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Risk factors for severe intraoperative hyperglycemia in patients undergoing elective neurosurgical surgery

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Thesis

**RISK FACTORS FOR SEVERE INTRAOPERATIVE HYPERGLYCEMIA IN
PATIENTS UNDERGOING ELECTIVE NEUROSURGICAL SURGERY**

by

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B.S., University of California, Santa Cruz, 2021

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DEDICATION

I would like to dedicate this work to my mother, Guadalupe, and my father, David.

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I would like to give a special thank you to Dr. Robert Canelli, Dr. Ala Nozari, Stephanie Malta, and Ciana Hartman for their support, contributions to this study, and great insight. They have made this an inspiring and knowledgeable experience.

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MARGARITA PERALES

ABSTRACT

Introduction: Severe intraoperative hyperglycemia (SIH) is defined as a blood glucose concentration above or equal to 180 mg/dL, and is associated with increased morbidity, including composite infections, leading to increased intensive care unit length of stay, hospital length of stay, and mortality. The pathophysiology of SIH is poorly understood but thought to be multifactorial, related to the catecholamine-releasing response to surgical stress and the body entering a catabolic state prior to surgery when traditional preoperative fasting guidelines are adhered to, amongst other factors. Previous studies have identified diabetes mellitus, elevated glycated hemoglobin (HbA1c), advanced age, increased body mass index (BMI), and steroid administration as risk factors for the development of SIH. The aim of this study was to determine the rate of SIH in patients undergoing elective intracranial procedures at Boston Medical Center in order to identify the common risk factors for SIH in this patient population. By identifying patients at risk for SIH before their procedure, medical care teams may be able to manage their blood glucose concentrations more tightly to avoid SIH and associated postoperative morbidity.

Methods: This prospective observational study screened patients for eligibility before their scheduled surgery between May 2021 and October 2022. On the day of surgery when the eligible patients arrived at the preoperative area, they were approached and consented for this study. The inclusion criteria for this study were all patients who were

scheduled for an elective intracranial procedure and were between ages 18 and 89. If patients had an emergency procedure, diagnosis of infection before surgery, were pregnant, or did not fit in the age range they were excluded. Patients who were enrolled had their charts reviewed, their intraoperative blood glucose levels were recorded three times during the procedure and daily for up to three days postoperatively, and the rate of SIH was recorded.

Results: In total 44 patients were recruited for this study, but four of these patients were eliminated due to lacking intraoperative blood glucose measures. Out of the 40 patients who had the required three intraoperative blood glucose measures, four patients developed SIH. This made the rate of SIH 10%. SIH-positive patients' mean age (SD) was 60 (9.99) years, and the mean age (SD) for SIH-negative patients was 51(16.69). There were no statistically significant findings for the predicted risk factors of SIH and there was no significant association between SIH and postoperative infections.

Discussion: As previous studies have also found, the rate of SIH was low, with the cited rate for neurological procedures being 17%. It is possible that the low number of patients enrolled in this study was a result of low volume of intracranial procedures and inconsistent protocols for collecting blood glucose intraoperatively lowered the rate of SIH and led to no statistically significant findings. Nevertheless, the lack of statistical findings means none of the measured patient and intraoperative factors can be correlated to predicting the likelihood of SIH developing. Another possibility is treatment with insulin in some patients was working in preventing or treating SIH. Further research is

needed to assess patient, surgical, and intraoperative factors for their potential as predicting factors for SIH to reduce SIH occurrences and improve patient outcomes.

TABLE OF CONTENTS

DEDICATION	iiiv
ACKNOWLEDGMENTS	v
ABSTRACT.....	vi
TABLE OF CONTENTS.....	ix
LIST OF TABLES	xi
LIST OF FIGURES	xii
LIST OF ABBREVIATIONS.....	xiii
CHAPTER ONE.....	1
INTRODUCTION	1
Section One: Postoperative Infection	1
Section Two: Postoperative Infection Risk Factors	2
Section Three: Glycemic Variability	3
Section Four: Severe Intraoperative Hyperglycemia	3
Section Five: Glucose Homeostasis	5
Section Six: Severe Intraoperative Hyperglycemia Risk Factors	8
Section Seven: Glycemic Management	13
SPECIFIC AIMS	18
CHAPTER TWO	19
METHODS	19
STATISTICAL ANALYSIS	23
CHAPTER THREE	24

RESULTS	24
CHAPTER FOUR.....	33
DISCUSSION.....	33
Section One: Findings	33
Section Two: Limitations	38
Section Three: Future Studies	39
Section Four: Conclusion	42
BIBLIOGRAPHY.....	45
CURRICULUM VITAE.....	47

LIST OF TABLES

Table 1. Exclusion and Inclusion Criteria for Patient Enrollment.....	20
Table 2. Data Collected in REDCap.	21
Table 3. Intraoperative blood glucose levels for the SIH patients.....	27
Table 4. Comorbidities and demographics univariate analysis results.	28
Table 5. Preoperative patient factors values.	30
Table 6. Raw Postoperative Data from SIH patients.	32

LIST OF FIGURES

Figure 1. Changes in metabolic functions due to stress hyperglycemia.....	7
Figure 2. Risk factors for stress hyperglycemia.....	9
Figure 3. Patient Enrollment selection process in the SIH study.....	25
Figure 4. Incidence of SIH in our cohort.	26

LIST OF ABBREVIATIONS

ASA.....	American Society of Anesthesiologists
ATP.....	Adenosine Triphosphate
BGC	Blood Glucose Concentration
BMC.....	Boston Medical Center
CDC	Centers for Disease Control
ERAS	Enhanced Recovery After Surgery
ICU.....	Intensive Care Unit
IL6.....	Interleukin 6
IRB	Institutional Review Board
POI.....	Post-Operative Infections
RA.....	Research Assistant
SIH.....	Severe Intraoperative Hyperglycemia c
SSI.....	Surgical Site Infection
TNFa	Tissue Necrosis Factor alpha

CHAPTER ONE

Introduction

Section One – Postoperative Infection

Postoperative infections (POI) are a major complication following surgery that can potentially alter a patient's recovery course. The development of a POI has been associated with worse surgical outcomes, longer hospital length of stays, and increased risk of morbidity and mortality. A longer hospital stay also has its own negative consequences, such as increased risk for complications and a significant increase in medical costs. Following a craniotomy, POI is the leading cause of morbidity and mortality amongst neurosurgical patients (Gruenbaum et al., 2017).

Although surgical site infection (SSI) is the most common type of postoperative infection in patients undergoing an elective craniotomy (Chiang et al., 2014), other systemic infections can occur and cause a significant increase in morbidity. The term composite infections are a general term describing all infections as defined by the Center for Disease Control (CDC), or in essence is a combination of all types of infections diagnosed following surgery (Gruenbaum et al., 2017). Examples of infections that can occur following surgery include pneumonia, urinary tract infection, meningitis, and bacteremia. In patients who have undergone any type of neurologic surgery, the development of an infection postoperatively is associated with a 15% increase in mortality. One strategy for SSI prevention includes the administration of intravenous antibiotics within one hour of the surgical incision (Kulikov et al., 2022). Other strategies for preventing postoperative infection can vary depending on the type of infection. For

example, urinary tract infections can be prevented by removing the indwelling foley catheter as soon as possible. Another example of strategies to avoid pneumonia include coughing, deep breathing, getting out of bed and walking, and by using an incentive spirometry. Given the numerous negative consequences associated with postoperative infections, there is a growing need to find methods for preventing and reducing these complications following surgery.

Section Two – Postoperative Infection Risk Factors

Identifying risk factors associated with the development of a POI is crucial to identifying those patients at highest risk for POI. Although factors such as weight, sex, ASA score, pre-/intraoperative steroid use, and pre-diagnosed diabetes mellitus have not been consistently shown to be associated with the development of a POI following neurosurgical procedures, hyperglycemia in one study has been strongly linked to postoperative surgical site infections (Kulikov et al., 2022). In this study, POIs were defined as blood stream, wound, urinary tract, central nervous system, or pulmonary infections (Kulikov et al., 2022). In liver transplant surgeries, severe hyperglycemia, defined as a blood glucose reading above 200 mg/dL, was independently associated with postoperative surgical site infection (SSI). Further, this study was able to rule out mild and moderate hyperglycemia as predictors for postoperative SSI which helps in further specifying a blood glucose concentration for the medical care team to target (Park et al., 2009). In general surgery patients, postoperative hyperglycemia increased the likelihood of the development of a POI by 30% and increased hospital length of stay in these patients (Ramos et al., 2008). In non-cardiac surgery patients, postoperative

hyperglycemia has been associated with worse surgical outcomes including increased POI, morbidity and mortality (Nair et al., 2016). Interestingly, in patients undergoing craniotomy for traumatic brain injury, preoperative hyperglycemia has been found to be a predictor for severe intraoperative hyperglycemia, despite not being the strongest predictor for POI (Pecha et al., 2011).

