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The effects of hyperglycemia on outcomes in surgical high-grade glioma patients

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ABSTRACT

Objective: To define the glucose values associated with an increase in complication rates in post-operative brain tumor patients.

Patients and Methods: Patients who underwent craniotomy for resection of WHO Grade III or IV glioma from 2011 to 2014 were retrospectively reviewed. Post-operative blood glucose values were recorded for post-operative day #0, #1, and #2. Medians were obtained and assessed for significance. Multivariate analysis was performed to assess patient demographics, pre-operative findings, steroid use, and blood glucose values with respect to post-operative complications and to 30-day readmission.

Results: 108 patients underwent craniotomy for resection of high-grade glioma and had postoperative blood glucose values documented. Median blood glucose values greater than 167 mg/dL were associated with increased serious post-operative complications, and values greater than 163 mg/dL were associated with increased 30-day readmissions.

Conclusion: Post-operative hyperglycemia in patients with high-grade gliomas places this vulnerable patient population to undue post-operative complications and readmissions, potentially delaying further treatment of their disease.

1. Introduction

Due to the limited survival of patients with high grade glioma (HGG), reducing post-operative complications and need for re-hospitalization is critical to ensure optimal quality of life [1,2]. Elevated blood glucose and diabetes is a known risk factor for surgical complications and morality [3,4]. Patients presenting with acute ischemic stroke, subarachnoid hemorrhage, and traumatic brain injury all have worse outcomes such as worsening neurological function, increased nosocomial infections, and longer hospitalizations with inpatient hyperglycemia or diabetes [5–15]. Therefore, glucose control is now a reported quality metric for both the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Medicare and Medicaid Services (CMS) [16].

Expert recommendation for the upper limit of serum glucose varies based on acuity of care (140–180 mg/dL for critically ill patients and < 140 mg/dL for non-critically ill patients) [17]. In patients with glioblastoma (GBM) elevated blood glucose is associated with poorer neurologic outcomes and reduced survival [14,18]. However, the glucose value that predicts worsened outcomes and the association between hyperglycemia and reported quality metrics has not been described. Due to the importance of complication avoidance in the post-operative period, which can delay needed medical treatment for HGG patients, we aimed to assess the role of hyperglycemia in HGG patients undergoing surgical resection. The purpose of this study was to define the glucose values associated with an increase in complication rates in post-operative HGG patients so that treatment for hyperglycemia could be targeted to a goal glucose value.

2. Material and methods

2.1. Patient population

The institution's Institutional Review Board (IRB) approved this study. Electronic medical records of patients who underwent a craniotomy for resection of HHG at the institution from May 2011 to December 2014 were retrospectively reviewed. Information collected included patient sex, age at diagnosis, pre-operative presenting symptoms, pre-operative medical comorbidities, pre-operative anti-hyperglycemic agents, pre-operative calculated KPS, pre-operative MRI

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lesion enhancing volume, cerebral edema evident on MRI, tumor chemical-histopathological findings reviewed by institutional neuropathologist, and pre-operative and post-operative glucocorticoid administration. The post-operative hospitalization period was reviewed through a chart review of the electronic medical record to assess for the development of any of the following post-operative complications: seizure, respiratory failure, pneumonia, venous thromboembolism, urinary tract infection, and sepsis. These complications were categorized, defined, and graded based on the National Institutes of Health Common Terminology for Adverse Events Version 4.0 (CTCAE) based on the data obtained in the chart review that fit CTCAE criteria. A severe complication was labeled as a grade 3 or higher (on 1–5 scale) based on the CTCAE's definition of severe adverse event being defined as 3 or higher. Those with a severe complication were analyzed. In addition, institutional 30-day readmissions and reason for readmission for this patient population was obtained. Any immediate pre-operative blood glucose value and post-operative blood glucose values for post-operative day (POD) #0, #1, and #2 (in which POD #0 was documented as a patient fewer than 24 h out of surgery) were recorded and used for analysis. The first two post-operative days were chosen as a the time period as a proxy for the time in which hyperglycemia would expected to be most abnormal and difficult to control given the recent post-operative state and lower likelihood of adequate glucose control from any glycemic control agent.

