Acta Neurochirurgica (2023) 165:1031–1040
https://doi.org/10.1007/s00701-023-05541-6

ORIGINAL ARTICLE - TUMOR - GLIOMA

Characterization of perioperative glycemic status and dexamethasone use with associated postoperative complications in glioblastoma patients

Sukhdeep Jatana[1] · Amro H. Mohammad[1] · Tariq D. Al-Saadi[1,2] · Mathew Carias[1,3] · Natalia Guevara-Moriones[4,5] · Miguel Angel Ruiz-Barrera[4,6] · Cristina S. Mindru[1,2] · Roberto Jose Diaz[1,2,7]

Received: 22 December 2022 / Accepted: 21 February 2023 / Published online: 6 March 2023

Abstract

Purpose Postoperative morbidity in glioblastoma (GBM) patients can be due to the disease course but can also come from postoperative complications. Our objective was to study the association of dexamethasone use and perioperative hyperglycemia with postoperative complications in GBM patients.

Methods A single-center, retrospective cohort study was conducted in patients who underwent surgery for primary GBM from 2014–2018. Patients with perioperative fasting blood glucose (FBG) measurements and adequate follow-up to assess for complications were included.

Results A total of 199 patients were included. More than half (53%) had poor perioperative glycemic control (FBG ≥ 7 mM for ≥ 20% perioperative days). Higher dexamethasone dose (≥ 8 mg) was associated with higher FBG on postoperative days 2–4 and 5 ($p = 0.02,0.05,0.004,0.02$, respectively). Poor glycemic control was associated with increased odds of 30-day any complication and 30-day infection on univariate analysis (UVA), and 30-day any complication and increased length of stay (LOS) on multivariate analysis (MVA). Higher average perioperative daily dexamethasone dose was associated with increased odds of 30-day any complication and 30-day infection on MVA. Elevated hemoglobin A1c (HgbA1c, ≥ 6.5%) was associated with increased odds of 30-day any complication, 30-day infection, and LOS on UVA. In a multivariate linear regression model, only the diagnosis of diabetes mellitus predicted perioperative hyperglycemia.

Conclusions Perioperative hyperglycemia, higher average dexamethasone use and elevated preoperative HgbA1c are associated with increased risk of postoperative complications in GBM patients. Avoiding hyperglycemia and limiting dexamethasone use in postoperative period may decrease the risk of complications. Select HgbA1c screening may allow the identification of a group of patients at higher risk of complications.

Keywords Dexamethasone · Glioblastoma · Glycemic control · Perioperative care · Postoperative complications

This article is part of the Topical Collection on *Tumor – Glioma*

✉ Roberto Jose Diaz
roberto.diaz@mcgill.ca

[1] Faculty of Medicine, McGill University, Montreal, Canada

[2] Department of Neurology and Neurosurgery, Montreal Neurological Institute - McGill University Health Centre, Montreal, Canada

[3] Department of Diagnostic Radiology, McGill University, Montreal, Canada

[4] Neuro-Oncology Research Group, National Institute of Cancer, Bogotá, Colombia

[5] Juan N. Corpas University Foundation, Bogotá, Colombia

[6] Department of Neurosurgery, National Institute of Cancer, Bogotá, Colombia

[7] Neurosurgical Oncology, Department of Neurology and Neurosurgery, Montreal Neurological Hospital - McGill University Health Centre, Montreal, Canada

Introduction

Glioblastoma (GBM) is the most aggressive primary brain malignancy in adults. Despite standard-of-care therapy, which consists of surgical resection, radiotherapy, and temozolomide chemotherapy, less than half of patients survive for 2 years. [12] The high morbidity experienced by patients undergoing surgical treatment of GBM can be attributed to the disease course [11]; neurological sequela of surgical resection [26]; side effects of adjuvant therapy [2]; and complications resulting from dexamethasone use [22].