Section Three- Glycemic Variability

There is some consideration in recent literature that glycemic variability, or the fluctuations of blood glucose concentrations, rather than persistent hyperglycemia alone, may contribute to poor surgical outcomes including increased morbidity. As the body enters into a catabolic state from preoperative fasting before surgery, the blood glucose concentrations will vary widely. There are multiple responses to the catabolic state in the body that potentiate glycemic variability. These include the increase in endogenous glucose production by the liver, impaired peripheral glucose uptake in skeletal muscle, and the release of stress hormones due to surgical stress. In critically ill patients, glycemic variability was an independent predictor for increased morbidity and mortality (Masla et al., 2011).

Section Four- Severe Intraoperative Hyperglycemia

Although perioperative hyperglycemia and glycemic variability can negatively impact surgical outcomes, severe intraoperative hyperglycemia (SIH), has demonstrated to be a stronger predictor for the development of a postoperative composite infection. Severe intraoperative hyperglycemia (SIH) is defined as blood glucose concentration greater than or equal to 180 mg/dL (Kulikov et al., 2022). SIH has been found to result in

four times the average hospitalization costs compared to patients that had normal blood glucose concentration measurements (80-110 mg/dL) (Palermo et al., 2016). Further, SIH was associated with an increase in mortality (Pecha et al., 2011). This highlights the importance of identifying, preventing, and properly managing hyperglycemia during and after surgery. Thus, it is important for healthcare providers to closely monitor and manage glucose levels in surgical patients to reduce the risk of postoperative infection.

Neurosurgical patients who experience SIH have poor neurological outcomes, which is likely not only caused by the direct effects of hyperglycemia but also because of associated complications such as increased risk of infections. In fact, 17% of patients who undergo brain surgery of any kind develop SIH, putting them at an even higher risk for infection developing post-operatively (Kulikov et al., 2022). Unfortunately, there is a lack of research on the relationship between SIH in neurosurgical patients specifically and the experience of developing postoperative complications such as infections. In patients with acute traumatic brain injury (TBI), SIH increases the rate of complications and mortality by 15% (Duggan et al., 2017). In one study, a significant 22% of neurosurgical patients with an intraoperative hyperglycemia episode developed a postoperative infection, compared to 7% of patients who developed an infection but did not have a severe hyperglycemia episode during their neurosurgery (Kulikov et al., 2022). In craniotomy procedures specifically, it has been found that 10% of patients developed a postoperative infection, and 26.32% of these patients experienced at least one episode of severe hyperglycemia intraoperatively, which is significantly higher than the reported 6.54% in patients with normoglycemia (Gruenbaum et al., 2017).

Normoglycemia in this study was defined as the blood glucose concentration being in a normal range, 80 mg/dL to 110 mg/dL (Gruenbaum et al., 2017). The evidence from these and other similar studies suggests that developing severe hyperglycemia during surgery is independently associated with the development of an infection within the first week following their operation.

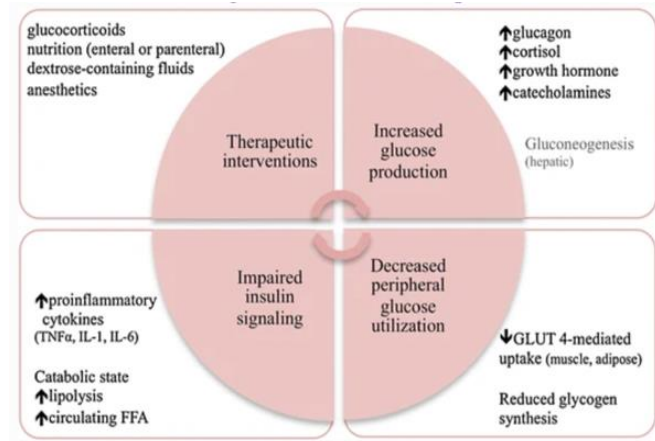
Section Five – Glucose Homeostasis

After identifying SIH as a risk factor for developing an infection postoperatively, the next aim is to better understand and develop methods to prevent, reduce, and treat hyperglycemia incidents. As was state above, severe hyperglycemia can occur during surgery because the body is under extreme stress, like when the body experiences trauma, and as a response, activation of a catabolic response that leads to increased gluconeogenesis which overproduces and releases high levels of glucose. Physiological mechanisms responsible for stress hyperglycemia also include insulin resistance and impaired insulin signaling (Palermo et al., 2016). Insulin resistance describes how hyperglycemia persists in the body, although there are sufficient or even elevated levels of circulating insulin. The probability of developing severe hyperglycemia due to insulin resistance increases as the type of surgery being performed becomes more intense and in turn becoming more stressful for the body (Akiboye & Rayman, 2017). Furthermore, insulin resistance can develop because of hyperglycemia, which can make the already present hyperglycemia much worse. In the population of patients undergoing craniotomies, their bodies are under extreme stress therefore increasing their risk for SIH. Additionally, insulin resistance can negatively affect wound healing and increase a

patient's vulnerability to infections, especially at the surgical site. Regarding the prevention of hyperglycemia, if there is a way to detect a patient's likelihood and extent of insulin resistance, it may be used as a predictor for intraoperative hyperglycemia.

When insulin signaling is impaired there is an increase of pro-inflammatory cytokines, small proteins involved in signaling for inflammation to occur (Palermo et al., 2016). This increase in pro-inflammatory cytokines triggers the body to enter a catabolic state leading to the increase in lipolysis, the breakdown of fat, and consequently the increase in free fatty acids in circulation. Available circulating glucose is not being utilized because GLUT-4, the glucose transporters in the muscle and fat, are not taking up glucose (Palermo et al., 2016). During surgery, certain mediators will shut down the GLUT-4 transporters thereby halting glucose uptake. The body responds as if there is no glucose available, increasing glucose production by gluconeogenesis in the liver and decreases synthesis of glycogen, the storage form of glucose. Both events are common causes of hyperglycemia detected during surgery (Ljungqvist, 2009). By increasing glucose production, blood glucose concentration levels will rise, as seen in stress hyperglycemia that develops intraoperatively. Hence, impaired insulin signaling will only worsen the SIH.

Insulin plays a crucial role in the body's adenosine triphosphate (ATP) production by initiating the glycolytic reaction, which involves breaking down glucose into pyruvate. There are many other metabolic functions that change in response to stress as summarized in Figure 1 which is describing the overall pathogenesis of stress hyperglycemia (Palermo et al., 2016).

Figure 1

Note: Changes in metabolic functions due to stress hyperglycemia. Adapted from “Stress Hyperglycemia During Surgery and Anesthesia: Pathogenesis and Clinical Implications,” by N.P., 2016, *Curr Diab Rep*, 16, 33. Copyright 2016 by Springer-Science.

Besides its main metabolic functions, insulin also plays a major role in protecting the body against endothelial dysfunction. It is important to maintain this function of insulin to avoid an upregulation of the endothelial dysfunction (Duncan, 2012), which is an essential component of the pathophysiology of many cardiovascular conditions that can lead to organ failure and death. These arteries may have no blockages due to plaque buildup but can constrict instead of dilating causing the lumen of the artery to become narrower and reducing tissue blood flow (Duncan, 2012). From these findings about the major role insulin plays in causing hyperglycemia and preventing detrimental postoperative outcomes such as organ failure, insulin should be monitored and adequately supplied when needed. Thus, insulin resistance and impaired insulin signaling should be

considered as patient factors that could make a patient more at risk for developing stress hyperglycemia.

In a study on the relationship between intraoperative glucose concentrations and postoperative outcome in non-cardiac surgeries, it was concluded that hyperglycemia is associated with increased inflammation, impaired chemotaxis and phagocytosis, and higher vulnerability to infections (Shanks et al., 2018). The stress response to surgery releases stress factors like interleukin 6 (IL6) and tissue necrosis factor alpha (TNFa) and suppresses the immune response, leading to changes in blood glucose concentrations. These changes in blood glucose concentration as an immune response increase the amount of glucose available for the body to use for metabolism (Kratzing, 2011). More dangerously, hyperglycemia can be responsible for heavily damaging the body by enhancing free radical production in the mitochondrion electron transport chain and causing severe oxidative damage that triggers cell death (Piconi et al., 2006). In a comparison of patients with SIH and those without, 30% of patients with hyperglycemia died, compared to only 13% mortality amongst those without hyperglycemia (Pecha et al., 2011). Therefore, monitoring the onset of inflammation can serve as a key indicator of the onset of stress hyperglycemia and its potentially harmful effects, making it a crucial aspect to consider in ensuring a positive postoperative recovery.

