secondary insult following TBI with harmful and beneficial implications depending on the temporal phase (acute or delayed). Notable pathways involving the release of inflammatory cytokines as well as inflammatory-

transcription factors such as Tumor necrosis factor-α (TNF-α), Transforming growth factor (TGF-β) and Interleukin 1β. These factors have been identified in raised levels in samples of blood, CSF and brain neuronal tissue following TBI with a statistical relationship with the severity of injury and poor outcomes[37].

Various other inflammatory pathways have been identified in the overall contribution to secondary brain insults in TBI. An in-vitro assay of the effect of hyperglycemia on the antioxidant capacity of human monocytes of the cell line U937 with walnut oil as a possible anti-inflammatory to counter this effect. Cells exposed to hyperglycemic conditions showed enhanced release of pro-inflammatory cytokines, reduced anti-oxidant capacity and DNA damage subsequently due to oxidative damage vs those in normoglycemic conditions. Hyperglycemia impaired the monocytes defense against Reactive oxygen Species (ROS). On the other hand, the cells exposed to the anti-inflammatory walnut oil showed significant preservation of the anti-oxidant properties which translated to less cell demise[38]. Microglia; the innate immune cells of the central nervous system are activated in TBI with similar cytokine pathways; leading to endothelial cell damage and microvascular leaking leading to edema further compounding secondary brain injury[39].

2.4.5 Secondary Implications

Hyperglycemia in TBI is responsible for further neuronal damage through indirect mechanisms such as infections, increased intracranial edema with intracranial hypotension as well as impaired brain energy metabolism. Several studies support this theory such as the potential for increased incidence of cerebral vasospasm[40]. Hyperglycemia is also known to impede local blood flow through its direct effect on increased blood viscosity and global small vessel disorders subsequently resulting in ischemia and hypoxia to add to secondary brain injury[41].

Hyperglycemia has also been implicated in exacerbation of endothelial edema, hindered glial cell function as well as BBB damage[42].

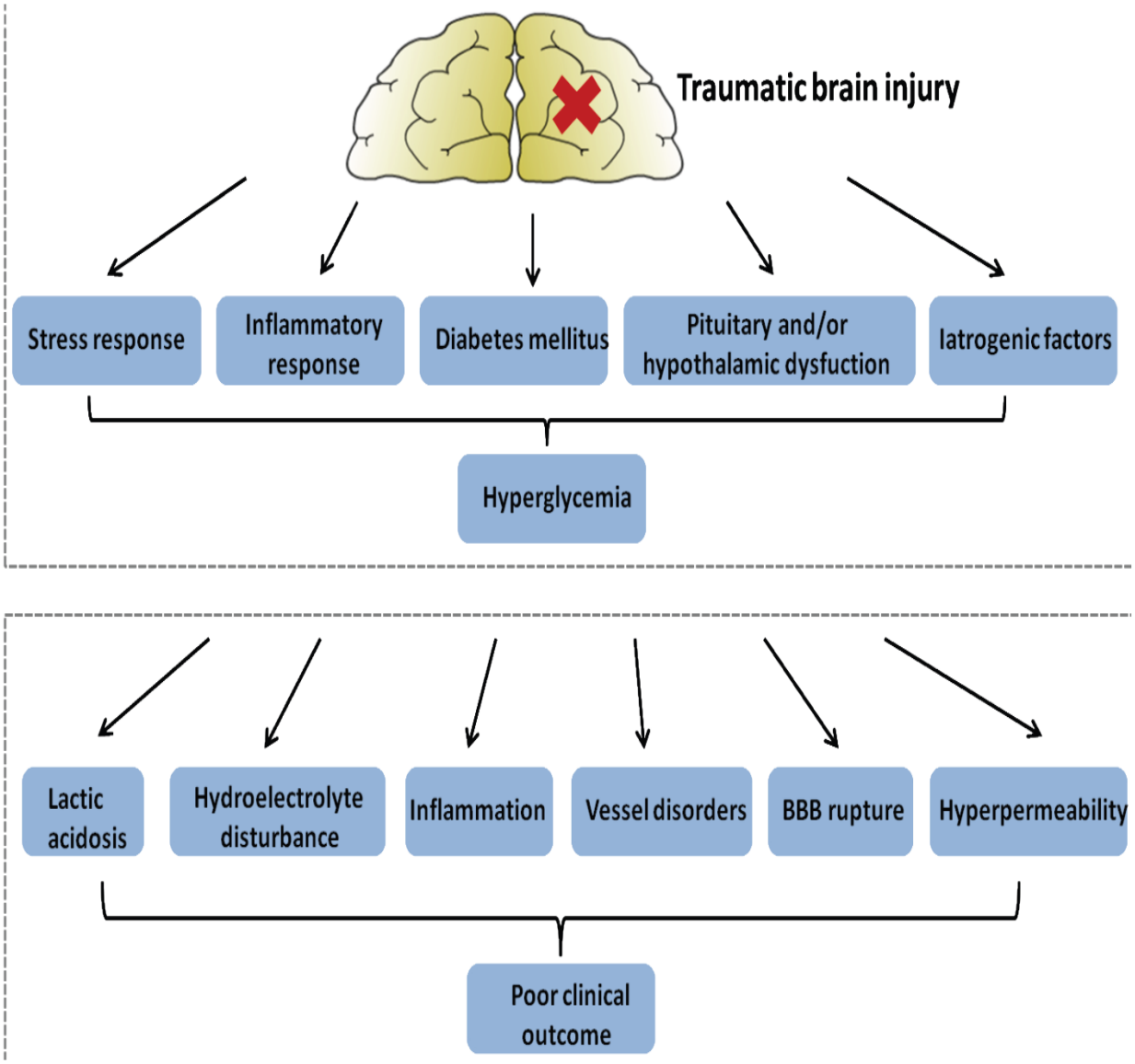


Figure 2: Figure illustrating hypothetical mechanisms: hyperglycemia in patients with traumatic brain injury (upper panel); and explaining a detrimental effect of hyperglycemia on clinical outcome (lower panel). BBB, blood-brain barrier.

`Summary of pathophysiological processes behind deranged regulation of blood sugar levels and mechanisms of neuronal injury[8].

2.5 Clinical Outcomes Related to Deranged Blood Sugar Levels in TBI.

2.5.1 Hyperglycemia and TBI.

The relationship between admission hyperglycemia and neurologic outcome of severely brain injured patients was investigated in a landmark study by Young et al in 1989. This was a prospective single center observational cohort study. The threshold for raised blood sugar levels was set at 11.1 mmol/l or more as per the hospital guidelines. Poorer initial GCS scores were associated with significantly higher admission blood sugar levels as well as the worst 18-day neurologic outcomes. The study found that the patients with peak 24-hour blood sugar levels above 11.1 mmol/l had a mean of 2 unit increase in GCS versus those with admission glycemic levels below the cut off had a mean 4-point rise in GCS during the 18-day study period. Favorable long term neurological outcomes after 3 months and 1-year outcomes associated with lower levels of admission and peak 24-hour blood sugar levels[43].

A similar study conducted by Lam et al in 1991 with the goal of investigating the association between hyperglycemia and traumatic brain injury. This retrospective single center study additionally reviewed the variation in blood sugar levels for patients with TBI following surgical intervention. This included correction of the primary neurosurgical pathology such as evacuation of hematomas or placement of a sub-arachnoid bolt for intra-cranial pressure monitoring. The study found a positive association between severity of injury with blood sugar levels. Those in the severe head injury group had higher admission blood sugars vs the moderately injured group with mean blood sugar levels of 10.6 mmol/l vs 7.2 mmol/l. The same extended for the association between blood sugar levels and neurological outcomes- average values of

12.1mmol/l for those with poor outcomes vs 9.3 mmol/l in the patients with favorable outcomes. It was also noted that the blood sugar levels 24 hours post admission and post-op also had a significant effect on the outcomes as patients with initial high blood sugar values that persisted at 24 hours had a larger proportion with poor neurological outcomes compared to those whose 24-hour blood sugar levels had dropped to <11.1 mmol/l[44].

In 2009, a retrospective study by Xi Liu-DeRyke established the role of early hyperglycemia as a prognostic indicator in patients with traumatic brain injury. This was a single center study review of admission and daily regular interval blood sugar levels. There was an overall mortality rate of 13.2%. A larger proportion of non-survivors were in the hyperglycemic range compared to the survivors group. Data analysis indicated an increased incidence of mortality for patients who at any point in the first 24 hours of admission had blood sugar levels above 8.8 mmol/l as well as an association of raised blood sugar levels with increased severity of injury. Peak 24-hour blood sugar levels above 8.8 mmol/l were associated with higher mortality as opposed to other studies that stated that admission blood sugar levels had a greater bearing on mortality. Another significant finding was that raised admission and 24-hour blood sugar levels had a higher association with mortality in contrast to blood sugar levels from day 2-5. The study concluded that raised peak and 24-hour blood sugar levels were a poor prognosticating factor for patients with severe TBI[45].

Griesdale et al in 2009 that set out to investigate the possibility of correlation between mortality and blood sugar levels in patients with severe traumatic brain injury (GCS of 8 or less). This was a single center retrospective cohort study that monitored average daily morning blood sugar levels for 10 days. 170 patients were included in the final analysis. Hyperglycemic episodes occurred in 65% of patients during the study period with no significant association of quintiles of

mean daily morning blood sugar levels and mortality. Final data analysis indicated that a single episode of raised blood sugar level was associated with 3.6-fold increased risk of hospital mortality. Episodes of low blood sugar occurred in 48% of patients and had no statistical association with mortality. This study suggested the benefit of maintenance of blood sugar levels of 10 mmol/l or less in patients with severe TBI[46].