Dexamethasone is commonly used in the management of GBM patients to control cerebral edema before and after surgery [16]. Nonetheless, dexamethasone use is associated with glucocorticoid-induced hyperglycemia and diabetes [30], and its chronic use may increase thrombosis risk in neurosurgical patients [17]. Furthermore, one study linked dexamethasone use in GBM patients to an increased risk of infection [22]. Perioperative hyperglycemia is independently associated with increased risk of venous thromboembolic events in breast and gastrointestinal cancers [6, 9]. Additionally, perioperative hyperglycemia has been linked to immune system dysfunction by causing lymphopenia [34] and other unfavorable innate immune system downstream effects [14]. GBM patients are at a heightened risk for perioperative hyperglycemia given the use of dexamethasone [7] and the physiological stress response induced by surgery [25]. To date, only two studies assessed the risk for perioperative hyperglycemia on postoperative complications in GBM patients [4, 19].

Although the prognostic burden of perioperative [10] and long-term postoperative hyperglycemia [20] in GBM patients was examined, a few studies [4, 19] reported on complications resulting from dexamethasone-induced hyperglycemia. We first assessed the relationship between dexamethasone use and hyperglycemia in the perioperative period for patients undergoing first surgery for GBM. We then examined the impact of perioperative hyperglycemia and dexamethasone use on postoperative complications, such as infection and thrombosis. Furthermore, we sought to create a regression model to identify clinical risk factors for the development of perioperative hyperglycemia.

Methods

Patient selection This study was approved by the McGill University Health Centre Research Ethics Board Neuroscience and Psychiatry Panel (study number 2021–7322) in lieu of individual patient consent given the retrospective nature of the study. Patients who were diagnosed with primary GBM and underwent surgical intervention at the Montreal Neurological Hospital (MNH) between 2014 and 2018 were included. Patients who had a previous grade II or III glioma, had an isocitrate dehydrogenase 1 gene mutation, had coexistent malignancy, did not receive their first tumor resection at our institution, had a biopsy only, had a biopsy outside our institution more than 3 months prior to presenting for resection, or did not receive follow-up at our institution were excluded from our study. Patients were followed up to 2 years after the initial diagnosis.

Standard of perioperative medical care Dexamethasone was usually started prior to or at the time of arrival to hospital. Point-of-care testing was used to monitor blood glucose. For patients with a pre-existing type 2 diabetes mellitus (T2DM) diagnosis or elevated blood glucose, an insulin sliding scale was used with or without metformin. Pre-operative anti-hyperglycemic medication was re-started once the patient was eating well after surgery. Patients underwent magnetic resonance imaging (MRI) prior to surgical resection via craniotomy. Sequential compression devices were used in all patients during surgery and postoperatively until prophylactic anticoagulation was started. Prophylactic anticoagulation was started once neuroimaging confirmed the absence of a hemorrhagic complication. Dexamethasone was tapered according to the degree of postoperative edema and duration of use, with variable regimens depending on surgeon preference.

Data collection Data was collected from the electronic medical record system, which included the following about demographics and tumor characteristics: age at diagnosis, gender, BMI, tumor O [6]-methylguanine-DNA methyltransferase (MGMT)-promoter methylation status, tumor isocitrate dehydrogenase 1 gene (IDH1) mutation status, and KPS [24] at presentation. Information collected about treatment included extent of surgery (dichotomized to biopsy only or subtotal resection and near- or gross total resection) and adjuvant therapy. Postoperative outcome data included duration of hospital stay (from time of surgery until discharge or death, if death during operative stay), all postoperative complications up to 30 days after surgery, death, thrombotic and infectious complications. Additionally, we collected data about perioperative dexamethasone and insulin dosing, presence of pre-operative T2DM and medication regimen, metformin use pre- or post-operation, pre-operative hemoglobin A1c (from 3 months prior up to 2 weeks after surgery), and perioperative FBG (if FBG measurement is unavailable pre-operative day 1, FBG up to pre-operative day 7 was adopted; if no perioperative FBG measurement is available, random FBG measurement was used as a surrogate if there is a value below 7 and the patient was not on anti-hyperglycemic medications as this would signify adequate blood glucose control).

For patients who underwent biopsy followed by resection, the FBG, dexamethasone dosing, and insulin data were collected at time of resection; for patients with multiple resections for margins, this data was collected at time of the first resection. For our study, "good" perioperative glycemic control was defined as having FBG ≥ 7 mM for ≤ 20% of perioperative days while "poor" control as FBG > 20% of perioperative days. The threshold 7 mM was chosen as that is the threshold recommended for the diagnosis of diabetes mellitus according to various guidelines [1, 5]. The average dexamethasone dose during perioperative period was used for statistical analyses.