2.2. Statistical analysis

Statistical analysis was performed by PK. To accommodate for a strong right-skewness of glucose values noted, glucose values were log-transformed. These values were then averaged at the patient level to estimate the median glucose for each patient during the first two post-operative days. Post-operative blood glucose and outcomes were assessed via two different methods. The first, considered mean post-operative log-glucose levels as a continuous linear predictor of the log-odds of having a particular outcome. This method estimated an odds ratio with 95% confidence intervals representing change in the outcome odds per doubling of a patient's median glucose level during the first two post-operative days.

The second method of evaluation, used ROC analysis to estimate the cutoff point for post-op median glucose levels that would yield the Youden Index value associated with the largest difference between true and false positive rates for a selected outcome. A bootstrap sampling of the original dataset (N = 2000 samples) was performed to generate empirical 95% bootstrap confidence intervals for the ROC performance characteristics achieved by the cutoff glucose value.

A logistic regression was performed using the cutoff value and various confounders to assess the odds of developing a severe post-operative complication or 30-day readmission based on those with a median blood glucose value above the cutoff values compared to those below the cutoff values. Because of the observational nature of our study, confounding of glucose effect estimates was a potential concern. We adjusted for confounding in our outcome models for severe complication and 30-day readmission. We fit logistic regression models for each individual confounder and estimated the percent change in the confounder-adjusted log-odds ratio for glucose relative to the corresponding unadjusted estimate, flagging confounders associated with a 10% or greater change in the adjusted estimate as confounders with significant influence.

3. Results

During the study period, 164 patients underwent craniotomy for surgical resection of a HGG with 108 patients having sufficient post-operative blood glucose monitoring. Out of these 108 patients, 47 were female and 61 were male with a median age of 60 years old (Table 1). Blood glucose values were obtained over the first 2 post-operative days and the average length of stay for the entire group was seven days (includes any pre-operative days). Over half were current or former smokers, and 85 were characterized as having GBM. Only 20% of patients had a pre-existing diagnosis of diabetes. Pre-operatively, approximately 74% of patients received steroid treatment and the median pre-operative blood glucose value was 117 mg/dL with a range of 71–255 mg/dL (3.94–14.15 mmol/L). Of the seventeen 30-day readmissions, two were wound complications, three were due to systemic infections, two were secondary to DVT or pulmonary emboli, three were secondary to seizures, and the remainder secondary to functional decline.

Table 1
Baseline characteristics of patients.

Age median (range)	60.50 (23-88)
Female n (%)	47 (43.52)
Diabetes n (%)	20 (18.52%)
CAD n (%)	14 (12.95%)
HTN n (%)	54 (50%)
Seizures n (%)	25 (23.15%)
Steroids n (%)	80 (74.07%)
Cerebral edema n (%)	68 (62.96%)
Recurrent n (%)	12 (11.11%)
GBM n (%)	85 (78.70%)
Preop glucose median (range) mg/dL	117.50 (71-255)
Preop tumor enhancing volume median (range) mm3	41.73 (1.60-218.0)

CAD = coronary artery disease; HTN = hypertension; preop = preoperative; KPS = karnofsky performance scale.

A Wilcoxon rank sum test was performed to assess the distribution of median glucose values compared to pre-operative comorbidities (Table 2). Diabetes (p-value < 0.01), hyperlipidemia (p-value < 0.01), and pre-operative glucose average (p-value < 0.01) were significant pre-operative comorbidities associated with a higher distribution of median postoperative blood glucose values. Pre-operative and post-operative steroid use were not independently associated with significant changes in median post-operative blood glucose values, while increasing age trended towards higher values.

Log-odds ratios were determined in having an outcome based on median post-operative blood glucose values when evaluated in a continuous linear value (Table 3). Having a severe complication was associated with significant odds ratio as median blood glucose values increased (10.147); specifically having a post-operative seizure (8.259). In addition, having any 30-day readmission was associated with significant odds ratio with increasing median glucose values (25.679).

To determine the glucose threshold for having an outcome, a receiver operating characteristic curve using Youden's Index was performed. Two outcomes were analyzed: those who developed a severe complication and those who had a 30-day readmission (Table 4). The median blood glucose cutoff values for each analysis was 167, and 163 mg/dL (9.27 and 9.05 mmol/L) respectively.