A prospective study by Kafaki et al published in 2016 set out to observe whether hyperglycemia on admission could be considered as a predictor of mortality in patients with traumatic brain injury. Blood sugar levels of the study subjects were obtained on admission and at 72 hours with the cut off for hyperglycemia set at 200mg/dl (11.1 mmol/l). 220 patients were recruited in the final study with 39% having admission blood sugar levels above the cut-off. In this category of patients, the mortality rate was at 65.8% in contrast to 23.7% in the group that had admission blood sugars of 11.1mmol/l or less. A sub-group analysis of those with admission blood sugar levels of above the cut off indicated a linear relationship between the increasing blood sugar levels and mortality. High admission blood sugars were also associated with increased ICU length of stay as well with shorter hospital length of stay although this may be attributed to the increased mortality rate in this group[47].

In East Africa, a Ugandan prospective observational cohort study involving consecutively sampled patients with severe TBI eventually admitted to the CCU with severe TBI with 99 making it into the final analysis. Cut-off for raised blood sugar was set at 11.1 mmol/l based on hospital guidelines. The study was consistent with related international studies as out of the 16.2% with hyperglycemia on admission, the group had a mortality rate of 68.8% compared to 43.7% in those without[48].

Adeolu et al in Nigeria investigated the relationship between plasma blood sugar levels and injury severity as well as outcomes. This was a prospective single center study done involving consecutive recruitment of patients with traumatic brain injury whose random blood sugar was measured in the accident and emergency department unit. For this study, a random blood sugar of >11.1 mmol/l was defined as hyperglycemia with blood sugar between 3.5-6.1 mmol/l was considered normal. The study found no statistical association between admission blood sugar level and injury severity. In terms of the management outcome; none of the patients who died were found to have raised blood sugar levels above 11.1 mmol/l- a finding not consistent with previously mentioned studies[49].

This is similar to a retrospective single center study done in the pediatric population by Parish and Webb et al[50]. The study found a higher proportion of patients with closed head injury had blood sugar levels above the cut-off of 15mmol/l compared to those without head injury. However, there was no correlation between blood sugar levels and poor neurological outcomes.

A prospective 6-month study conducted by Opondo and Mwang'ombe et al investigated the outcomes of severe traumatic brain injury at the main critical care unit in Kenyatta National hospital[51]. This involved recruitment of 87 consecutively sampled patients admitted over the study period with admission GCS of 8 or less and the main outcome measure being survival or mortality. The cut-off for hyperglycemia in this study was set at 10 mmol/l. Severe traumatic brain injury contributed to a 14.3% admission rate in the critical care unit during the study period with a total mortality rate of 54% of those cases. 75 patients had their admission blood sugars recorded and it was noted that while the majority (66.7%) of these patients had blood sugar levels of more than 10 mmol/l and this group had an 88.8% mortality rate.

Salim H. et al in 2009 conducted a retrospective two center study that consecutively recruited patients with traumatic brain injury as the primary illness and had serial blood sugar measurements for a 7-day period. Persistent hyperglycemia was defined as daily average blood sugar levels of 8.3 mmol/l. Out of the final 834 patients who met the recruitment criteria it was found that 105(12.6%) had persistent hyperglycemia with majority in the old and those with worse injury severity scores. Persistent hyperglycemia was found to be an independent risk factor for mortality as this group had higher mortality rates[52].

A single center, cross-sectional study whose focus was on the pediatric and adolescent population admitted with TBI. The study findings were also consistent in highlighting the statistical relationship between severity of brain injury and poor short-term outcomes with hyperglycemia. Persistent hyperglycemia on the second- and third-days following admission was noted to have a 5- and 10-fold risk of mortality in the study and was thus considered as a significant prognosticating factor in TBI[53].

2.5.3 Use of Insulin Therapy

A landmark single-center prospective randomized clinical trial conducted by Van Den Berghe et al investigated the potential benefits of stricter blood sugar control[54]. The setting was a surgical Intensive care unit for patients receiving mechanical ventilation. Critically ill patients in hospitals are particularly predisposed to hyperglycemia and insulin resistance even in the absence of diabetes and the aim was to investigate whether stringent use of insulin therapy resulted in favorable outcomes. Patients were randomized into 2 groups. In the first one- insulin infusion therapy was used to maintain blood sugar levels between 4.4-6.1 mmol/l; also known as intensive insulin therapy (IIT). The second group involved the use of insulin when the blood sugar level was raised above 11.9 mmol/l to target blood sugar levels 10-11.1 mmol/l. The study

had significant implication in the world of critical care as IIT reduced overall mortality reduced to 4.6% vs 8.0% in the CIT Group. For those who required mechanical ventilation for 5 days or more; mortality was reduced- 20.6% in the CIT Group vs 10.6% in the IIT group. As per the secondary outcomes the study highlighted reduction in bloodstream infections up to 46%, reduction of red cell transfusions up to 50% and critical illness polyneuropathy by 44%.

A later, unplanned sub-group review of this study was done with the main focus of patients with TBI as the primary diagnosis to assess whether any statistical inference could be derived from this. Out of a total number of 63, key observations included better neurological and functional outcomes after 1 year as well as lower intracranial pressure and lesser incidences of convulsions and diabetes insipidus[55].

The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm regulation (NICE-SUGAR) conducted in 2015 is to-date, the largest international multi-center randomized clinical trial investigating the use of intensive insulin therapy in a heterogenous group of critically ill patients[56]. A sub-group analysis of patients with TBI from the study were followed up over a 2-year period. The main neurological outcome measures using the extended Glasgow Outcome Scale (GOSE) while secondary ones including incidence of hypoglycemia (blood sugar 2.3-3.9 mmol/l) and severe hypoglycemia (blood sugar of 2.2 mmol/l or less), ICU and Hospital length of stay. The study found that both groups had almost similar rates of mortality and neurological outcomes. There was no statistically significant advantage with the use of IIT over CIT in patients with TBI[57].

A similar study- a single center prospective randomized clinical trial by Wang et al conducted over a 3-year period set out to investigate the effect of IIT to CIT. The main outcome measures in the study were the incidence of infections, mortality and the neurological outcomes assessed at

6 months using the Glasgow outcome scale. The study found that out of the final 81 study subjects those in the IIT limb had a decreased infection rate at 31.9% vs 52.3% as well as reduced ICU duration of stay and better neurological outcomes[58].

Vespa et al conducted a single-center retrospective review to assess the effects of insulin therapy on the cerebral neuronal environment. This was done through the use of cerebral microdialysis catheters for analysis of neuronal extracellular environment and global brain metabolism. Patients were stratified based on the Van Den Berghe trial[54]. In the stricter blood sugar control group, there was a 70% reduction of microdialysis glucose as compared to a 15% reduction in the loose control group. This was consistent with increased markers of cellular distress in the group with stricter blood sugar control namely elevated glutamate levels as well as higher levels of lactate-pyruvate ratios. There was no reduction of cerebral metabolic rate of glucose. The study findings indicate that stricter control of blood sugar levels are associated with markers of neuronal stress and may in fact be detrimental to the brain. Furthermore, while admission glucose levels were associated with higher mortality levels (39% vs 11%) there was no indication that they could be considered as 6-month predictors of outcome. Further analysis of mortality and 6-month neurological outcomes conferred no significant benefits between the two groups[59].

2.5.4 Hypoglycemia in TBI

Hypoglycemia is defined as blood sugar level of 2.7 mmol/l or less and is a pathophysiological state with detrimental effects to the brain cell. Increased sympathetic outflow occurs as a result of stress response involving the activation of the sympatho-adrenal system[60]. The resultant production of insulin counter-regulatory hormones such as cortisol, glucagon and adrenaline are the body's mechanism for increasing the blood sugar level. This stress response however has

been associated with neurological symptoms such as slowing of EEG waves, convulsions and later cognitive impairment. The exact cause for neurological demise is unknown but postulated to be as a result of neurotransmitter dysfunction following hypoglycemia-induced impaired amino acid synthesis.

Altered brain metabolic patterns have been observed in hypoglycemic conditions. Changes in protein synthesis occur as a result of hypoglycemia leading to altered membrane function, neurotransmitter synthesis and impaired pH control. Progressive hypoglycemia is associated with correlating low levels of cerebral glucose concentrations as well as lactate and glycogen levels[61]. The degree of these changes is proportional with the degree of hypoglycemia. This is responsible for the associated EEG slow wave changes and clinical symptoms such as convulsions and comatose state in severe cases. Due to the advancements in diagnostics that have allowed for extensive research, experimental studies on the cerebral effects of hypoglycemia have shown a proportional drop-in EEG activity with the degree of drop in neuronal glucose levels with EEG silence occurring in all brain areas except the cerebellum and hypothalamus in critical levels of glucose concentrations[62].

Hypoglycemia also instigates changes in cerebral blood flow. It's been shown to impair the auto regulation of cerebral blood flow as well as impaired cerebral vasoreactive response to changes in the partial pressure of carbon dioxide[63]. These changes effectively translate to an increase in cerebral blood flow which increases intracranial pressure. The degree of increase in cerebral blood flow is directly proportional to the severity of hypoglycemia with noted increments up to 300% from the baseline[64]. This effect on cerebral auto regulation is compounded by systemic hypotension leading to differential blood supply to parts of the brain, aggravating secondary brain injury. For TBI patients with hypocapnia as a result of tachypnea, the cerebral

vasoconstriction effect has been shown to be abolished by hypoglycemia and associated with slow wave activity on EEG[65].