Section Six– Severe Intraoperative Hyperglycemia Risk Factors

Several surgical, patient, and intraoperative risk factors have been identified as potential predictors of stress intraoperative hyperglycemia. Figure 2 summarizes all the

potential factors that require further investigation regarding their relationship with intraoperative hyperglycemia, some of which will be discussed and explored here (Palermo et al., 2016). More specifically, the factors that will be considered here are the type of procedure and its level of invasiveness, the administration of steroids, insulin deficiency or resistance, the role of hemoglobin A1C (HbA1C), a previous diagnosis of diabetes mellitus, and patients with severe traumatic brain injuries. Since BMC’s patient population are more susceptible to having poorly controlled medical conditions including diabetes mellitus, this study’s sample may have more of the risk factors suggested for SIH.

Figure 2

Surgical	<p>More invasive procedure (open vs. laparoscopic) Anatomic location involving thorax and abdomen General anesthesia (vs. epidural) Intraoperative fluids with >5% dextrose</p>
Perioperative	<p>Glucocorticoids Parenteral/enteral nutrition Physical inactivity</p>
Patient factors	<p>Degree of illness Pre-existing state of insulin resistance and/or deficiency Advanced age Higher BMI Higher HbA1c Baseline glucose on day of procedure</p>

Note: Risk Factors for Stress Hyperglycemia. Adapted from “Stress Hyperglycemia During Surgery and Anesthesia: Pathogenesis and Clinical Implications,” by N.P., 2016, *Curr Diab Rep*, 16, 33. Copyright 2016 by Springer-Science.

The first potential risk factor for developing severe hyperglycemia during surgery that will be discussed is a patient's preoperative glycated hemoglobin count, or better known as HbA1C. HbA1C is a patient's average blood glucose concentration over approximately a 3-month period (Kulikov et al., 2022). In patients with a previous diagnosis of diabetes mellitus, HbA1C levels can predict the level of insulin resistance a patient will likely experience during their surgery (Sato et al., 2010). By measuring a patient's preoperative HbA1C, their medical care team can determine if a patient's susceptibility to hyperglycemia which could possibly worsen as the body succumbs to the stress of surgery (Kulikov et al., 2022). Furthermore, HbA1C has also been found to be associated with insulin resistance (Sato et al., 2010), which as previously stated can cause the intraoperative hyperglycemia. Another study concluded that a preoperative HbA1C measure that is greater than 6.5% predicted the development of SIH, but there is limited evidence connecting HbA1C to intraoperative hyperglycemia (Kulikov et al., 2022). In fact, there is only enough evidence to support HbA1C as an independent predictor of *postoperative* hyperglycemia in cardiac surgery patients (Gianchandani et al., 2015). Regardless, given that this is a main predictor for persistent hyperglycemia to diagnose glycemic illness such as diabetes mellitus, HbA1C remains an important potential predicting factor of intraoperative hyperglycemia to investigate further.

In patients undergoing brain surgery, it is speculated that the use of corticosteroids, which are administered during the procedure to prevent swelling in the brain, may contribute to intraoperative stress-induced hyperglycemia (Bilotta et al., 2009). Since neurosurgical patients on average tend to receive higher doses of this

medication, they may have an increased risk for steroid-related hyperglycemia. As a result, there are some clinical questions surrounding whether corticosteroids could be a predictive factor for the development of hyperglycemia, especially in patients who already have other risk factors for developing SIH.

Other factors that were identified to increase patient susceptibility to SIH were previously diagnosed diabetes mellitus or any general poor preoperative glycemic control. Studies on non-cardiac surgeries have demonstrated that patients with pre-existing diabetes mellitus were more likely to develop a stress hyperglycemia response (Shah et al., 2020). However, the postoperative outcomes of these non-cardiac surgical patients that developed hyperglycemia were no different than non-affected, or non-hyperglycemic patients. When comparing patients who have previously diagnosed diabetes mellitus or just normoglycemia to those who only developed hyperglycemia during surgery, those with hyperglycemia development in surgery had a 16% increase in hospital mortality (Palermo et al., 2016). In contrast, numerous studies have found that patients with no previous diagnosis of diabetes mellitus are more susceptible to having preoperative hyperglycemia. According to one study, 38% of patients had hyperglycemia, but only 26% of these patients had a pre-existing diabetes mellitus diagnosis (Umpierrez et al., 2002). It is important to note that although a patient experiencing preoperative hyperglycemia upon admission may not have a previous diabetes mellitus diagnosis, they may be more at risk for SIH because their glycemic levels are already highly variable. When assessing diabetes mellitus as a risk factor for SIH, it is important to differentiate between the population of patients who have a newly diagnosed hyperglycemia that first

appears during surgery and patients who have previously developed diabetes mellitus or have poor glycemic control. Patients who experience hyperglycemia despite normal glycemic levels pre-operatively most likely represent “true stress hyperglycemia” during their surgery (Dungan et al., 2009).

In elective craniotomy patients, a previous diabetes mellitus diagnosis was associated with higher probability of SIH, but the evidence is insufficient to determine a correlation between diabetes mellitus and SIH during a craniotomy. Patients with diabetes mellitus who typically monitor their blood glucose concentrations and maintain active regulation seem to experience less episodes of intraoperative hyperglycemia compared to diabetic patients who do not maintain glycemic control. One study did show that patients with diabetes mellitus had a significantly less in-hospital mortality than those who had experienced SIH (16%) (Palermo et al., 2016). However, the population at Boston Medical Center (BMC) tend to have poorer knowledge when it comes to managing their health and consequently have poorly managed diseases such as diabetes mellitus therefore possibly increasing their chances of developing SIH. The evidence for diabetes mellitus as a predicting factor for hyperglycemia is controversial with different findings and limited information for diabetic craniotomy patients specifically. Still, it is a pertinent patient factor that should be considered by the medical care team to be prepared for SIH during surgery.

Another study has demonstrated that SIH is a common complication among patients who undergo craniotomy for traumatic brain injury, and its occurrence can be influenced by various factors. Patients who underwent a craniotomy for a traumatic brain

injury were more likely to have an episode of severe hyperglycemia during their surgery depending on the severity of their injury, the presence of a subdural hematoma, preoperative hyperglycemia measurements, and if the patients were above the age 65 (Pecha et al., 2011). Severely injured patients, or those with a worse head injury, were more likely to develop hyperglycemia (Salim et al., 2009). There is limited clinical information to confirm the findings of this study in craniotomy patients, so one goal of this study is to corroborate these findings in craniotomy patients.

Section Seven– Glycemic Management

Due to the relatively high prevalence of hyperglycemia during a craniotomy, the recommended therapeutic window for treatment occurs during the surgery and is achieved by controlling the patient's glycemic variability intraoperatively. If severe hyperglycemia is detected during an operation, the anesthesiology team should evaluate the patient's blood glucose concentration and determine the appropriate dose of insulin to be administered (Bilotta et al., 2017). Research has shown that craniotomy patients with a traumatic brain injury who received insulin therapy during their operation had a lower in-hospital death rate than those who did not receive insulin therapy (Pecha et al., 2011). Another important finding was that treating hyperglycemia during surgery results in a decreased amount of post-operative complications (van den Berghe et al., 2001). These findings and others have led to increased attention on insulin therapy administration during a craniotomy because it has shown to be effective in reducing the risk of severe hyperglycemia intraoperatively and its associated complications, highlighting its importance as a therapeutic approach for this patient population.

Unfortunately, despite the increasing awareness, there are inconsistencies in the effectiveness and safety of insulin therapy in treating hyperglycemia during a craniotomy and is still debated in the medical community. Although the amount of insulin given will vary amongst patients, one study suggested the implementation of a more uniform protocol, administering four units of insulin for blood glucose concentration between 180-200 mg/dL, six units for 200-220 mg/dL, and eight units for 220-240 mg/dL (Kulikov et al., 2022). In another study investigating critically ill patients, intensive insulin therapy was used to keep glucose levels below 110 mg/dL. This method of treatment showed to be effective in treating intraoperative hyperglycemia and reduced mortality and infection. However, other studies have brought up the concerns about intensive insulin therapy potentially causing hypoglycemia. Hypoglycemia is defined as low blood glucose concentration under 70 mg/dL and is often considered to be more dangerous than hyperglycemia. In the comparison of intensive and moderate intraoperative insulin therapy, it was found that patients who received intensive glycemic control did have a shorter hospital length of stay and infection rate, but unfortunately, they had a higher incidence of hypoglycemic episodes. In another comparison study, 18.7% of patients who received intensive insulin therapy developed hypoglycemia in comparison to the 3.1% who received moderate insulin therapy (Lipshutz & Gropper, 2009). Although studies on intensive insulin therapy have shown promise to effectively reduce hyperglycemia, its use as a primary method of treatment should be avoided.