Next, the 167 mg/dL cutoff was used to evaluate frequency in pre-operative risk factors and severe post-operative complications. Patients with diabetes, hyperlipidemia and higher preoperative blood glucose values were more likely to have median post-operative blood glucose values above 167 mg/dL (Table 5), mirroring the results from analyzing median blood glucose values shown in Table 2. Patients with a median post-operative blood glucose above 167 mg/dL were more likely to have a severe complication (p = .0039), readmitted with serious complication (.0002), have postoperative seizures (p = 0.0458), to have a readmission within 30 days (p = 0.0004) or to die within 30 days (p = 0.0087) (Table 6).

Odds ratios were calculated for developing a severe post-operative complication using the median cutoff blood glucose value of 167 mg/dL. The unadjusted log odds ratio of developing a severe post-operative complication for those with a median blood glucose value greater than 167 mg/dL was 2.08 (p = 0.0001) (Table 7). Individual variable confounder adjustments were performed to avoid overfitting of data. Pre-

Table 2
Comparison of distribution of median glucose values between groups defined by baseline variables.

Variable	Group	Number (n)	Median Blood Glucose (mg/dL)	p Value
Gender	Female	47	136.66	0.8047
	Male	61	137.84	
Coronary Artery Disease	Not Present	94	136.98	0.2574
	Present	14	145.77	
Hypertension	Not Present	54	137.57	0.7246
	Present	54	112.08	
Diabetes	Not Present	88	135.60	*< 0.0001*
	Present	20	203.98	
History of Smoking	Not Present	65	137.84	0.8217
	Present	43	137.29	
Hyperlipidemia	Not Present	71	135.74	*0.0055*
	Present	37	152.95	
Pre-Op Seizure	Not Present	83	136.63	0.8787
	Present	25	138.32	
Pre-Op Steroid Administration	Not Present	28	136.64	0.3772
	Present	80	137.57	
Cerebral Edema	Not Present	40	138.28	0.6731
	Present	68	136.64	
Post-Op Steroid Administration	Not Present	5	135.32	0.4315
	Present	103	137.84	
Pre-operative Glucose Value as a Continuous Variable		108	117.5	*< 0.0001*
Age as a Continuous Variable		108	60.50	0.0604
Pre-operative KPS as a Continuous Variable		108	80.00	.7709
Pre-operative Enhancing Tumor Volume as a Continuous Variable		108	41.73	0.8282

Table 3
Change in Odds of Outcome per Doubling of Median Glucose in Postoperative Period.

Outcome	Odds Ratio	p value
Complication	10.147	*.0039*
Post-Op Respiratory Failure	.390	.6400
Seizure	8.259	*0.0458*
Pneumonia	8.968	.2338
Fever	.663	.8038
Sepsis	.057	.4152
Return to the OR	.062	.3278
30 day mortality	12.479	.1196
30 day readmission	25.679	*.0004*
Complication or Mortality	10.618	*.0034*

operative blood glucose contributed to the greatest percentage change in the log odds ratio (-16.7% change). Even with this confounder adjustment, median blood glucose values of greater than 167 mg/dL in the postoperative period were associated with an increased risk of complication. Similarly, the unadjusted log odds ratio of having a readmission within 30 days of surgery for a HGG was 2.25 in patients with a median blood glucose value greater than 163 mg/dL ($p = 0.0001$) (Table 8). Again, individual confounder adjustments were made to avoid overfitting. Pre-operative glucose values and having a history of hyperlipidemia led to having the largest impact on the log odds ratio adjustment (12.2% and -14.7% respectively).

4. Discussion

In this study, we investigated the association between severe post-operative complications, mortalities, and 30-day readmissions with post-operative hyperglycemia. We found that a median post-operative blood glucose value above 167.0 mg/dL (9.27 mmol/L) or higher was associated with an increase in rates of severe post-operative complication risk and a median post-operative blood glucose value above 163.0 mg/dL (9.05 mmol/L) was associated with an increase of 30-day readmission. Of the complications investigated, those who had a post-operative seizure, 30-day readmission, or 30-day mortality were statistically more likely to have a median post-operative blood glucose greater than 167 mg/dL.