Recognition of hypoglycemia in the clinical setting is a matter of documentation of the current blood sugar levels as well as behavioral changes in the awake patients or Electroencephalogram (EEG) changes. Recognition of hypoglycemia in patients with TBI poses a challenge to the clinician as the patients already impaired cognitive status makes it difficult to recognize common neuroglycopenic signs and symptoms such as tachycardia, confusion and even convulsions; all of which can be explained by the brain injury itself.

The occurrence of low blood sugar levels in patients with TBI occurs largely as an iatrogenic complication rather than as a direct consequence of the injury. This stems from the rising use of insulin infusions with stricter blood sugar control targets due to observed benefits in previous heterogeneous critically ill populations[59]. The challenge is that the optimum range for blood sugar levels in patients with TBI is not well defined. The stress increase in blood sugar levels has been theorized to confer benefit to brain tissue thus lower targets would impede this. Another fact to be taken into consideration is the dynamic change- in the temporal sense- of blood sugar targets- as highlighted in the study that indicated better outcomes with CIT in the first week (defined as the acute phase) and IIT during the next week of the study.

Hypoglycemia is associated with poorer outcomes in patients with TBI. Bilotta et al conducted a prospective randomized clinical trial to evaluate the frequency of hypoglycemic episodes in TBI patients who were undergoing IIT and CIT as the control group. IIT was associated with not only more frequent hypoglycemic episodes but also significantly lower mean blood sugar levels. A further analysis of outcomes did not correlate any increase in poor neurological outcomes in the

patients in the IIT limb of the study although this group had lesser CCU and hospital length of stay as well as reduced infection rates[66].

Vespa et al conducted a clinical trial that employed micro dialysis catheter monitoring of TBI patients who were grouped into alternate insulin strategies. The IIT group had frequent hypoglycemic episodes and raised glutamate as well as lactate/pyruvate ratios indicating neuronal metabolic stress. The study ultimately concluded that IIT had no overall effect on reduction of cerebral metabolic rate and that the reduction of extracellular glucose may have had negative implications on the long-term outcome[67].

2.6 Current Practices in Neurocritical Care

2.6.1 Management of Blood Sugar Levels in TBI

2.6.1.1 Blood Sugar Control with Insulin.

Exogenous insulin is considered the mainstay of blood sugar lowering therapy in critical care. Some studies support stringent blood sugar control with dynamic blood sugar monitoring. Later studies suggest that a lower targeted window of blood sugar i.e., 4.5-6.1 mmol/l had a higher chance of worse outcomes and even severe hypoglycemia (<2.2 mmol/l) in the group on IIT[68]. This was postulated to be secondary to the effects of IIT on cerebral glucose homeostasis. A retrospective review by Oddo et al investigated this from patients that had cerebral microdialysis catheters as part of their monitoring. From the twenty study subjects it was found that IIT was associated with increased incidences of brain energy crisis (defined as cerebral microdialysis glucose levels of ≤ 0.7 mmol/l) which was associated with increased mortality rates. This underlines the fact that optimum blood sugar levels in TBI remain undetermined and stricter control may potentially contribute to neurological insult[69].

Following the general lack of consensus then, blood sugar control in TBI remains the subject of recent studies. One study investigated outcomes after insulin treatment in patients with severe TBI. The 2 main groups; one with stricter glycemic control aiming for blood sugar levels between 3.6-6.5 mmol/l versus those with higher targets between 5-8 mmol/l[70]. The study was done over a 2-week period with the first week classified as the 'acute' stage. The group with higher blood sugar targets was found to have lesser untoward outcomes including that of hypoglycemic episodes than the group of stricter blood sugar control but what's interesting to note is that the findings were inverse in the second phase of the study in that stricter glycemic control was associated with reduced incidence of increased intracranial pressure and infections. This suggested benefit of higher glycemic levels as the brain has increased demand at this point as opposed to later on in the course of the disease.

2.6.1.2 Nutritional Support

Patients presenting with TBI usually present in a hypercatabolic, hyperglycemic state. Recent body of evidence has established gastrointestinal dysregulation in patients with TBI as well as a higher incidence of mortality associated with malnutrition[71]. Early onset effective nutritional support has been shown to reduce insulin resistance and improve overall patient outcomes[74]. The overall recommendation in the approach of nutritional support favors enteral nutrition. This is due to documented benefits such as the maintenance of gastrointestinal immune function with lower financial implications as well as adding to the fact that it is more physiologically appropriate for the patient. However parenteral nutrition- regularly employed in the presence of contraindications to enteral nutrition- has been suggested to have better outcomes in TBI[72]. Feeding thereby falls upon the discretion of the critical care team hence the need for strict limitation of the glucose dose be it via enteral feeding with carbohydrates or even intravenous

glucose. Current recommendations support providing up to 140% of metabolic requirements for non-paralyzed patients vs 100% caloric requirements in the paralyzed. There's increasing evidence on the benefit of limited caloric provision for critically ill patients but none so far as to whether it would benefit patients with TBI.

2.6.1.3 Other Treatments

Several novel therapies are on the uptick in an attempt to aid in the management of secondary complications and improve glycemic control in patients with TBI. The use of naloxone has been identified as a possible treatment stratagem. Naloxone is an opioid receptor antagonist commonly used as an antidote in opioid toxicity or overdose. Following data from CSF analyses of patients with Severe TBI that correlated increased levels of the endogenous opioid peptide β-endorphin to the severity of injury and also as a prognosticating factor in these cases naloxone was examined as a possible modality in improving outcomes in TBI. The application of naloxone reduces the overall inflammatory response and improves neuronal metabolism in the acute phase of TBI. Naloxone is also implicated in the reduction of amino acid excito-toxicity as well as reduction of calcium influx, both known to be involved in local secondary neurological insults[73].

Therapeutic hypothermia is another avenue with promising prospects in the management of blood sugar levels in TBI. A prospective randomized single center study by Zhao et al investigated the effect of mild hypothermia (32.5-33ºC) on blood sugar and lactate levels and the relationship with 3-month neurological outcomes measured via the Glasgow Outcome Scale[74]. The study was consistent with other studies regarding the negative effect of hyperglycemia-defined as blood sugar ≥10.0 mmol/l on neurological outcomes but no statistical association between lactate levels and outcomes. A notable drop of blood sugar levels was appreciated in the mild hypothermia group with 32.5% prevalence of hyperglycemia compared to 58.5% in the

normothermia group. The hypothermia group had a significant statistical percentage with favorable 3-month neurological outcomes 75% with GOS of 4-5 vs 51.2% in the same neurological outcome.

Mannitol and Hypertonic saline reduce ICP thus reducing the intracranial pressure through osmotic means. This allows for perilesional perfusion thus reduced oxidative stress in the affected area. These agents when administered in the appropriate time window and at correct dosages have been shown to reduce the hyperpermeability and increased intracranial pressure associated with hyperglycemia occurring in the background of TBI[75].

2.9 Study Justification

TBI is associated with increased morbidity and mortality in neurointensive care. In Kenyatta national hospital TBI represents a monthly average of 30% of CCU admissions and 22% of CCU mortalities yearly. Management of this condition involves recognition and treatment of secondary systemic insults. Hyperglycemia and hypoglycemia are frequently occurring secondary insults as observed by Jeremitsky et al[7]. Opondo et al found poorer outcomes in patients with severe TBI at KNH who had blood sugar levels above 10 mmol/l[51].

Active intervention of blood sugar levels has not been recommended by the 4th edition guidelines by the brain trauma foundation in the management of TBI[76]. The KNH neurosurgical and critical care departments also lack recommendation on the management of blood sugar levels in TBI patients[77]. This is due to the lack of sufficient evidence indicating its benefit.

The patterns of blood sugar levels in patients with TBI at KNH critical care units have not been investigated. A large data gap exists here. This study will aid in development of knowledge

about this subject. It will also aid in raising awareness regarding the scope of the issue and potentially provide the basis upon which future research can be carried out.

2.10 Study Question

What is the pattern of blood sugar levels for patients admitted at the KNH critical care units with Traumatic Brain Injury?

2.12 Broad Objective

To assess the pattern of blood sugar levels for patients admitted at KNH CCUs with traumatic brain injury.

2.13 Specific Objectives

1. To review admission blood sugar levels for patients upon admission at KNH with TBI.
2. To determine trends of blood sugar levels of patients admitted at the KNH CCUs with TBI.
3. To evaluate blood sugar control methods for patients admitted at the KNH CCUs with TBI.

CHAPTER THREE

3.1 METHODOLOGY

3.2 Study Design

This study was a prospective observational study.

3.3 Study Location

The study was carried out in KNH, a tertiary level 6 teaching and referral hospital in Nairobi, Kenya. The facility has 8 Critical Care units with a capacity of up to 65 critically ill patients. In addition to this emergency critical care services can be provided to an additional 8 patients in the Accident and Emergency Resuscitation rooms A and B (RRA and RRB). TBI patients were recruited primarily from the Resuscitation rooms as well as the Main and Neurosurgical CCUs.

3.4 Study Population

The study population were critically ill patients admitted at the Kenyatta National Hospital with traumatic brain injury.