Maintaining a patient's blood glucose concentration levels within a certain limit has been suggested as another approach to monitoring and preventing hyperglycemia.

This approach involves a tighter control of the patients' blood glucose concentration range and closer monitoring of blood glucose range during the perioperative period. The optimal blood glucose concentration is still being researched, but the available literature is consistent in the importance of treating hyperglycemia. However, when patients were held under a very tight blood glucose range, from 80 to 110 mg/dL, they were more likely to develop hypoglycemia (Gruenbaum et al., 2017). A study found that the practices for managing blood glucose in craniotomies is still highly variable, highlighting the need for more evidence to determine the best way to avoid both hypoglycemia and hyperglycemia during brain surgery (Gruenbaum et al., 2021). Therefore, managing blood glucose levels during a craniotomy is a complex issue that requires careful consideration of multiple factors and further research to determine the best approach to avoid both hypoglycemia and hyperglycemia.

Due to the risks of intensive insulin therapy and tight glycemic control, blood glucose concentration should be continuously monitored during an operation for the potential danger of developing hypoglycemia. Critically ill patients under treatment in the intensive care unit (ICU) can contract hypoglycemia, and experiencing as few as one episode of hypoglycemia is enough to require a longer hospital stay (Kransley et al., 2011). Unlike hyperglycemia, hypoglycemia has more dangerous immediate effects, due to the brain's reliance on glucose as its sole metabolic source. Without sufficient glucose levels to feed the brain necrosis will occur in brain tissue. Persistent hypoglycemia in critically ill patients increases the risk of seizures, neurological deficits or even a coma (Lipshutz & Gropper, 2009). If hypoglycemia is detected because of insulin

administration, patients can be quickly treated with an infusion of a dextrose-containing solution.

Intensive insulin therapy has been found to be effective, despite not being safe. This has prompted clinical research to attempt to treat stress hyperglycemia with a more moderate approach. Conventional insulin therapy has been shown to have the same efficacy as intensive insulin therapy, but it is uncertain whether this method would prevent hypoglycemia while reducing hyperglycemia. One study outlined conventional insulin therapy as giving the patient insulin when their blood glucose concentration exceeded 215 mg/dL and was adjusted to maintain the patient's blood glucose concentration in the range of 180 mg/dL to 198 mg/dL. In this treatment protocol, if blood glucose dropped below 180 mg/dL, insulin infusion was immediately stopped (Bilotta et al., 2009). Unfortunately, the results showed that conventional insulin therapy still yielded the same hypoglycemia results as seen in intensive insulin therapy. Specifically, 63% of patients who received conventional insulin therapy had at least one episode of hypoglycemia in comparison to the 94% who received intensive (Bilotta et al., 2009). Despite the efforts to find a more moderate approach to treating intraoperative stress hyperglycemia with insulin therapy, conventional insulin therapy was still found to result in high and unacceptable levels of hypoglycemia.

In the current state of research, the most effective method in avoiding hyperglycemia among surgical patients is maintaining a moderate blood glucose concentration through continuous insulin administration as an infusion rather than administering boluses of insulin. The study conducted by Gruenbaum et al. (2017)

recommends maintaining a moderate BGC of 140-180 mg/dL during neurosurgery with constant monitoring and a continuous insulin infusion. Any blood glucose concentration between 140 and 180 mg/dL is considered appropriate in treating hyperglycemia and avoiding hypoglycemic levels which is BGC below 70 mg/dL. Although this method has been effective in one clinical study, there is still no agreement on what approach should be taken for proper glyceic control.

There is a clear link between SIH and postoperative infection in neurosurgery; however, it is unclear that a reduction in SIH will lead to a reduction in the composite infection rate postoperatively. Additionally, the literature does not suggest a best method for intraoperative glyceic management to prevent SIH, and thus prevent infection. Understanding the risk factors for the development of SIH will help providers to identify patients at risk. The aim of this study was to determine the rate of SIH in patients undergoing neurosurgery at Boston Medical Center (BMC) and to identify the risk factors for SIH development in their surgical population. By identifying these risk factors, the medical care team can be better prepared to manage and even prevent SIH from occurring, thus reducing morbidity and mortality for these patients. It is important to note that this study occurred at BMC which treats the underserved and low socioeconomic status patients of Boston. Since these patients tend to have lower knowledge of health and are at a higher risk for having poorly controlled medical conditions, such as diabetes mellitus, in comparison to the general population of Boston this patient population is possibly at a higher risk for developing SIH and thus contributing to the postoperative morbidity and mortality.

Specific Aims

The risk factors that are believed to predict severe intraoperative hyperglycemia (SIH) that previous studies have identified include increased age, higher BMI, intraoperative steroid use, higher HbA1c, and previous diagnosis of diabetes mellitus. The rate of SIH after an elective neurosurgical procedure in prior studies has been found to be about 10%-17%.

Because Boston Medical Center treats the underserved and low socioeconomic status patients in Boston and since these patients tend to be at a higher risk for poorly controlled medical conditions, the hypothesis is proposed that the rates of SIH may be higher at BMC than proposed in previous studies.

The first aim of this study was to report the rate of SIH in Boston Medical Center's intracranial procedure population. This task was completed by a chart review analysis of the patients enrolled in the study to further analyze the development of severe hyperglycemia during an elective intracranial procedure.

The next aim of this study was to identify any risk factors for predicting SIH by performing statistical analysis on all factors taken from the patients who did develop SIH during their elective intracranial procedure. By identifying potential risk factors, new ways of preventing SIH and postoperative infection can be further developed.

Finally, this clinical research study aimed to observe if patients who developed SIH received insulin therapy intraoperatively or postoperatively developed a postoperative infection and had a lengthened hospital stay.

CHAPTER TWO

Methods

This prospective observational study was approved by the Institutional Review Board (IRB) at Boston Medical Center (BMC) on February 11, 2022. The IRB protocol number for this study was H-41050. This was a multicenter study of adult patients who underwent elective intracranial surgery for tumor removal, with the goal of investigating the role of severe intraoperative hyperglycemia (SIH) as a risk factor for developing a postoperative infection. Furthermore, this study observed other patient, intraoperative, and surgical factors that could reliably predict the occurrence of SIH in elective intracranial procedure patients. Since this study was solely observational of usual care at BMC, no intervention or change was made to the patients' clinical course. However, this institution has developed a perioperative glycemic management algorithm for medical care teams to use. Research assistants did not instruct care teams to use the glycemic management algorithm.

Trained research assistants (RAs) screened patients for study eligibility by checking the daily operating room schedule at BMC. The screening was done through a chart review of the BMC electronic health record system known as Epic Systems. Inclusion criteria used to assess eligibility included adults between the ages 18 to 89 years that were scheduled for elective intracranial surgery, underwent general anesthesia, and had a hospital stay of at least one day post-operation. Patients were excluded from enrollment into the study if they had an infection diagnosed preoperatively or were undergoing an emergency procedure. Patients undergoing a transsphenoidal craniotomy

were also excluded because this procedure is often performed to remove pituitary tumors which tend to be hormone secreting. A summary of inclusion and exclusion criteria are included in Table 1.

Table 1. Exclusion and Inclusion Criteria for Patient Enrollment. This table summarizes the parameters used for including or excluding the patient from the clinical research study's cohort.

Inclusion Criteria	Exclusion Criteria
Age 18-89	Patients younger than 18 years
Scheduled surgery is an elective intracranial procedure (open)	Patients older than 89 years
Requires general anesthesia.	Diagnosis of infection in the preoperative period
Stay at least 1-day post-procedure	Emergency procedures
	Endoscopic procedures

If a patient met inclusion criteria during the screening step, the research assistants approached the patient in the preoperative area the day of the procedure to obtain consent for Health Insurance Portability and Accountability Act (HIPAA) authorization. Before receiving consent from patients, RAs informed the eligible patient of the risks and benefits of the study and that this study was completely observational, meaning participation in the study would not result in any change to their care while at the hospital. HIPAA authorization was obtained from eligible patients who agreed to participate in the study. If a patient met all the eligibility requirements and was consented by the research assistants, they were enrolled in this clinical research study. Only after enrollment, the anesthesia team was informed about the patient's inclusion in this

observational study. Enrolled patient data was accessed by the RAs on postoperative day 7. Intraoperative and postoperative data was collected to determine if the patient developed any type of infection postoperatively. All variables of interest to the study were recorded by research assistants in the Research Electronic Data Capture (REDCap) database. These data collected are listed in Table 2.