Residual tumor volume measurement Total residual tumor volume was measured in all patients who had a partial resection as reported in the imaging or physician report. All volumes were calculated from a post-operative MRI that was obtained within 2 days of the operation. Patients who underwent a partial resection but did not have a post-operative MRI ($n = 3$), had poor quality images due to movement ($n = 2$), or who were allergic to gadolinium ($n = 1$) did not have post-operative volumes measured. Similar methods were used as previously described to measure residual tumor volumes [8]. The volumes were measured by 3 individuals: a medical student, radiology resident, and a senior neurosurgeon attending who were blinded to the outcomes of each patient. All volumes were measure on T1-weighted post-gadolinium axial sequences on either 1.5-T or 3.0-T scanners. Three-dimensional reconstructions were then obtained, and volumetric region of interests were manually chosen in each slice. The region of interest chosen was defined as the gadolinium contrast enhancing hyperintense area in the volume of interest, that being in the surgical resection area. As previously described [8], care was taken to not include hyperintense blood or post-operative blood products as part of the residual tumor volume. Pre-operative T1-weighted post-gadolinium images aided the 3-users in selecting only residual tumor volume. It should also be noted that patients who had multifocal disease, the definition of residual tumor volume also included tumors that were not resected.

Statistical analysis Statistical analysis was completed with R, version 4.0.0 (Foundation for Statistical Computing) and IBM SPSS Statistics for Macintosh, version 28.0.0.0 (IBM Corp., Armonk, N.Y. USA). Categorical variables were compared with odds ratios and Chi Square *p*-values. Continuous variables were compared with independent two sample t-test and Mann–Whitney U test, where appropriate, and non-parametric variables were determined using Kolmogorov–Smirnov. Multivariate odds ratios were calculated using multinomial logistic regression. Survival analysis was done with Kaplan–Meier curves with log-rank test for univariate analysis. Simple linear regression was used to test risk factors that significantly predicted perioperative hyperglycemia. Variables with $P \leq 0.2$ were used for the final multivariate linear regression model for predicting perioperative hyperglycemia. Values are presented as mean ± SD or median ± interquartile range (IQR) unless stated otherwise. All multivariate models for odds ratio account for BMI, age, KPS at presentation, extent of resection, average daily dexamethasone use, and diabetes mellitus diagnosis pre-operatively. Hemoglobin A1c was not considered for any multivariate analysis as it was only available for limited number of patients. P-value < 0.05 was considered significant. Data analysis was partly performed by a hired statistician including the multivariate linear regression model and all analyses were reviewed by a senior author with statistical background (MARB).

Results

Study patients There were 441 patients who underwent biopsy or surgical resection of GBM at the MNH between 2014–2018, of which 199 patients were included in this study. Flow diagram of included patients is available in Supplementary Fig. 1. Study participants had a mean age of diagnosis of 63.1 ± 11.1 years, 40.2% were female, and the median presentation KPS was 80 ± 30 (range 90). MGMT promoter methylation was observed in 39.6% of tumors. For patients diagnosed with T2DM pre-operatively (15.7%), 28.6% were on metformin monotherapy, 46.4% were on combination of anti-hyperglycemic medications excluding insulin, and 21.4% were on insulin with or without additional agents. Median pre-operative hemoglobin A1c was 6.4% ± 1.3 ($n = 47$, 23.6%). Most patients had appropriate follow-up to identify any complication, infection, and thrombosis by 30 days (98.5% for each). Patient characteristics are available in Table 1. Median overall survival for patients was 401 days and was longer for those with MGMT promoter methylated tumors (median 597 days vs. 326 days, log rank $P < 0.001$). Survival curves are available in Supplementary Fig. 2.