3.5 Sample Size Estimation.

In determining the sample size, the finite population formula was used;

$$n = \frac{NZ^2pq}{E^2(N-1) + Z^2pq}$$

Where;

n= the desired sample size,

N= population size (average number of TBI patients admitted to the KNH main CCU per month is 30. Data from the patient's admission register)

Z= value from the standard normal table corresponding to the desired confidence level. (Z= 1.96 for 95% CI)

P= expected proportion of hyperglycemia in the population- Matovu et al found to be 16.3%[50]

E= desired precision (0.05)

q = 1- p

$$n = \frac{90 \times 1.96^2 \times 0.163 \times 0.837}{0.05^2(90-1) + 1.96^2 \times 0.163 \times 0.837}$$

This gave us a sample of 63

The final sample size was determined to be **66** after factoring 5% margin for errors in data collection and follow up loss.

3.6 Eligibility Criteria

3.6.1 Inclusion Criteria

- Patients with TBI requiring admission to the critical care units.
- Patients with consent from next of kin/legal proxy were included in the study.
- Unidentified patients with waiver of consent to be included in the study.

3.6.2 Exclusion Criteria

- Patients who had diabetes from history or a screening HbA1c of 7% or more.
- Patients who had a history of concurrent chronic liver or renal disease.
- Patients who were on steroid therapy of more than 1 month

3.8 Recruitment and Sampling Procedure

The sampling method employed was consecutive sampling. This was conducted by recruiting patients within the study locations with traumatic brain injury. TBI patients were assessed for eligibility then recruited within 24 hours of admission.

The lead investigator explained the study procedure in English or Kiswahili to the next of kin and obtain informed consent.

After recruitment, the critical care nurses and doctors in their respective units were informed of the intended procedure and the potential risks and benefits.

The study subjects' demographic data, CT scan diagnosis, Admission GCS and admission blood sugar were recorded at this point by the lead investigator/research assistant.

The patient's blood sugar level upon admission to the critical care unit was then recorded. This was followed by daily blood sugar levels at 6 hourly intervals for the follow up period of up to 5 days. The principal investigator/research assistant electronically recorded the blood sugar levels for the study subjects in real time. HBa1c levels will also be determined within the first 24 hours of admission.

The mode of blood sugar control was recorded for the same period although the choice of management modality left to the discretion of the critical care practitioner.

3.9 Quality Assurance

Data collection was be done by means of a hand-held glucometer for the measurement of blood sugar concentrations of the study subjects. The glucometer in use is branded *On Call*® Pro Blood Glucose Monitoring Systems (BGMS) by ACON LABS of the United States and has Food and Drug Administration (FDA) approval for use in clinical settings. It has the capability of measuring blood sugar levels between 1.7 mmol/l to 33 mmol/l with alarms for hypoglycemia and hyperglycemia based on pre-set variables. Only the single brand was used across all study subjects to avoid inter-glucometer variability. The glucometer used was only handled by the principal researcher and research assistants only. Sample collection procedure involved collection of fresh capillary whole blood through minimally invasive finger prick testing procedure- similar to standard patient care with no pain implications to the patient- as well as the placement on the sample on the test strip. The instructions were shared to the research team for further adherence to procedure.

The glucometer was calibrated by qualified lab personnel on a scheduled basis i.e., at least once every 5 days and/or for every 100 samples taken. Test strips were not reused once sample collection was done as well as prompt replacement of the used ones. Each test strip packaging was encoded with a unique serial number from the manufacturer and was verified before use in addition to confirmation of the expiration date before opening of a new batch of test strips.

3.10 Validity

A standardized electronic data collection tool was used to gather the desired information through the Research Electronic Data Capture (REDCap) software which is an open-source secure

application accessible on handheld mobile devices. Data entry fields were created in the fully customizable software on designated mobile devices which were secured. The software can be installed with regards to international standards to ensure regulatory compliance.

The research assistant was be trained on proper use of the data collection tool to minimize errors.

The collection tool will have a user-friendly interface for ease of use.

The language used was simple and precise.

3.11 Ethical Considerations.

Permission to proceed was sought from the KNH/University of Nairobi Institutional research and ethics committee as well as K.N.H administration before study commencement.

A detailed explanation about the risks and benefits were explained to the next of kin in a language they understood.

The next of kin were duly informed regarding the study procedure and informed consent obtained with the knowledge that refusal to participate in the study did not result in any variation in care accorded to the patient.

Study subjects who consent was declined or if consent was withdrawn during the course of the study were allowed to do so without any victimization or change in the level of care accorded to them.

Patient identifiers were not used throughout the study period.

The study shall not expose the patient/study subject to any harm or additional cost.

Instances where significant derangement of blood sugar levels noted during data collection were brought to the attention of the critical care team and prompt intervention initiated.

Confidentiality was maintained at all levels of data handling.

The information obtained shall be disseminated through relevant departmental presentations, peer-reviewed journals and scientific conferences.

3.12 Data Management and Analysis

Data collection tools (electronic data collection forms) were developed and validated before study commencement. Data was collected and logged in to the registration forms. Storage of data was done under a password protected encrypted electronic data collection tool whose access limited to the principal researcher and research assistant.

Data was checked for accuracy, consistency and completeness and any inconsistencies immediately amended every 10 days.

Backups were stored in encrypted cloud-based storage for remote access as well as a storage drive that was under lock and key and offline to prevent against hacking/viruses. The forms were also locked in a safe-guarded cabinet.

The data was analysed using SPSS version 26. Descriptive statistics were used to describe the sociodemographic and clinical characteristics of patients. Categorical data was summarized as frequencies and percentages while Continuous data described as means and standard deviations or medians and interquartile ranges.

The admission blood sugar levels are summarized as the mean with standard deviation as well as being categorized into the various groups; hypoglycemic (<4 mmol/l), normal (4 mmol/l -10 mmol/l) and hyperglycemic (>10 mmol/l).

The blood sugar levels recorded over the course of 5 days are analyzed and summarized into mean daily blood sugar levels with corresponding standard deviations. Any occurrence of a hyperglycemic or hypoglycemic event was recorded to achieve the proportion of extreme events

among patients. The mean daily blood sugar levels were also assessed for the degree of deviation from the mean and percentage of blood sugar excursions noted.

The blood sugar control methods used are tabulated using frequencies and percentages then compared with blood sugar levels of patients at different stages using the chi-square test of association. Admission and final blood sugar levels are also compared for any differences using paired t-test/Wilcoxon signed-rank test. For all statistical tests, a p-value of <0.005 will be taken to show statistical significance.

3.14 Study Results Dissemination Plan

The results of the study were presented to the members of the department of Anaesthesia of the University of Nairobi and critical care units at KNH. The results will be shared in conferences organized by the critical care society of Kenya as well as a formal report made to the KNH/UON ERC. The results will be published in a peer reviewed journal.

3.15 Materials

This study required stationery supplies; electronic devices installed with REDCap and SPSS version 26 for the principal investigator, research assistants and a statistician. Internet access was also required for data upload into an online database. The principal investigator was the research coordinator and oversaw the work of two research assistants and a statistician.

CHAPTER FOUR: RESULTS

4.1 Demographic data

There were 66 patients enrolled in the study (60 male, 6 female). The mean age of the patients was 35 years (SD 12.5, range 18 – 91). All the patients had TBI graded by GCS scoring on first contact as either mild (13 - 15), moderate (9 - 12), or severe (3 - 8) with confirmed diagnoses on CT. 53% of the patients had severe TBI while 44% had moderate and 3% had mild. The median GCS on arrival was 8 (Mode of 10). The most common CT diagnosis was subdural hematoma at 39%. In addition to TBI, at least 47% of the patients had accessory injuries with long bone injuries being the most common at 33%. On admission, 44% of the patients had craniotomies performed and an additional 3% had EVDs placed.

Table 1: Participant characteristics.

		Frequency (n)	Percentage (%)
Age (Mean ± SD)		35 (12.47)	
Age group	<25	11	17%
	25-35	28	42%
	>35	27	41%
Gender	Female	6	9%
	Male	60	91%
Estimated hours since injury	< 6 hours	7	11%
	> 24 Hours	14	21%
	12-24 Hours	12	18%
	6-12 Hours	33	50%
CT Scan diagnosis	Epidural Hematoma	20	30%
	Subdural Hematoma	26	39%
	Intracerebral Hematoma	8	12%
	Skull Fracture	13	20%
	Diffuse Axonal Injury	5	8%
	Cerebral Oedema	8	12%
	Bifrontal contusion	1	2%
	Tension pneumocephalus	1	2%
Associated injuries	Long-bone fractures	22	33%
	Abdominal Injury	2	3%
	Thoracic Injury	6	9%
Surgical Intervention	Craniotomy	29	44%
	EVD insertion	2	3%

4.2 Admission blood sugar levels

The mean RBS reading on admission was 7.9 mmol/l (SD 2.4, range 3.7 – 15.9). There was no hypoglycemic event recorded and 6 hyperglycemic events (9%). In a majority of the patients (50%), evaluation for blood sugar levels was conducted between 12 and 24 hours from the primary injury. In severe TBI, the admission RBS value was 7.4 mmol/l (SD 2.1, range 3.7 – 13.2) whereas the value in moderate TBI was 8.2 mmol/l (SD 2.2, range 5.2 – 15.9).

		Frequency (n)	**Percentage (%)**
GCS on arrival	<=3	4	6%
	4-8	31	47%
	>8	31	47%
GCS on admission	<=3	2	3%
	4-8	49	74%
	>8	15	23%
Blood sugar level on arrival	(Mean ± SD)	7.92 (2.37)	
	<4	0	0%
	4-6.9	24	36%
	7.0-9.9	36	55%
	>10	6	9%
Blood sugar level on CCU admission	(Mean ± SD)	8.70 (3.23)	
	<4	0	0%
	4-6.9	16	24%
	7.0-9.9	37	56%
	>10	13	20%

Table 2: Admission GCS and Blood sugar level.