Table 2. Data Collected in REDCap. A list of all the variables collected from the patient's chart. ASA= American Society of Anesthesiologists; BMI= body mass index; ADHD= attention deficit disorder; COPD= chronic obstructive pulmonary disease; DVT= deep vein thrombosis; GERD= gastroesophageal reflux disease; ICU= intensive care unit; REDCap= Research Electronic Data Capture.

Demographics	<ul style="list-style-type: none"> • Redcap • Age on day of surgery • Patient Race • Surgery Name • Patient Biological Sex • Patient Height • Patient Weight • Patient BMI
Comorbidities Risk Factors	<ul style="list-style-type: none"> • Patient's frequency of alcohol use • Patient's history of tobacco use • Patient's history of drug use • Does the patient have any of the following comorbidities: <ul style="list-style-type: none"> - Depression - Anxiety - ADHD - Asthma - Bipolar Disorder - COPD - Coagulopathy Bleeding Disorder - DVT - Fibromyalgia - GERD

	<ul style="list-style-type: none"> - Gynecomastia/Hyperprolactinemia - Hypertension - Low back pain - Malignant hyperthermia - Motion sickness - Pulmonary embolism - Sleep apnea - Diabetes Mellitus
Surgical Data	<ul style="list-style-type: none"> • Patient's ASA physical status • Preoperative HbA1C (any A1C 3 months of procedure or prior to the procedure) • Pre procedure blood glucose level • Intraoperative blood glucose level #1 • Intraoperative blood glucose level #2 • Intraoperative blood glucose level #3 • Post Anesthesia Care Unit (PACU) blood glucose levels • Postoperative day 1 blood glucose levels • Postoperative day 2 blood glucose • Intraoperative insulin dose • Intraoperative steroid dose • Antibiotics (name, dose, frequency) • Which of the following was the patient administered <ul style="list-style-type: none"> - Inhaled anesthetic - Inhaled with propofol infusion - Inhaled with remifentanil infusion - Total intravenous anesthesia (TIVA) • Anesthesia start time • Anesthesia end time • Induction time • Emergence time • Extubation time • Estimated blood loss

	<ul style="list-style-type: none"> • Estimated blood transfusion
Postoperative Data	<ul style="list-style-type: none"> • Did the patient develop postoperative infection within 7 days? • Antibiotic regimen (name, dose, frequency) • ICU length of stay • Hospital length of stay

Statistical Analysis

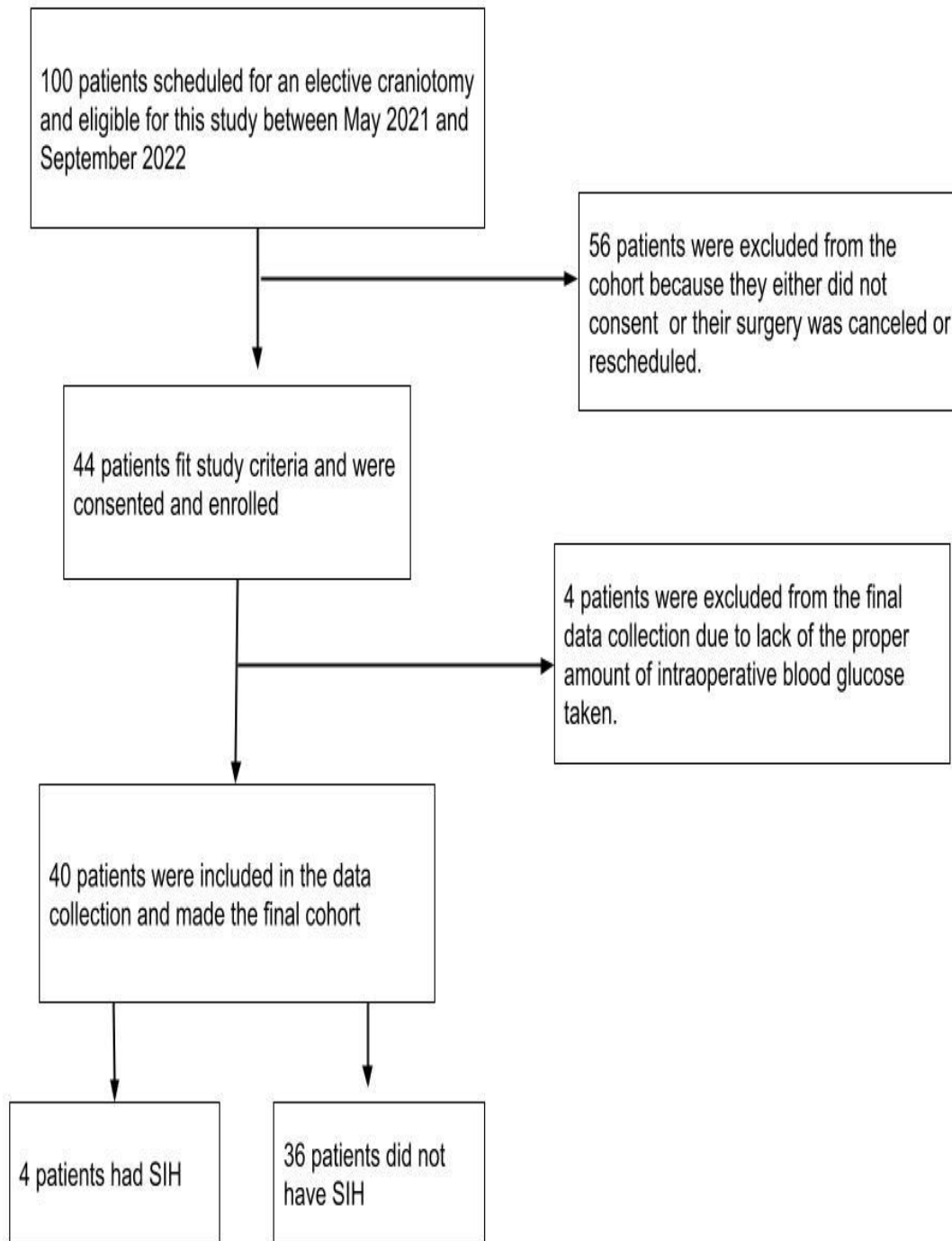
All statistical analyses were performed using R software. To describe categorical data, count and percentages were used. Categorical and continuous variables were compared using two different types of univariate analysis. Categorical variables (e.g., insulin administration, comorbidities, and development of a postoperative infection) were compared using a chi-squared test. Continuous variables (e.g., ICU length of stay, age, height, and BMI) were compared through the T-test and presented as mean and standard deviation. If a p-value was less than 0.05 ($p < 0.05$), then the variable was considered statistically significant.

CHAPTER THREE

Results

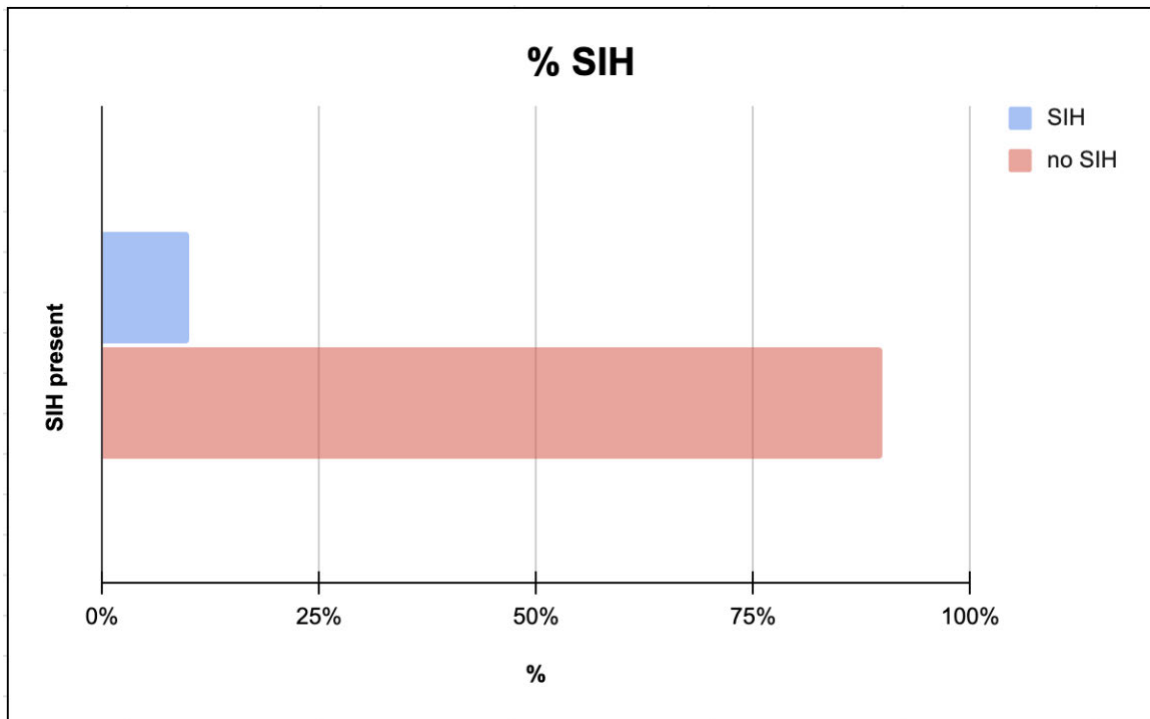
There was a total of 100 eligible patients who met the inclusion criteria for an elective intracranial procedure between May 2021 and October 2022. From the 100 eligible patients, 44 were consented to enrollment and were included in the study. The remaining 56 patients were excluded from enrollment because the patient or their health proxy declined to participate and consent, or the originally scheduled surgery was postponed. Figure 3 summarizes enrollment in the study by illustrating how the final patient cohort for this clinical research study was defined. This includes the exclusion process for patients that are eligible. Four of the 44 enrolled patients were excluded from the final data collection because they did not have enough intraoperative blood glucose levels taken during their surgery. The basic characteristics for the 40 remaining patients taken are summarized in Table 2. From the 40 remaining patients, 4 patients experienced severe intraoperative hyperglycemia defined as blood glucose concentration > 180 mg/dL, during their surgery. The remaining 36 patients did not experience severe intraoperative hyperglycemia episodes.