Perioperative hyperglycemia and high-dose dexamethasone use The average daily perioperative dexamethasone dose ranged from 8.8 to 15.3 mg, with the highest usage on postoperative day (POD) 1 of 15.3 ± 4.3 mg (Fig. 1A). Average perioperative FBG measurements ranged from 7.0 to 7.7 mM (Fig. 1B). POD 3 had the highest average FBG of 7.7 ± 2.8 mM (Fig. 1B) and POD 2 had the highest percentage (53.4%) of patients with FBG values ≥ 7.0 mM (Fig. 1C). Approximately half of patients (53%) were noted to have FBG ≥ 7.0 mM for more than 20% of perioperative days (Fig. 1D). Patients receiving high dexamethasone doses (≥ 8 mg per day) tended to have higher FBG measurements

Table 1 Characteristics of patient cohort

Patient Characteristics	All patients ($n=199$) N (%), unless otherwise stated
Age at diagnosis (mean ± SD)	63 ± 11
Gender (% female)	40.2
BMI (mean ± SD) ($n=187$)	26.5 ± 5.3
Tumor MGMT promoter methylation ($n=192$)	76 (39.6%)
KPS score at presentation	
80–100	107 (53.8%)
50–70	78 (39.2%)
0–40	14 (7.0%)
Surgery type	
Partial resection (including subtotal and near-gross total)	85 (42.7%)
Complete resection	114 (57.3%)
Patients having biopsy prior to resection	12 (6.0%)
Residual tumor volume (mean cm^3 ± SD) ($n=193$)	0.67 ± 3.17
Adjuvant therapy received	
Adjuvant chemotherapy only	9 (4.5%)
Adjuvant radiotherapy only	12 (6.0%)
Adjuvant chemo- and radiotherapy	164 (82.4%)
None	14 (7.0%)
Diagnosis of T2DM ($n=198$)	31 (15.7%)
Metformin monotherapy ($n=28$)	8 (28.6%)
Sulfonylurea monotherapy ($n=28$)	1 (3.6%)
Combination of agents, no insulin ($n=28$)	13 (46.4%)
Insulin therapy with or without other medications ($n=28$)	6 (21.4%)
HbA1c pre-operatively (median ± IQR) ($n=58$)	6.4 ± 1.3

BMI body mass index; *HbA1c* hemoglobin A1c; *KPS* Karnofsky Performance Scale; *IQR* interquartile range; *MGMT* O [6] -methylguanine-DNA methyltransferase;*T2DM* type 2 diabetes mellitus

the following day (Fig. 2) and this was most prominent on POD 2 – 6 ($P=0.02$, 0.05, 0.004, 0.02, 0.11, respectively).

Complication rate The following complications were observed within 30 days of surgery: infection, venous thromboembolism, death, hemorrhage, seizure, thrombocytopenia, hydrocephalus, pneumocephalus, stroke secondary to vasospasm, elevated intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, re-intubation, coma/unresponsiveness, cerebrospinal fluid leak, heart failure exacerbation leading to renal failure, myocardial infarction, and upper gastrointestinal bleed. A total of 30.6% (60/196) patients had postoperative complications by day 30 (Supplemental Table 1). Thromboembolic events occurred in 3.6% (7/197) by 30 days and included deep vein thrombosis ($n=4$), pulmonary embolism ($n=1$), embolic stroke ($n=1$) and superficial thrombophlebitis ($n=1$). Infection occurred in 13.2% (26/197) of patients by 30 days. These infectious events included wound infection at surgical site ($n=3$), respiratory infection ($n=8$), urinary tract infection ($n=12$), and CNS infection ($n=3$) (Supplemental Table 2).

Association of perioperative dexamethasone use with postoperative complications On multivariate analysis, higher daily average dexamethasone use during the perioperative period was associated with increased odds for any postoperative complications by 30 days (aOR 1.21, $P=0.002$) and infection at 30 days (aOR 1.28, $p=0.004$). There was a near-significant association between high average dexamethasone use and thrombosis at 30 days (aOR 1.34, $P=0.072$) or LOS (Coefficient, β Unstandardized ± SE 0.04 ± 0.64, $P=0.948$) (Table 2). These associations were independent of age, KPS, residual tumor volume, and BMI. The odds ratios of other variables included in the multivariate analysis on outcomes are available in Supplemental Table 3.