There was a strong association between arrival blood sugar levels and the severity of the TBI based on GCS scoring. The chi-square test of independence yielded a likelihood ratio of 7.293 ($p = 0.026$)

There was no statistically significant correlation between the patients' ages and the GCS score or the RBS on arrival at the emergency department ($r = 0.022$ and -0.138, respectively, $p > 0.05$). Regarding the association of other demographic factors with the Admission RBS levels and the

GCS scores, the following could be demonstrated. There was a statistically significant association by chi-square test of independence, between the sex of the patient and the severity of the TBI on the admission of the patient (likelihood ratio 8.428, p=0.015).

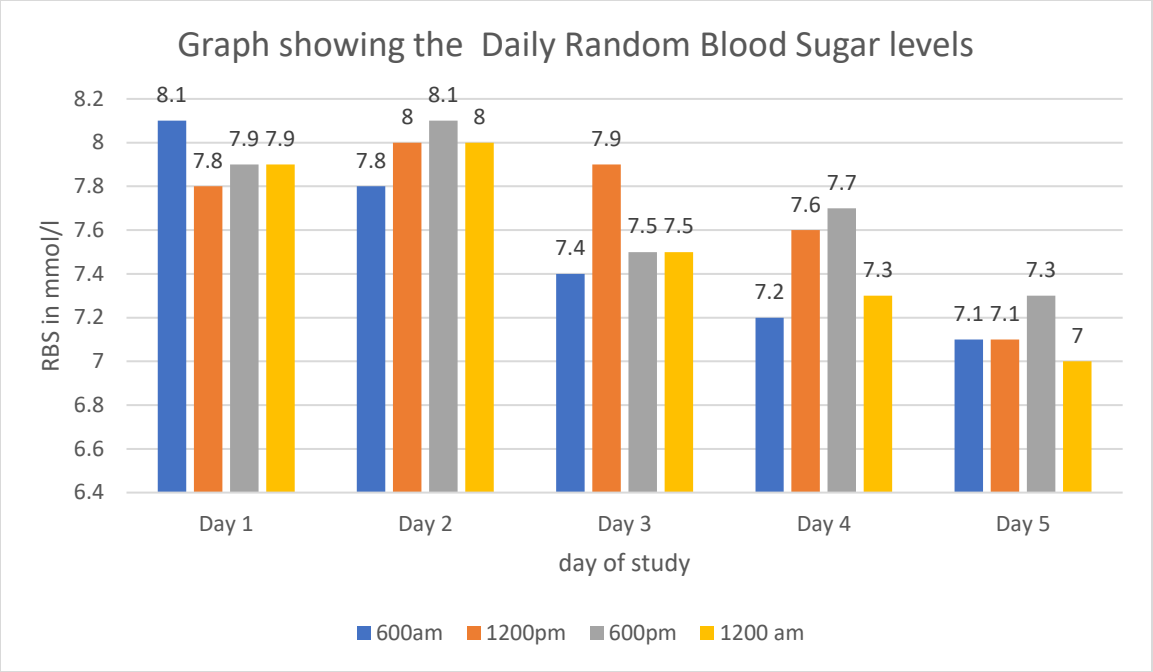
Table 3: GCS level on arrival cross tabulated with gender.

		Female		**Male**	
		Frequency	**Percentage**	**Frequency**	**Percentage**
GCS on arrival	Severe	5	83%	30	50%
	Moderate	1	17%	30	50%

4.3 Daily blood sugar trends- hyperglycemic and hypoglycemic events

The mean daily RBS readings were 7.9, 7.9, 7.6, 7.4, and 7.1 mmol/l for days 1 through 5 respectively (Table 4). Day 2 had the highest standard deviation from the mean at 3.9. The greatest range of recorded values was on day 1 (3.4 – 31.2) while the lowest range was demonstrated on day 5 (4.5 – 14.9). The mean daily blood sugar levels are seen to be decreasing over time in the 5 days of observation (graphic 1).

When the glycemic variability is considered, the percentage of excursion (POE) from the set points of 4 – 10 mmol/l was highest on day 1 as well at 18.9%, with hyperglycemic events making the bulk of the excursions. Glycemic variability is also seen to reduce consistently over the 5 days of record.



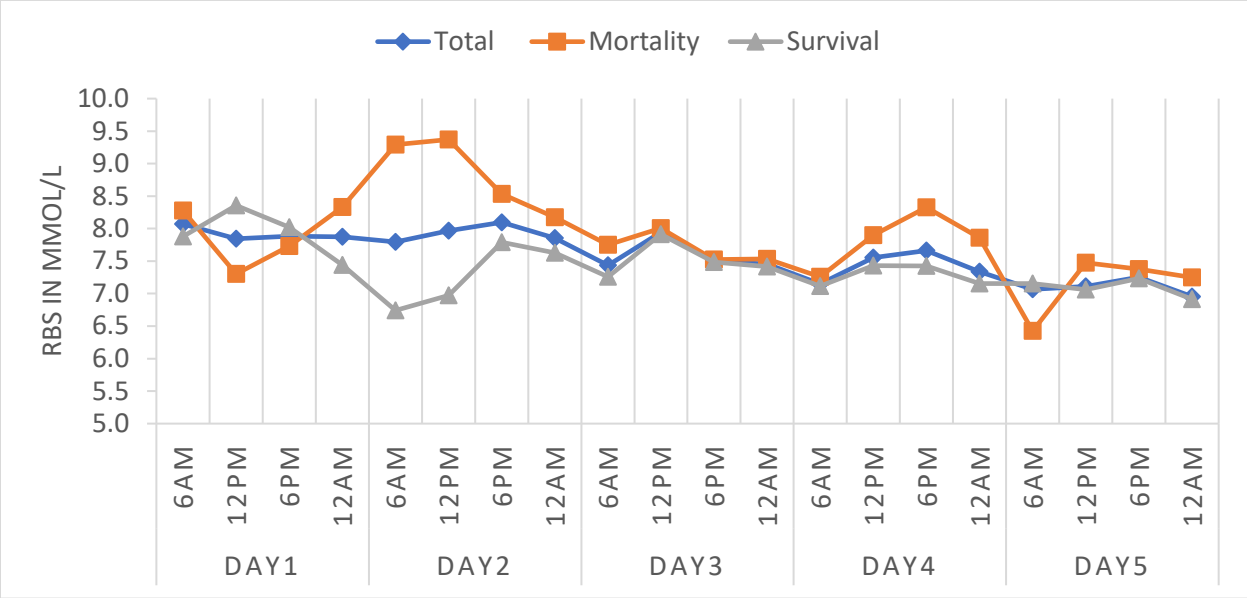
Graphic 1: daily random blood sugar levels

Day	**RBS mean**	**SD**	**Range**	**Hyperglycemia %**	**Hypoglycemia %**	**POE %**
1	7.9	3.2	3.4 - 31.2	17.4	1.5	18.9
2	7.9	3.9	3.3 – 29.9	15.1	1.7	16.8
3	7.6	2.4	3.7 – 16	13.1	0.5	13.6
4	7.4	2.3	3.9 – 18.1	12.0	0.5	12.5
5	7.1	2.0	4.5 – 14.9	11.4	0.0	11.4

Table 4: Table showing the daily mean and distribution of RBS levels across the study period

Key: RBS -random blood sugar; SD – standard deviation; POE – percentage of excursion

There was an overall raised mean blood sugar level in the mortality group throughout the 5-day period vs the survival group other than 2 instances in the first and fifth days (graphic 2).



Graphic 2: trends in daily blood sugar levels in mortality and survival groups

4.4 Blood sugar control methods and other interventions

Interventions performed on the patient such as craniotomy and EVD showed a significant association between the GCS on arrival and the serum glucose levels at admission and after the 5-day point. EVD was performed on only two patients who had also received craniotomies. The two patients both had epidural hematomas and were initially normoglycemic on admission before deteriorating days later.

71.2% of the patients had had at least one form of sedation within the first 24 hours of admission. In addition, there were 8 incidences of the use of insulin as a method of glycemic control. There were on regular dosing, 5 infusions, and in 3 patients, 2 of whom had both regular dosing and infusion therapy. All the 3 patients deteriorated to mortality before the 5 days. Both glycemic control and sedation had no statistically significant association with the RBS on arrival and at the 5-day point ($p>0.05$).

4.5 Comparison of blood sugar levels and GCS during admission and at the end

The mean RBS level at arrival is 0.8 mmol/l greater than the mean RBS level by the 5th day of the study. The median GCS score at the beginning is 8 while at the end it is 10.

Table 5: Comparison of blood glucose results.

Blood Glucose level (mmol/l)	**Total** **N= 66**	**Survival** **N= 34**	**Mortality** **N= 32**
	P-value[1]	P-value[2]	P-value[3]
Arrival – Admission to ICU	0.079	0.065	0.667
Admission – Final	**0.001**	**0.001**	**0.023**

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Demographic data

Traumatic Brain Injury is an important outcome that results usually from motor vehicle accidents, particularly in developing countries like Kenya. Kinyanjui in 2016[13] highlights that almost more than 50% of TBIs result from road traffic accidents. There is additionally a propensity for more males than females to be involved. This is demonstrated in the current study where 91% of the patients involved were male. The finding is consistent with the study from Kenya by Shisoka et al.[78] which reports that 89% of road traffic accident victims are indeed male, in the Kenyan context. accordingly, as a result of the nature of road traffic accidents, there is an increased likelihood of multiple associated injuries in relation to the impact. Other sources indicate furthermore that the male to female ratio regarding traumatic brain injury is likely 2:1 or more (**Georges & M Das, 2022)** in most settings.