Figure 3. Patient enrollment selection process in the SIH study. A flowchart of the patient selection criteria. SIH=Severe intraoperative hyperglycemia.



The incidence of severe intraoperative hyperglycemia in our patient cohort at Boston Medical Center was 10%. Figure 4 summarizes the incidence of SIH-positive patients compared to patients who did not develop SIH.

Figure 4. Incidence of SIH in our cohort. A bar graph depicting the 10% incidence of developing SIH. SIH= Severe Intraoperative Hyperglycemia.



As described in the study design, three intraoperative blood glucose levels were taken throughout a patient's procedure. These three intraoperative blood glucose levels for each patient who developed SIH during their intracranial procedure are summarized in Table 3.

Table 3. Intraoperative blood glucose levels for the SIH patients. This table represents the three raw intraoperative blood glucose levels taken by the anesthesiologist during the patients who developed SIH surgery.

Patient n	Intraop BGL #1 (mg/dL)	Intraop BGL #2 (mg/dL)	Intraop BGL #3 (mg/dL)
Patient a	157	176	217
Patient b	308	168	291
Patient c	310	393	325
Patient d	237	259	199

To identify the common comorbidities, demographics, and preoperative risk factors in this study's cohort of patients, univariate analyses were performed between the patients (4) who did have a SIH episode during their intracranial procedure and the patients (36) that did not have SIH. As seen in Table 4, none of the variables that were collected in the comparison of patients with and without SIH had a p-value less than or equal to 0.05. Therefore, there were no statistically significant comorbidities and demographic variables that SIH patients had. The lack of statistically significant results indicates that none of these factors can be utilized as a predicting factor for severe hyperglycemia during an intracranial procedure. Furthermore, these results indicated that probably due to the small sample size, this study was too underpowered to detect associations.

Table 4. Comorbidities and Demographics Univariate Analysis Results. Results between patients with SIH and those who did not. Continuous variables are described using mean and SD values. Categorical variables were reported as counts (n) and percentages. BMI= body mass index; COPD= chronic obstructive pulmonary disease; DVT= deep vein thrombosis GERD= gastroesophageal reflux disease; NS= not statistics.

Factor	Negative for SIH (n=36)	Positive for SIH (n=4)	p-value
Age, mean (SD)	51.01 (16.69)	60.79 (9.99)	0.26
Race			0.841
- Asian, n (%)	3 (8.3)	1 (25)	
- Black or African American, n (%)	8 (22.2)	1 (25)	
- White, n (%)	14 (38.9)	1 (25)	
- Two or more races, n (%)	9 (25)	1 (25)	
- Unknown n (%)	2 (5.6)	0 (0)	
Biological Sex			1
- Male n (%)	20 (50.6)	2 (50)	
- Female n (%)	16 (44.4)	2 (50)	
Height, mean (SD)	1.68 (0.11)	1.67 (0.08)	0.868
Weight, mean (SD)	80.94 (19.65)	72.26 (9.52)	0.393
BMI, mean (SD)	28.61 (5.92)	25.85 (1.24)	0.364
History of tobacco use			0.333
- Never, n (%)	31 (86.1)	3 (75)	
- Former, n (%)	2 (5.6)	1 (25)	
- Current, n (%)	3 (8.3)	0 (0)	
History of drug use			.525
- No, n (%)	31 (86.1)	3 (75)	
- Yes, n (%)	2 (5.6)	1 (25)	
- Unknown	2 (8.3)	0 (0)	
Mental Health Comorbidities			
- Depression, n (%)	3 (8.3)	0 (0)	1
- Anxiety, n (%)	3 (8.3)	1 (25)	0.861

Other Comorbidities:			
- Asthma, n (%)	3 (8.3)	0 (0)	1
- COPD, n (%)	1 (2.8)	0 (0)	1
- DVT, n (%)	3 (8.3)	0 (0)	1
- GERD, n (%)	9 (25)	3 (75)	0.135
- Gynecomastia/Hyperprolactinemia, n (%)	1 (2.8)	0 (0)	1
- Hypertension, n (%)	16 (44.4)	3 (75)	0.527
- Low back pain, n (%)	3 (8.3)	0 (0)	1
- Pulmonary Embolism, n (%)	3 (8.3)	0 (0)	1
- Sleep apnea, n (%)	5 (13.9)	0 (0)	1
- Diabetes Mellitus, n (%)	4 (11.1)	3(75)	NS

All four of the SIH-positive patients scored an ASA score of 3 during the preoperative period in comparison to 22 SIH-negative patients who also had an ASA 3 score. The five classes of ASA scores describe the patient's overall health. The first class being the healthiest a patient can be and five represents patients expected to die within a 24-hour window. Class 3, which is what all four of our patients with SIH were classified as, is described as a patient having a severe but not incapacitating disease. Previous studies have shown that ASA scores are not related to the development of SIH during surgery.

Furthermore, although not statistically significant, the four patients with SIH had a preoperative HbA1c measurement in the range of 6.5-8.5%. An HbA1c score above 6.5% is considered in the diagnosable range for diabetes mellitus. Only 2 SIH-negative patients had an SIH score in the diabetes mellitus diagnosable range, but it is important to note that 20 of the SIH-negative patients did not have an HbA1c taken. Another preoperative factor which was not statistically significant, was the patient's preoperative blood glucose levels: only two of the SIH-positive patients had a preoperative blood

glucose measure that was considered as preoperative hyperglycemia. None of the SIH-negative patients had a preoperative blood glucose in the hyperglycemia range. In fact, 33 SIH-negative patients had normoglycemia before their procedure. The raw data value of each of the SIH-positive patients' preoperative HbA1c and blood glucose readings are listed in Table 5.

Table 5. Preoperative patient factors values. This table provides data for the four patients that developed SIH, their raw data for their preoperative HbA1c and blood glucose concentration. HbA1c= Glycated Hemoglobin

Patient n	Preoperative HbA1c (%)	Preoperative blood glucose concentration (mg/dL)
Patient a	7.1	135
Patient b	6.7	315
Patient c	8.5	244
Patient d	7.1	123

During the operation, only two of the four patients with SIH received intraoperative insulin therapy, whereas none of the 36 SIH-negative patients received insulin therapy during their operation. The amount of insulin given to the two SIH-positive patients varied. One patient received 49 units of insulin, while the other patient received 20 units. All four SIH-positive patients did receive some type of steroid during their surgery, and 33 of the SIH-negative patients also received steroids intraoperatively. Most commonly, the steroid used in all patients (40) of this study was dexamethasone, but again all varied in the amount and type of steroid received. The range of steroids given to these four SIH-positive patients was between 8mg-12mg of dexamethasone

whereas the range for the SIH-negative patients was between 4mg-30mg. Furthermore, during surgery all four SIH-positive patients received antibiotics, and except for one patient all SIH-negative patients also received antibiotics during their surgery. However, the type of antibiotic varied between Cefazolin and Ceftriaxone, and the dosage varied widely. Regarding anesthesia type, three SIH-positive patients and 18 SIH-negative patients received inhaled anesthetics with propofol with remifentanyl infusion. All four SIH-positive patients did have a small amount of blood loss, less than 300 mL, and none received a blood transfusion. Similarly, 30 SIH-negative patients had less than 300 mL of blood loss and 34 did not receive a blood transfusion. It is important to note that these results for intraoperative period values including insulin therapy, steroid and antibiotic administration, anesthesia type, and blood loss did not have any statistical significance, and the results demonstrated here discuss the raw data variables that were received for the patients positive for SIH.