The association with a patient having a pre-operative diagnosis of diabetes and hyperlipidemia leading to increased risk for post-operative hyperglycemia is consistent disorders with metabolic homeostasis.

Table 5
Comparison of baseline categorical variable proportions between groups defined by the 167 mg/dL blood glucose cutoff.

Variable	Frequency (n)		p Value
	Median Blood Glucose < = 167 mg/dL	Median Blood Glucose > 167 mg/dL	
Gender (Male)	50	11	.8070
Coronary Artery Disease	10	4	.4669
Hypertension	41	13	.2223
Diabetes	6	14	*< 0.0001*
History of Smoking	34	9	.7517
Hyperlipidemia	24	13	*0.0037*
Pre-Op Seizure	21	4	.7767
Pre-Op Steroid Administration	63	17	.4110
Cerebral Edema	56	12	.5412
Post-Op Steroid Administration	82	21	.5807
Pre-Op Blood Glucose Value	87	21	*< 0.0001*
Pre-Op KPS	87	21	0.7024

Table 4
Receiver Operating Characteristic for Glucose Cutoff for Risk of Serious Postoperative Complication or Readmission.

Outcome	Prevalence (%)	Area Under Curve	Glucose Cutoff Point, mg/dL (95% Confidence Interval)
Complication	19.44	.654	167 (135-197)
30-Day Readmission	14.82	.771	163 (132-197)

Table 6
Comparison of outcome proportions between groups defined by a 167 mg/dl cutoff.

Variable	Frequency (n)		p Value
	Average Glucose < = 167 mg/dL	Average Glucose > 167 mg/dL	
Complication	11	11	*0.0002*
Post-operative Respiratory Failure	3	2	.2492
Seizure	5	5	*.0229*
Pneumonia	1	1	.3525
Fever	6	2	.6514
Sepsis	2	0	1.000
Return to OR	3	0	1.000
30-Day Mortality	0	3	*0.0065*
30-Day Readmission	7	9	*.0004*
Complication or Mortality	10	12	*< .0001*

Table 7
Risk of Serious Complication in Patients with Median Postoperative Blood Glucose > 167 mg/dL versus < = 167 mg/dL.

Confounder Adjustment	Log Odds Ratio	Log OR Adjustment Change (%)	p Value
Unadjusted	2.0897	N/A	0.0001
Age	1.9200	−8.1	0.0007
Gender (Male)	2.0706	−.9	.00002
Coronary Artery Disease	2.0709	−.9	0.0002
Hypertension	2.0840	−.3	0.0002
Diabetes	2.0443	−2.2	0.0038
History of Smoking	2.1465	2.7	0.0001
Hyperlipidemia	1.9252	−7.9	0.0007
Pre-Op Seizure	2.1151	1.2	0.0001
Pre-Op Steroid Administration	2.0450	−2.1	0.0002
Cerebral Edema	2.0513	−1.8	0.0002
Post-Op Steroid Administration	2.0323	−3.2	0.0002
Pre-Op Blood Glucose Value	1.7401	−16.7	*0.0042*

Table 8
Risk of 30 day Readmission in Patients with Median Postoperative Blood Glucose > 163 mg/dL versus < = 163 mg/dL.

Confounder Adjustment	Log Odds Ratio	Log OR Adjustment Change (%)	p Value
Unadjusted	2.2525	N/A	0.0001
Age	2.2175	−1.6	0.0004
Gender (Male)	2.2648	.5	0.0001
Coronary Artery Disease	2.2077	−2.0	0.0002
Hypertension	2.1777	−3.3	0.0002
Diabetes	2.1811	−3.2	0.0034
History of Smoking	2.2377	−.7	0.0001
Hyperlipidemia	1.9208	−14.7	*0.0016*
Pre-Op Seizure	2.3329	3.6	0.0001
Pre-Op Steroid Administration	2.2028	−2.2	0.0002
Cerebral Edema	2.1793	−3.2	0.0002
Post-Op Steroid Administration	2.1875	−2.9	0.0002
Pre-Op Blood Glucose Value	2.5275	12.2	*0.0003*

Those with an elevated pre-operative blood glucose value having higher likelihood of post-operative blood glucose values also suggests underlying metabolic derangement. Both points suggesting a way to pre-operatively identify those more at risk of hyperglycemia in the post-operative period.