This study similarly demonstrates that the peak age of TBI is around 35 years. Some studies indicate that there are 3 peaks of the incidence of TBI, including the young (0 – 4 years), young adults (15 – 24 years), and in the elderly who are above 65 years old **(Galgano et al., 2017)**. Skaansar et al.[79] highlight the importance of age in the management of TBI in that increasing age increases the complexities of management regardless of the severity of the injury. In the current study, this may not be the case as there are more than 70% of cases below the age of 40 years. However, it is also worth noting that a majority of the TBI in the patients recruited are severe, at 53%, which potentially adds to the toll of management. Furthermore, 47% of the patients have associated injuries which increase the risk for mortality[79]

5.2 Admission blood sugar levels

Hyperglycemia is reported to be associated with poorer outcomes in TBI and yet research for optimal glycemic control in TBI continues actively. The effects of hyperglycemia have been studied extensively and certain studies highlight that high admission serum glucose levels, as well as high peak 24-hour blood sugar levels above 11.1 mmol/l, are linked to poor initial GCS scores, poor clinical progression, and poor neurological outcomes both short term and long term. In the current study, it has been demonstrated that the prevalence of early hyperglycemia in TBI patients is 9.1%. This is from a cut-off of 10 mmol/l. The presence of early hyperglycemia has been reported in several studies with various implications on the prognostic outcomes of TBI. The current study reports values that are much lower than studies by Kafaki et al published in 2016[47], a Ugandan prospective observational cohort study published in 2009, and a retrospective cohort study by Opondo and Mwang'ombe in 2008[51]. These studies report initial hyperglycemic prevalence of 39%, 16.2%, and 66.7% respectively. It should be noted that only Opondo and Mwang'ombe's study, set in the same setting as this study, used an upper limit of 10 mmol/l while the rest use a cut-off of 11.1 mmol/l.

The implications of early hyperglycemia have been widely reported to include poorer outcomes in general, with mortality as high as 68.8% of patients with initial hyperglycemia in the Ugandan study. This is perhaps not adequately reflected in this study owing to the sample size and the limited follow-up time. Nevertheless, the patients with recorded hyperglycemia had demonstrated good outcomes in less than 50%, with 2 mortalities before the 5th day of the study. The mean blood glucose level at admission was 7.9 which is below the cut-off point for overt hyperglycemia. This is a further indication of the low prevalence of hyperglycemia in this sample of patients with TBI.

This could imply that there would be less burden of the effects of hyperglycemia in this population of TBI patients and possibly lower mortality as well.

In other studies, the mean serum glucose levels on arrival of the patient were 10.6 mmol/l in severe injury while only 7.6 mmol/l in moderate injury. As such, the worst outcomes were recorded in patients who had blood sugars averaging 12.1 mmol/l. This further ascertains that the lower prevalence may be beneficial in this case[46].

5.3 Daily blood sugar trends- hyperglycemic and hypoglycemic events

There were 6 cases of early hyperglycemia in the current study. The mean blood sugar levels at admission were 7.9 mmol/l and continued to decline through day 1 to remain at 7.1 mmol/l on day 5. Matovu et al.[48] recognize the paucity in the documentation of the daily average glucose levels in TBI patients and the failure to recognize trends in the progression of the glycemic condition of the patient vis a vis its implications on patient outcomes. In other populations, there is documentation of glycemic variability in several ways including the use of the percentage of excursion (POE). As described by Matsushima et al.[80], glycemic variability can be determined through POE by getting what percentage of data points that lie outside the setpoint values. In this case, normoglycemia, which the current study has set at 4 – 10 mmol/l. moreover, some studies impress upon the importance of keeping the glycemic variability low as large variability increases the risks of mortality[81]. The authors describe the variability as a result of the proposed pathophysiology of stress-induced changes, inflammation, and sympathetic response. Lage variability can cause untoward damage. The study recommends continuous insulin infusion to reduce the risk of large variability. Other studies remain uncertain of the appropriate therapeutic window for glycemic control as the debate for and against strict glycemic control continues.

There was no case of hypoglycemia at initial contact. Hypoglycemia in early TBI is especially considered a poor prognostic factor in the management of the condition. The manifestation of hypoglycemia is thought to be a complication of the adverse events following TBI and not necessarily a direct consequence. Hence, its presence is somewhat ominous in the early stages **(The George Institute, 2009).** Monitoring should be more stringent in such patients. In keeping with this, the current study reports that necessary steps should be undertaken should hypoglycemia present on arrival.

Patient sex was found to be strongly associated with the severity of the TBI in the study sample. Accordingly, there was far fewer female than male patients recruited into the study owing to the disproportionate ratio of involvement against men in road traffic accidents[48,78]. In addition, 5 out of 6 of the females included had severe TBI as opposed to one who had a mild TBI. Therefore, it could be interpreted that although females are less involved in motor vehicle accidents, their occasional involvement results in more severe outcomes. This is consistent with the study by Matovu et al.[48] that demonstrates that females are at an increased risk of 30-day mortality following TBI with an OR of 5.45 against 1 in males. Another study reports that there are significant differences in the manifestation and progress of TBI between males and females. The authors report that there are especially suspect changes seen on imaging. Additionally, the mechanism of injury may often differ. A high index of suspicion should therefore be maintained to curtail any adverse events **(Munivenkatappa et al., 2016).**

The severity of TBI was also strongly associated with the initial serum glucose levels. The study by Lam et al. in 1991 is also in accordance with this finding, where mean levels of serum glucose were higher in the severe group versus the mild to the moderate group[44]. In the same study, there was a strong association with the outcome measures as well case **(Griesdale et al., 2009).** This is

supported by findings also in other studies in the region[47,48] (**Kumar et al., 2015**). An exception remains to be the study by **Adeolu et al. (2015)** that reports no association between the severity of TBI and serum glucose levels. This they theorize to result from lower ability to mount a stress response in African individuals, which might not be the case. In this case, however, the 5-day mean serum glucose level was not associated with the severity of the patient's condition during the initial contact. This could be attributed to the time of follow-up being shorter as well as the lower prevalence of hyperglycemia by the end of the study.

5.4 Blood sugar control methods and other interventions

Glycemic control provided was minimal in this study. The impact of the insulin administration was not apparent by the end of the study. Although, some studies recommend the use of insulin infusion with different effectiveness in comparison, either of the interventions is considered more beneficial than no intervention. The failure of the intervention, in this case, could be attributed to the lack of clear-cut protocols for its administration, insufficient resources such as adequate personnel to patient ratios, and supply chain issues. The study is set up in Kenyatta National Hospital, which is one of the largest referral hospitals in the region. The overwhelming patient numbers require sufficient support and the introduction of more effective glycemic control protocols in the ICU for TBI patients.

Some of the patients receive surgical intervention as well as sedation. Although previous studies indicate that there is demonstrated improvement following surgical intervention by craniotomies and EVD, this was not the case in the current study[8]. Craniotomy did not have any association with the initial glycemic level, nor did it have any significant association with the final day’s blood glucose levels. On the contrary, there were worse outcomes in the two patients that received EVD.

5.5 Conclusion

Following moderate to severe TBI, hyperglycemia does occur albeit in varying prevalence. Consequently, there is a strong association between patient serum glucose levels and the severity of TBI. Consistent monitoring of serum glucose levels and applying appropriate interventions may minimize complications that arise from hyperglycemia and untoward glycemic variability in TBI. This study could form the basis for extended research into understanding glycemic derangement and control in patients with TBI as well as help in the design of a suitable glycemic control protocol for TBI patients in ICU settings in the region.

5.6 Study limitations

The study was conducted in a busy resource-constrained center that handles numerous critically ill patients. The single-center nature of this study means that it lacks external validity and thus results could only be extrapolated to this center only. Accordingly, the state of patients on arrival and their progress thereafter may not wholly reflect the influence of factors of interest in this study.

The study was not a randomized clinical trial and hence any relationships described do not allow inferences on causality. This was further compounded with the heterogeneity of the disease process in question. Additionally, resource constraints may be responsible for insufficient patient support that could also contribute to adverse events.

5.7 Recommendations

The study expands our current understanding regarding a significant metabolic response in a high-risk population. However, the implications from it are inconclusive based on the heterogeneity of the disease and could form the basis upon which future studies could build upon.

Continuous blood sugar monitoring is highly recommended for this population to capture instances of high glycemic variability which would potentially lead to untoward effects.

The development of an appropriate and effective glycemic control protocol in the management of TBI patients in the ICU will be beneficial in the long term. Furthermore, ensuring the reduction in the prevalence of hypoglycemia as well as hyperglycemia is recommended.

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APPENDICES

APPENDIX 1: THE GLASGOW COMA SCALE (NICE 2003)

Feature	Response	Score
Best eye response	Open spontaneously	4
	Open to verbal command	3
	Open to pain	2
	No eye opening	1
Best verbal response	Orientated	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No verbal response	1
Best motor response	Obeys commands	6
	Localising pain	5
	Withdrawal from pain	4
	Flexion to pain	3
	Extension to pain	2
	No motor response	1

APPENDIX 2: Guidelines of management of TBI from the KNH/UON Neurosurgical departments.

FOR ADMITTED PATIENTS UNDERGOING NEUROOBSERVATION

The aim of observation and monitoring is to detect Neurological deterioration prompting urgent reappraisal.

The nursing staff on concert with the neurosurgical service should observe patient every 15 minutes for the first 2 hrs then 2 hourly thereafter. If the patient deteriorates more than 2 points on the Glasgow coma scale (see appendix), arrange for urgent ct-scanning.