Three of SIH-positive during their surgery continued to experience hyperglycemic blood glucose readings during the Postanesthesia Care Unit (PACU) phase of their postoperative care. In comparison, all SIH-negative patients experienced normoglycemic blood glucose readings while in the PACU. During the first two days postoperative, three SIH-positive patients continued to have experienced severe hyperglycemia. Interestingly, two of the SIH-negative patients also developed severe hyperglycemia during the first two days postoperative, but the remaining SIH-negative patients continued to experience normoglycemic blood glucose readings. None of the patients enrolled in this study (40) developed a postoperative infection, but all patients continued to receive prophylactic

antibiotics while in the ICU. The length of stay (LOS) in the ICU and hospital were recorded but there was no statistically significant LOS amongst the four patients who developed SIH versus the SIH-negative patients. The ICU LOS for SIH-positive patients was 3.25 (+/- 2.06) and was 2.86 (+/-3.07) for SIH-negative patients ($p=0.737$). Hospital LOS for SIH-positive patients was 7.75 (+/-5.12) and 6.69 (+/-5.71) for SIH-negative patients ($p=0.698$). The postoperative data collected for each SIH-positive patient is summarized and presented in Table 6.

Table 6. Raw Postoperative Data from SIH patients. This table contains the raw value for the SIH positive patients PACU blood glucose readings, 2-day postoperative blood glucose readings, and their length of stay. PACU=Post Anesthesia Care Unit; BGL= blood glucose levels; ICU= intensive care unit; LOS= Length of Stay.

Patient n	PACU BGL (mg/dL)	Post op Day 1 BGL (mg/dL)	Post op Day 2 BGL (mg/dL)	ICU LOS (days)	Hospital LOS (days)
Patient a	232	276	306	1	3
Patient b	246	170	237	2	6
Patient c	210	270	321	5	15
Patient d	135	318	192	5	7

CHAPTER FOUR

Discussion

Section One- Findings

Out of the 40 patients who were eligible and enrolled, four patients had an episode of severe hyperglycemia during their elective intracranial procedure. Therefore, there was a 10% SIH incidence in elective intracranial surgeries found in the patient population at Boston Medical Center (BMC). This finding from the current study is consistent with other studies findings of a relatively low SIH in neurological procedures. For example, 17% of patients who underwent brain surgery in Kulikov et. al's (2022) study developed severe hyperglycemia during their operation. Although SIH occurred at a higher rate than what this clinical study found, it could be due to the difference in the number of eligible procedures between the two studies. However, this result did contradict our hypothesis that the BMC patient population would be sicker with more poorly controlled diseases such as diabetes mellitus than the average population in Boston due to the poor health knowledge amongst these patients. Due to these characteristics of BMC's patient population, we predicted that our study would find a higher incidence of SIH, but only a 10% rate of SIH was seen at BMC.

Another potential factor which many have contributed to the low rate of SIH at BMC is this institution's development of a perioperative glycemc management algorithm for their healthcare providers to use. The use of the perioperative glycemc management algorithm is up to the discretion of each healthcare provider, meaning some use it while others do not. Due to the observational nature of this study, investigators did not instruct

medical care teams to use the glycemic management algorithm leading to the inconsistent use of this glycemic management in our study's sample. Therefore, the low rate of SIH at BMC could be due to the consistent use of the perioperative glycemic management algorithm by medical care teams.

When comparing the comorbidities and demographics of the four patients who developed SIH, there were no factors of statistical significance that could identify potential predicting factors for SIH. These results were not as expected because it was predicted that at least some patient demographics, such as advanced age, higher BMI, or pre-existing diagnosis of diabetes mellitus were potential predicting patient factors for them developing SIH during an intracranial procedure. It is important to acknowledge that three of the four patients who developed SIH had diabetes mellitus. Therefore, although no statistical significance was found relating diabetes mellitus and SIH, future studies should continue researching diabetes mellitus as a predicting factor because this result could be due to this study being underpowered because of the small sample size. A preoperative diagnosis of diabetes mellitus can inform a patient's medical care team that this patient is already susceptible to glycemic variability during their operation due to either insulin resistance or insulin deficiency.

Another variable that was hypothesized to be a predicting factor for SIH was elevated HbA1c taken in the preoperative period. The preoperative HbA1C in the four SIH-positive patients were all above 6.5% which is considered in the diagnosable range of diabetes mellitus. Although these findings concur with what previous studies have predicted about elevated levels of HbA1c, these findings of HbA1c in this study did not

reach statistical significance. Higher HbA1c should continue to be closely examined in other studies as a potential predicting factor for SIH because HbA1c is a predicting factor for insulin resistance. As was discussed earlier, insulin resistance is a physiologically contributing factor to hyperglycemia developing in the body when the body enters a catabolic state due to the stress of surgery. Furthermore, since an HbA1c above 6.5% is considered diabetic level, this could further support the idea that diabetes mellitus is a strong potential predicting factor for SIH developing during an elective intracranial procedure. Since all four patients had a HbA1c above 6.5% but only 3 had preoperative diabetes mellitus diagnosis, this result suggests that the fourth patient possibly had undiagnosed diabetes mellitus preoperatively. Although our study did not find statistically significant evidence supporting HbA1c as a predicting factor for SIH, it provides information about a patient's glycemic homeostasis for clinicians and future studies to pay attention to in patients undergoing an elective intracranial surgery.

From previous studies which assessed intraoperative blood glucose levels, it was hypothesized that there would be four distinct groups of patients seen in the results. The first group was predicted to be composed of patients that did not experience a severe hyperglycemia episode during surgery. Observations of this clinical research aligned with this prediction, as the data showed evidence that most of the cohort, 36 patients or 90%, did not have SIH during their operation, as seen in Figure 4. The second group includes the patients who developed SIH and received insulin therapy which correlates to only 2 patients, or 5%, of this study's sample. The third group was hypothesized to contain the patients who also developed SIH but did not receive insulin therapy, which was found in

2, or another 5% of this study's sample. It is important to note that this was an observational study of "usual care" at BMC, meaning there was no intervention forced on anesthesia teams to take to treat hyperglycemia with insulin. This finding of 5% receiving insulin therapy supports the idea that SIH although very important, may not be appreciated by medical teams. The lack of consensus on what is defined as SIH and how to treat it may explain the confusion amongst medical care teams when it comes to treating elevated blood glucose levels. Finally, the last group that was predicted to appear in this study population were the patients with no blood glucose levels taken during their operation. These patients, n=4, were eliminated from the final cohort. All the groups predicted to be present in the study were confirmed by the results in this subject population.

Other parts of this study examined the intraoperative and postoperative factors between the patients with SIH and the patients without SIH and found no statistically significant variables. One intraoperative factor that was hypothesized to be a predicting factor for intraoperative hyperglycemia was the delivery of steroids during their surgery. Although not statistically significant, all four patients were given steroids. However, this study was not designed to examine if the steroids made the glycemic variability worse or contributed to the severe hyperglycemia. Another important factor about steroids is that they are given with the intention to reduce or prevent swelling. Since inflammation was described in previous studies as a predictor for stress hyperglycemia in surgery, the time at which steroids are administered for inflammation could be a warning factor for possible severe hyperglycemia.

On important purpose for investigating and identifying potential risk factors for severe hyperglycemia during an intracranial procedure was to verify findings from previous studies suggesting SIH to be a strong predicting factor for developing a postoperative infection. Although not the main purpose of this study, when postoperative factors for the four patients who did develop SIH were analyzed, none of the patients developed a postoperative infection within seven days of their surgery. However, these findings were not statistically significant, so no conclusion can be made from this raw data. This finding counters the previous statement that SIH is a predicting factor for postoperative infection. The lack of statistically significant findings about postoperative infection are possibly because most patients in the cohort, including all the SIH-positive patients, were given antibiotics during, and immediately following their surgery. Prophylactic administration of antibiotics most likely played a role in preventing these patients from developing a postoperative infection. Furthermore, it is possible that intra- and postoperative insulin therapy to control SIH in 5% of this study's sample may have contributed to preventing postoperative infections.