The cutoff value results in this study are consistent with recommendations of inpatient blood glucose control values of 140–180 mg/dL for critically ill patients and less than 140 mg/dL for non-critically ill patients [17]. Hyperglycemia as a clinical predictor of post-operative morbidity has been echoed in other studies examining patients with malignant glioma in other clinical settings. Link et. al. demonstrated that patients with GBM and persistent hyperglycemia (defined as a blood glucose value > 160 mg/dL) had worse post-operative function and were more likely to require inpatient rehabilitation [14]. McGirt et al. demonstrated that persistent hyperglycemia in the outpatient setting (chosen as blood glucose > 180 mg/dL in three or more occurrences as an outpatient) led to decreased survival in patients undergoing craniotomy for resection of HGG [19]. Derr et al. also demonstrated decreased survival in patients with persistent hyperglycemia in the outpatient setting in patients with HHG irrespective of KPS [18]. These patients were placed within quartiles, with patients with BG > 137 mg/dL assigned to the last quartile and having the highest hazard ratio associated with survival.

The risk of hyperglycemia with administration of dexamethasone and physiological response due to hospitalization and surgery. Patients with HGG are often prescribed high-dose dexamethasone for symptomatic relief, and as prescribers, management of its significant side-effect of hyperglycemia should also be considered. However, management of hyperglycemia in brain tumor patients on dexamethasone is often complex due to the decreasing dose of the steroid after surgery and is quite commonly performed using a sliding-scale insulin dose to respond to hyperglycemia rather than pre-emptively control hyperglycemia. A University Health System Consortium survey revealed that 38% of Type I and Type II inpatient diabetics had persistent hyperglycemia (> 200 mg/dl) while inpatient despite treatment with a sliding scale correctional insulin protocol [6]. Therefore, sliding scale insulin is not enough. Formal endocrine recommendations describe the need to continue hypoglycemic medications from home. For patients who are kept fasting or have limited oral intake (which can be frequently seen in post-operative neurosurgical patient), subcutaneous or intravenous insulin is recommended [5,6]. For this population and for those with hyperglycemia and who were not on glycemic control medications pre-operatively, a weight-based basal bolus with prandial correctional insulin is recommended. A long-acting agent such as glargine should be given 0.4-0.5 units per day per kilogram and short-acting insulin should be used prior to meals. This approach has demonstrated better glycemic control without increased hypoglycemic events [20]. However, applying these recommendations to patients on a dexamethasone taper may be challenging.

The data from this study have important patient safety and quality implications. Quality and patient outcome metrics such as inpatient blood glucose control, post-operative complications, mortality, and readmission rates are routinely collected to determine quality of healthcare systems, hospital system ratings, reimbursement and potential financial penalizations. The Centers for Medicare and Medicaid Services has projects partnering with the National Quality Forum for measuring diabetic patients with hyperglycemia (defined as > 200 mg/dL) and severe hypoglycemia (defined as < 40 mg/dL) [21]. Therefore, it is not unreasonable to predict that, in the future, poor inpatient blood glucose control for any patient could significantly effect a hospital's accreditation, medical payments, or quality metric ranking.

The weaknesses of this study include its retrospective design. This may introduce selection bias and prevents a more long-term blood glucose analysis in post-operative patients. These data are being used to achieve better post-operative blood glucose control in surgical brain tumor patients at the institution. Proper blood glucose control in this patient population is vital, as having a post-operative complication or readmission will lead to delay in further treatment of a patient's glioma.

5. Conclusions

This study demonstrates that persistent hyperglycemia with median blood glucose values greater than 167 mg/dL (9.27 mmol/L) within the

post-operative period is associated with increased post-operative complications and a median blood glucose greater than 163 mg/dL (9.05 mmol/L) is associated with increased 30-day hospital readmission. Recognition of hyperglycemia is important to patient outcomes as indicated in this study and is substantiated by the findings of several other studies. Therefore, optimizing blood glucose during the surgical period should be of the utmost important to patients and physicians in order to maximize outcomes and minimize post-operative complications. Further studies which explore the efficacy and feasibility of possible blood glucose management strategies would help health care teams determine how to best care for patients following surgery.

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