Monitor and record the following:

- Glasgow coma scale
- Pupil size and reactivity.
- Limb movement
- Respiratory rate
- Blood pressure
- Temperature
- Blood oxygen saturation

If in doubt fill out the standard KNH Head injury chart as a basic minimum.

Any of the following re-evaluation:

- Development of agitation or abnormal behaviour.
- Development of severe or increasing headache or persistent vomiting.
- New or evolving neurological symptoms or signs such as pupil inequality or asymmetry of facial or limb movement.
- A sustained (more than 30 minute) drop in GCS.
- Any drop of greater than 2 points in GCS regardless of duration.

If any abnormalities are detected, ask a second member of staff to confirm the findings. If confirmed, `involve the neurosurgical service.

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APPENDIX 3: Guidelines on the management of TBI from the KNH main CCU department.

6. PROTOCOLFOR MANAGEMENT OF SEVEREHEAD INJURYINKNH –CCU

16

1. *Definition*:Severeopenorclosedinjuryoftheheadaffectingthebrainandsignificantlyalteringthe G.C.S. to alevelof8orbelow,eitherimmediately or within several hoursoftheincident.

2. The firstdoctor/clinicianathandshouldimmediatelyassesstheAirway,Breathing,CirculationandDeficitso ftheCentralNervousSysteminthepatient.

3. Iftheairwayisatriskofbeingcompromisedandadecisionhasbeentakentoperformanendotrachealint ubation,appropriatecareshouldbetakentoavoidworseningapossiblecervicalspineinjury.Ifthereisn oneindicationforintubation,acervicalcollarshouldneverthelessbeapplied,tillradiologicalexaminati onconclusivelyrulesoutcervicalspineinjury.
4. Casualty/ A&E Acute room/ general ward staff should alert on call registrar from the following specialties; neurosurgery, general surgery, **orthopedic**, maxillofacial, obs/gyn, ENT and ophthalmology as the case may demand, to immediately address issues in the patient affecting their area of specialty.
5. If decision is then made to take the patient into theatre, there should be no further delays. However, if a decision is made for conservative management, the patient should be nursed in the acute room at A&E, as plans are made to admit him/her at the main CCU on the first floor, or the head injury ward, if the patient does not require ventilatory support.No patient who requires operation will be admitted in ccu before being operated on.
6. OncethepatientisadmittedinthemainCCU,thenewpatientadmissionprotocolshouldbeapplied asis usualforany other new CCUadmission.
7. A urethral catheter and NG Tube should be passed if there are no contraindications for the same. An attempt should be made at inserting a CVP line as soon as the situation allows.
8. A repeatCTscanshouldbeorderedwithin 48hoursof admission**OREARLIER**if deemednecessary,whetherthepatienthadbeenoperatedonor not.

9. Attemptearlyextubation byday 7–10,butconsideran earlytracheostomy if theGCS is still lessthan8bythistime.

10. If anticipated to stay longer, Consideran earlytracheostomy &PercutaneousEndoscopicguidedGastrostomy(PEG)Tubeforfeedingpurposes.

11. HeadinjurypatientsshallbeconsideredfitfortransfertotheHeadTraumaUnitoncetheysatisfythelaid downCCUdischargecriteria.

PreparedbyDr.DavidMisangoassisted byDr.MarkGacii
andDr.M.QureshiFORTHEKNHHEADINJURYMANAGEMENTCOMMITTEE
25TH OCTOBER2010

APPENDIX 4: INFORMED CONSENT FORM (ENGLISH)

1.1.Consent form (English Version)

This informed consent form is for patients admitted to the Kenyatta National Hospital main and neurosurgical Critical Care Units. The informed consent contains 3 main parts i.e., 1. Information sheet 2. Certificate of Consent 3. Statement by the researcher.

PART 1: INFORMATION SHEET

TITLE: PATTERNS OF BLOOD SUGAR LEVELS IN PATIENTS ADMITTED TO KNH MAIN AND NEUROSURGICAL CCUs.

I am Dr. Abel Odhiambo Oduor, a medical doctor currently pursuing a postgraduate degree in Master of Medicine in Anesthesiology and Critical care medicine. I am conducting a study on "Patterns of Blood sugar levels in patients admitted to Kenyatta National Hospital main and Neurosurgical Critical Care Units". I intend to request for your participation in the study. Before you make any decision, you are at liberty to seek for clarification in any matter that may arise. If this consent form may bear words that you do not understand kindly stop as we go through the information and I will take the time to explain. If any questions come up later; you are still at encouraged to seek clarification on the matter.

Purpose of the research.

The intent of this study is to observe the pattern of blood sugar concentrations in patients admitted to critical care units with the primary diagnosis of Traumatic Brain injury and evaluate if disturbance in blood sugar levels in these patients is a commonly occurring phenomenon in the local setting that would warrant further investigation. Data will be collected using a standardized glucometer and electronic data entry using dedicated software. Blood sugar levels will be recorded daily at 12-hour intervals for 5 days with the blood sample to be obtained via a minimally invasive finger prick procedure by trained research team member. The information collected will be used in assessment of blood sugar patterns as a consequence of traumatic brain injury in the local setting and may prompt further investigations to ultimately improve outcomes in these patients.

Type of Intervention.

Should you agree to allow for participation into the study or as legal proxy for the patients' participation, consent will be written and appended by a signature at the designated area in the consent form.

Risk Involved in the study.

There are no risks or adverse events in the participation of the study. There will be no collection of personal identification information and data collected will be kept securely, anonymous and cannot be traced back to you.

Benefits of Participation in the study.

Your participation is likely to help us build to the body of knowledge on the patterns of blood sugar levels in patients with TBI.

Questions and Choices.

You are free to address any questions to the principal investigator via the contact information duly provided at the end of Your participation is fully on a voluntary basis. There will be no monetary compensation or added treatment advantage for being a participant to this study. Refusal to participation to this study is at your discretion and consent can be withdrawn at any point during the study. There will be no discrimination to refusal of participation and the care accorded will be to the same standard as those involved in the study.

PART 2: CERTIFICATE OF CONSENT.

I have fully read this consent form or had the contents read to me. My questions, if any, have been answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is completely voluntary and I may choose to withdraw at any time without repercussions. I freely choose to take part in this study.

Signed: ……. Date: ……

PART 3: RESEARCHER'S STATEMENT.

I, the undersigned, have fully explained the relevant details of this research study to the participant or legal proxy and believe the participant or legal proxy for the study subject has understood and has freely and willingly given his/her consent.

Researcher's name: ……

Signature: ……

Date: ……

For more information please contact: DR. ABEL ODUOR ODHIAMBO

Phone: +254 711 300 383

APPENDIX 5: INFORMED CONSENT FORM (SWAHILI)

SEHEMU YA 1: KARATASI YA HABARI

KICHWA: MFUMO WA VIWANGO VYA SUKARI KWA DAMU YA WAGONJWA WANAOLAZWA KATIKA KNH CHUMBA CHA WAGONJWA MAUTUTI. (NEUROSURGICAL CCUs)

Mimi ni Dkt. Abel Odhiambo Oduor, daktari ambaye kwa sasa anasomea shahada ya uzamili katika Udaktari Unusuru na Utibabu muhimu. Ninafanya utafiti kuhusu "Miundo ya viwango vya sukari kwenye Damu ya wagonjwa waliolazwa katika Hospitali kuu ya Kitaifa ya Kenyatta na Vitengo muhimu vya Upasuaji". Ninakusudia kukuomba ushiriki wako katika utafiti. Kabla ya kufanya uamuzi wowote, una uhuru wa kutafuta ufafanuzi katika jambo lolote linaloweza kutokea. Iwapo fomu hii ya idhini inaweza kuwa na maneno ambayo huelewi, acha tunapopitia maelezo na nitachukua muda kueleza. Ikiwa maswali yoyote yatakuja baadaye; bado unahimizwa kupata ufafanuzi juu ya jambo hilo.

Madhumuni ya utafiti.

Madhumuni ya utafiti huu ni kuangalia muundo wa viwango vya sukari kwa damu ya wagonjwa waliolazwa katika vitengo vya utunzaji muhimu na utambuzi wa kimsingi wa jeraha la Kiwewe la Ubongo na kutathmini ikiwa usumbufu katika viwango vya sukari ya damu kwa wagonjwa hawa ni jambo la kawaida katika mazingira ya ndani ambayo ingehitaji uchunguzi zaidi. Data itakusanywa kwa kutumia glukometa sanifu na kuingiza data za kielektroniki kwa kutumia programu maalum. Viwango vya sukari katika damu vitarekodiwa kila siku kwa vipindi vya saa 12 kwa siku 5 huku sampuli ya damu ikipatikana kupitia utaratibu wa kuchomwa kidole kidogo na mshiriki wa timu ya utafiti aliyefunzwa. Taarifa zitakazokusanywa zitatumika katika kutathmini mifumo ya sukari ya damu kama tokeo la jeraha la kiwewe la ubongo katika mazingira ya ndani na inaweza kusababisha uchunguzi zaidi ili hatimaye kuboresha matokeo kwa wagonjwa hawa.

Aina ya Uingiliaji kati.

Iwapo utakubali kushiriki katika utafiti, wakala wa kisheria wa ushiriki wa wagonjwa, idhini itaandikwa na kuambatanishwa na sahihi katika eneo lililoteuliwa katika fomu ya idhini.

Hatari inayohusika katika utafiti.