Regarding the length of stay, patients with SIH varied greatly in how long they stayed in the ICU and their length of stay in the hospital once they were transferred out of the ICU to continue recovery. Previous studies had predicted that SIH is associated with an increased hospital length of stay, leading to increased hospital care costs. Therefore, investigating whether SIH increases the length of hospital stay is inconclusive in our study since there is no statistically significant evidence regarding their length of stay. However, continuing to monitor severe hyperglycemia during an operation would not

hurt in ensuring length of stay can be reduced as much as possible to avoid increased hospital care and costs.

Section Two- Limitations

This study had many limitations, the biggest being the small sample size, owing to the low number of elective intracranial procedures scheduled at Boston Medical Center (BMC). Due to the high number of hospitals in the local area, the number of intracranial surgeries performed in Boston, Massachusetts is spread out across the city, resulting in the low number of elective intracranial procedures at BMC. For example, when research assistants were screening for eligible patients, they found about one intracranial surgery case per week. This limitation of the number of surgeries limited this study's pool of potential candidates, leading to the low number of patients that were recruited.

Another limitation of this study was the inconsistent protocol of collecting blood glucose concentrations during surgery. Although the attending anesthesiologist were informed about the enrollment of patients in the study, sometimes a patient's blood glucose readings were not taken, or not enough readings were recorded. This was one of the main reasons why 56 enrolled patients were excluded from the final data inclusion. This was a huge loss in the number of patients in our final data collection cohort. Furthermore, the times at which the blood glucose levels were recorded were not always consistent and in even intervals, which may not have affected the results of this study. This is an inherent weakness of observational studies, whereas prospective randomized trials offer a more controlled protocol, making results more generalizable and consistent. Therefore, the observational nature of this study was another limitation.

Section Three- Future Studies

For future studies, many changes can be made to provide better results to help clinicians and future patients more effectively. First, future studies need to ensure access to a high volume of elective intracranial neurosurgical procedures. This allows for a larger patient population available to pool from to make the study's sample. It turns out that the small patient sample in our study was a major limitation that greatly affected the results. Transsphenoidal craniotomies were excluded in this study because these surgeries usually are for removing pituitary tumors which secrete hormones. These craniotomies and pituitary tumors challenge the medical care team in managing blood glucose levels. However, perhaps these surgeries should be included in future studies because we can observe more cases of SIH or glycemic variability to develop treatment and prevention methods. Furthermore, there needs to be a more consistent system so that patients enrolled in the study consistently get three intraoperative blood glucose concentrations taken. For example, perhaps future studies at BMC can instruct medical care teams to use the perioperative glycemic management algorithm to have better results regarding the effectiveness of this glycemic management method. Furthermore, another future study should perform a randomized controlled trial to determine the appropriate insulin therapy for SIH.

It will be important to examine how the body responds to surgical stress and enters the catabolic state which potentiates intraoperative hyperglycemia and blood glucose variability. First, although this clinical research study did not consider blood glucose variability, since the results showed a small incidence of SIH perhaps future

studies should shift their focus from studying SIH to studying glycemic variability. Previous studies have suggested that glycemic variability may be more dangerous than severe hyperglycemia during an operation. Furthermore, future research into reducing the stress response or preventing the catabolic state the body enters during surgery can prove to be vital in preventing severe hyperglycemia from developing at all. There has been recent interest in the idea of preoperative carbohydrate loading and reducing the current preoperative fasting protocol which directs patients to not eat after midnight, or for > 8 hours prior to their operation. The ASA established these preoperative fasting guidelines to reduce the risk of patient aspiration during surgery. However, multiple studies found that if the patient is not at risk for aspiration and is given a carbohydrate loading drink up to 2 hours before their surgery, these patients were able to maintain normoglycemia during their surgery. Furthermore, preoperative carbohydrate pre-loading given up to 2 hours before their craniotomy led to better glucose homeostasis in patients and decreased their hospital length of stay (Liu et al., 2019). Since these results have been demonstrated in several studies, new enhanced recovery after surgery (ERAS) protocols suggests that prolonged fasting not only deprives the patient of nutrients and hydration but increases insulin resistance and further puts the body into a catabolic state which can cause SIH. The body enters a catabolic state when patients have not eaten because the body is starved for glucose which triggers a depletion in the storage of glucose and produces more glucose by the liver. Reducing patients' fasting time before their surgery or offering a carbohydrate loading drink 2 hours before surgery while still preventing aspiration may be an effective method for preventing severe hyperglycemia or glycemic variability

during intracranial procedures. Moreover, having eaten, the body is less likely to enter a catabolic state since the body will not be starved of glucose. This provides the body with enough glucose that it will not need to break down glucose storage or produce more glucose. Therefore, blood glucose levels can be held at a more stable, or normoglycemic, level and are less variable. Finally, a more stable blood glucose concentration upon entering surgery can reduce the likelihood of the patient experiencing SIH. A future study is needed to determine if preoperative carbohydrate loading in neurosurgical patients would reduce glycemic variability or SIH, thus reducing morbidity and mortality in this patient population.

Although HbA1c and diabetes mellitus factors in SIH patients were not statistically significant enough to be identified as predicting factors, future studies should consider these patient factors as potential predicting factors for SIH or glycemic variability and surgical infections after craniotomies. HbA1c indicates what the average blood glucose levels have been over a period of three months; therefore, if elevated can inform the patient's medical care team that this patient will be more susceptible to developing severe hyperglycemia. Furthermore, future studies researching HbA1c should require HbA1c to be measured at defined intervals while the patient is in the preoperative period so the medical care team can be better prepared. Similarly, diabetes mellitus can hint at a patient's pre-existing glycemic variability, insulin resistance, or deficiency. Therefore, future clinical studies and clinicians can use previously diagnosed diabetes mellitus to better prepare for glycemic variability or hyperglycemia, the potential need for insulin therapy, and increased risk for postoperative complications such as

postoperative infection. Although this study did not investigate the success of insulin therapy as a treatment option for SIH, future studies should focus on whether continuous insulin therapy combined with maintaining the blood glucose concentration in a moderate range is efficient in treating SIH while avoiding hypoglycemia. In addition to analyzing the effectiveness of insulin therapy, future studies should attempt to define a standard protocol for when and how much insulin to administer to patients depending on their blood glucose levels. This will result in obtaining more consistent findings on what is and is not effective in treating SIH.

Intraoperative steroid administration was one factor that previous studies had hypothesized to be a predicting factor for SIH. This clinical study did not find statistically significant evidence that steroid administration contributes to worsening SIH, but it is interesting that all four patients who developed SIH received steroids during their surgery. Future studies can find a way to assess if corticosteroids are linked to worsened hyperglycemia. This would only be able to be an observational study since withholding steroid treatment would be contraindicated in patients at risk for cerebral edema.

Although the findings in this study are limited, the study provides evidence on how to guide future clinical research studies to have a better understanding of glycemic control, insulin therapy, and most importantly, reduce the postoperative infections that can occur after intracranial procedures.

Section Four- Conclusion

Severe intraoperative hyperglycemia has been demonstrated to be a predicting factor for postoperative infections following neurosurgical procedures. Due to the many

complications associated with postoperative infections and SIH, including increased length of hospital stay, increase in medical costs and care, and increased morbidity and mortality, it is crucial to find methods to prevent both SIH and postoperative infections from occurring. This study aimed to identify the rate of SIH in the Boston Medical Center elective intracranial surgery population between May 2021 and October 2022, identify potential risk factors for SIH, and observe if those patients who developed SIH did continue to have a postoperative infection or have a lengthened hospital stay. This clinical research study found a 10% SIH rate in the patient cohort. Our study failed to confirm previously identified risk factors for SIH and an association between SIH and postoperative infections. Given all the patients with SIH received prophylactic antibiotics and two of the SIH-positive received insulin therapy, we suspect these interventions may significantly reduce the risk for postoperative infections despite pre-existing risk factors. Due to the small sample size, the rate this study found was lower than other studies had predicted. In the small sample of patients who underwent an elective intracranial surgery, no risk factors were identified to predict a patient's probability of developing severe hyperglycemia during their operation.

The low incidence of SIH at Boston Medical Center compared to previously published literature is possibly due to our small sample size. Future studies should continue to investigate ways to prevent SIH by identifying risk factors or focusing on establishing an acceptable protocol for treating SIH with therapies such as continuous insulin therapy.

The identification of severe intraoperative hyperglycemia risk factors for patients undergoing an elective intracranial procedure can reduce many postoperative complications like postoperative infections and improve patients' outcome. Therapy protocols should be developed to treat SIH or glycemic variability as it arises during surgery. More research projects should be conducted to measure the incidence of SIH and postoperative outcomes.

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CURRICULUM VITAE