Hakuna hatari au matukio mabaya katika ushiriki wa utafiti. Hakutakuwa na mkusanyo wa maelezo ya kitambulisho wa kibinafsi na data itakayokusanywa itawekwa kwa usalama, bila kujulikana jina na haiwezi kufuatiliwa kwako.

Faida za Kushiriki katika utafiti.

Kushiriki kwako kunaweza kutusaidia kujenga maarifa mengi juu ya mifumo ya viwango vya sukari ya damu kwa wagonjwa walio na TBI.

Maswali na Chaguo.

Uko huru kujibu maswali yoyote kwa mpelelezi mkuu kupitia maelezo ya mawasiliano yaliyotolewa mwishoni mwa ushiriki wako ni kwa hiari. Hakutakuwa na fidia ya pesa au faida ya matibabu ya ziada kwa kuwa mshiriki wa utafiti huu. Kukataa kushiriki katika utafiti huu ni kwa hiari yako na idhini inaweza kuondolewa wakati wowote wakati wa utafiti. Hakutakuwa na ubaguzi wa kukataa kushiriki na utunzaji utakaotolewa utakuwa wa kiwango sawa na wale waliohusika katika utafiti.

SEHEMU YA 2: CHETI CHA RIDHAA.

Nimesoma kikamilifu fomu hii ya idhini au nimesomewa yaliyomo. Maswali yangu, kama yapo, yamejibiwa kwa lugha ninayoielewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu katika utafiti huu ni wa hiari kabisa na ninaweza kuchagua kujiondoa wakati wowote bila madhara. Ninachagua kwa hiari kushiriki katika utafiti huu**.**

Imetiwa saini: …… Tarehe: ……

SEHEMU YA 3: TAARIFA YA MTAFITI.

Mimi, aliyetia sahihi hapa chini, nimeeleza kikamilifu maelezo muhimu ya utafiti huu kwa mshiriki au wakala wa kisheria na ninaamini kuwa mshiriki au wakala wa kisheria wa somo la utafiti ameelewa na ametoa ridhaa yake kwa hiari na kwa hiari.

Jina la mtafiti: ……

Sahihi: ……

Tarehe: ……

Kwa habari zaidi tafadhali wasiliana na: DR. ABEL ODUOR ODHIAMBO

Simu: +254 711 300 383

APPENDIX 6

Application for waiver of consent.

Principal Investigator;	Dr. Abel Oduor. Part IV MMED Anaesthesia.
Project title;	Patterns of blood sugar levels in critically ill patients with TBI at Kenyatta National Hospital.

To,

KNH-UoN ERC.

Dear Sir/Madam,

RE: APPLICATION FOR WAIVER OF CONSENT.

I would like to apply for waiver of consent to conduct the above-named study in partial fulfilment for the requirements for the award of master in medicine degree in Anaesthesiology at the University of Nairobi.

Traumatic Brain Injury patients have an altered sensorium and are incapable of giving an informed consent to participate in the study. The waiver of consent is requested for those with significant impairment to higher function that affects their ability to communicate and understand in the event that no next of kin or legal proxy is available to give consent.

TBI contributes a significant proportion of Critical care unit mortalities therefore identifying and management of its secondary systemic insults is key. Dysregulation of blood sugar has been identified as a commonly occurring secondary insult. This study aims to collect data regarding blood sugar regulation in critically ill TBI patients. Highlighting the occurrence of dysregulation of blood sugar levels may help change treatment protocols to improve outcomes.

The study variables being investigated form a crucial part of critical care monitoring and are part of standard care. The study bears no harm to the participants. There will be no additional cost at the expense of the participants should they be included in the study.

The patient's next of kin, when available shall give informed consent after explanation of study details by the research team. This will include potential risks and benefits of enrolment into the study. Any next of kin not willing to participate in, or withdraws consent will be allowed to do so without any discrimination or alteration in the level of care accorded to the patient.

APPENDIX 7: DATA COLLECTION TOOL.

Patient Specific Serial number: ……

DEMOGRAPHICS:

Age: …….

Sex: ☐M ☐ F

ACUTE CARE:

Date of initial injury: ……/……/……. (dd/mm/yyyy)

Estimated hours since injury:

- ≤6 hours: ☐
- 6-12 Hours: ☐
- 12-24 Hours: ☐
- ≥24 Hours: ☐

Casualty Date arrival: ……/……/……. (dd/mm/yyyy)

GCS on arrival: E☐/4 M☐/6 V☐/5

Blood Sugar Level on admission: ……. /mmol/l

CT Scan Diagnosis (tick all that apply):

- Epidural Hematoma: ☐
- Subdural Hematoma: ☐
- Intracerebral Hematoma: ☐
- Skull Fracture: ☐
- Diffuse Axonal Injury: ☐
- Cerebral Oedema: ☐
- Other(specify): ☐

Associated Injuries (tick all that apply):

- Long-bone fractures: ☐
- Abdominal Injury: ☐
- Thoracic Injury: ☐

Surgical Intervention: Craniotomy: Y☐ N☐ EVD Insertion: Y☐ N☐

CRITICAL CARE INTERVENTION/PROGRESSION:

Admission to the CCU Date: …….

Blood Sugar Level on Admission: ……. mmol/l

GCS on admission: E☐/4 M☐/6 V☐/5

Admission HBA1c: …… %

Daily recording of Blood Sugar levels and Blood sugar control methods:

	Blood Sugar (mmol/l)	EVD:	Sedated:	GCS: (/15)	Insulin Therapy:
6 AM:		Y☐ N☐	Y☐ N☐	E☐/4 M☐/6 V☐/5	Infusion☐ Regular dosing ☐ None☐
12 PM:		Y☐ N☐	Y☐ N☐	E☐/4 M☐/6 V☐/5	Infusion☐ Regular dosing ☐ None☐
6 PM:		Y☐ N☐	Y☐ N☐	E☐/4 M☐/6 V☐/5	Infusion☐ Regular dosing ☐ None☐

12 AM:		Y☐ N☐	Y☐ N☐	E☐/4 M☐/6 V☐/5	Infusion☐ Regular dosing ☐ None☐

Did the patient have a discharge or mortality before 5 days?

Discharge: Y☐ N☐ Day:

Mortality: Y☐ N☐ Day:

APPENDIX 8: DUMMY TABLES

1. **Biodata, Diagnosis and type of Surgery**.

Respondent characteristic:	Number (n):	Percentage (%):
Age: ● <20: ● 20-30: ● 30-40: ● 50-60: ● >60:		
Gender ● Male ● Female		
CT Scan Diagnosis: ● Epidural Hematoma: ● Subdural Hematoma: ● Intracerebral Hematoma: ● Cerebral Edema: ● Diffuse Axonal Injury:		
Associated Injuries: ● Long bone fractures: ● Abdominal Injury: ● Thoracic Injury:		
Surgical Intervention done: ● Craniotomy: ● EVD Insertion:		

2. **Admission Blood Sugar level and GCS.**

Respondent Characteristic:	Number (n):	Percentage (%):
Admission GCS: ● 3 ● 4-8 ● 8-12		
Admission Random Blood Sugar (mmol/l):		

3. **Daily blood sugar trends- hyperglycemic and hypoglycemic events**

	Day 1.	Day 2.	Day 3.	Day 4.	Day 5.

Hyperglycemic events:					
Hypoglycemic events:					
GCS: ● E ● M ● V					
Daily mean blood sugar level (mmol/l): ● <4mmol/l ● 4 - 6.9 mmol/l ● 7.0 - 9.9 mmol/l ● >10 mmol/l					

4. **Blood sugar control method**

	Day 1.	Day 2.	Day 3.	Day 4.	Day 5.
Insulin Infusion:					
Regular Dosing:					
None:					

5. **Comparison of control method and blood sugar level**

	Mean blood Sugar level (mmol/l)				P-value
	<4	4 – 6.9	7 - 9.9	>10	
Insulin Infusion:					
Regular Dosing:					
None:					

6. **Comparison of blood sugar levels and GCS during admission and at the end**

	N= 66 P-value
Admission Blood Sugar level – Final Blood Sugar level	
Admission GCS – Final GCS	

APPENDIX 9: ETHICAL APPROVAL

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/11

7th January, 2022

Dr. Abel Odhiambo Oduor
Reg. No. H58/11537/2018
Dept. of Anaesthesia
Faculty of Surgery
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 07 JAN 2022 KNH/UoN-ERC P.O. Box 20723 - 00202 NAIROBI

Dear Dr. Oduor,

RESEARCH PROPOSAL: BLOOD SUGAR PATTERNS IN CRITICALLY ILL PATIENTS WITH TRAUMATIC BRAIN INJURY AT KENYATTA NATIONAL HOSPITAL (P896/11/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P896/11/2021.** The approval period is 7th January 2022 – 6th January 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

PROF. M.L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Dean-Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Chair, Dept. of Anaesthesia, UoN
Supervisor: Dr. Susanne M. Nabulindo, Dept. of Anaesthesia, UoN

APPENDIX 10: PLAGIARISM CHECK

Blood Sugar Patterns In Critically Ill Patients With Traumatic Brain Injury At Kenyatta National Hospital.

ORIGINALITY REPORT

9%	6%	5%	1%
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6	Elan Jeremitsky, Laurel Omert, C. Michael Dunham, Jack Protetch, Aurelio Rodriguez. "Harbingers of Poor Outcome the Day after Severe Brain Injury: Hypothermia, Hypoxia, and Hypoperfusion", The Journal of Trauma: Injury, Infection, and Critical Care, 2003 Publication	<1%
7	www.swissbraincouncil.ch	