Association of perioperative hyperglycemia with postoperative outcomes Patients with poor perioperative glycemic control

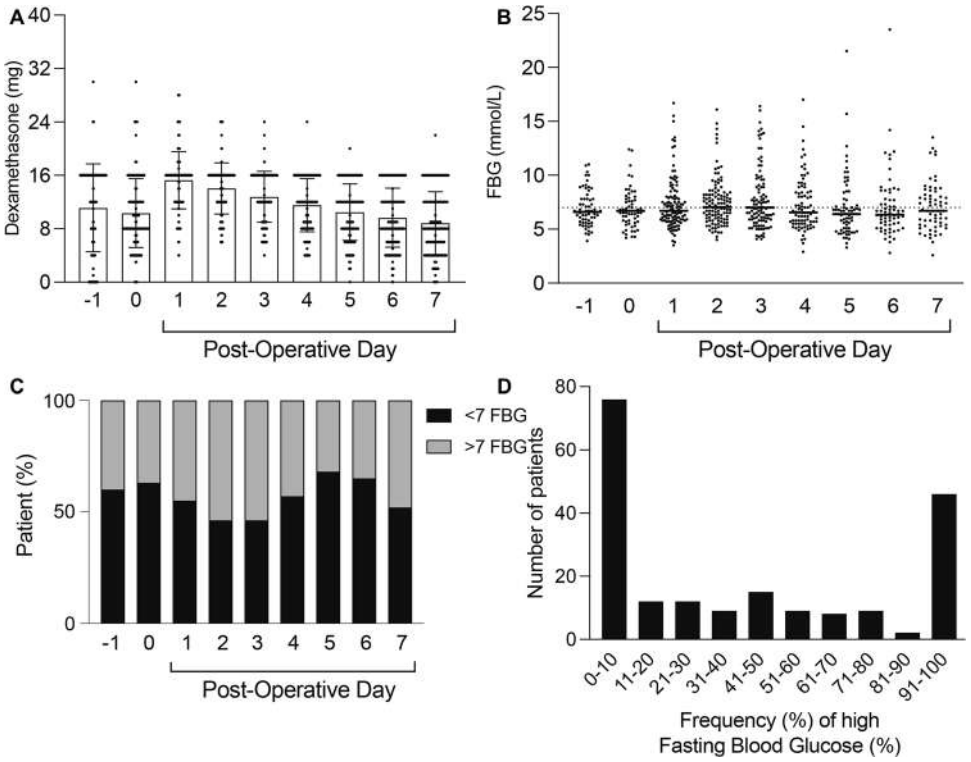

Fig. 1 Distribution of perioperative FBG measurements and dexamethasone use. **a** Perioperative dexamethasone daily dose. Individual data points represent dexamethasone dose received by individuals on the respective days and the bar graph represents average dose. **b** Perioperative FBG. Pre-operative day 2–7 (not shown here) $n=38$, pre-operative 1, $n=65$; POD0, $n=64$, POD1, $n=115$; POD2, $n=116$; POD3, $n=109$; POD4, $n=84$; POD5, $n=73$; POD6, $n=64$; POD7, $n=63$. Dashed horizontal line indicates FBG level of 7.0 mM. Lines indicate the mean and the SD on different days. **c** Proportion of patients with high (≥7 mM) and low (<7) FBG measurements. This figure is generated from the population data in Fig. 1B and displayed to represent trends in hyperglycemia. **d** Distribution of patients based on % of perioperative days with high fasting blood glucose (FBG) measurements, $n=199$. Abbreviations: FBG, fasting blood glucose; POD, postoperative day

had higher odds of 30-day complications on univariate analysis (odds ratio (OR) 2.61, 95% CI 1.35–5.01, $p=0.004$) and multivariate analysis (adjusted OR (aOR) 4.41, 95% CI 1.89—10.27, $p<0.001$) (Table 2). Poor perioperative glycemic control did not increase the odds of thrombotic events at 30 days on univariate (OR 1.04, $P=0.956$) or multivariate analysis (aOR 2.55, $P=0.365$) (Table 2). Poor perioperative glycemic control was associated with increased infectious event at 30 days on univariate analysis but did not reach statistical significance (OR 2.33, $P=0.065$); this was similar for multivariate analysis (aOR 2.69, $P=0.102$) (Table 2). Mean hospital length of stay (LOS) was not increased in patients with poor perioperative glycemic control on univariate analysis (17.2 days, standard error (SE) 3.5 vs. 11.7 days, SE 1.7, $P=0.566$) but was longer on multivariate analysis (11.3 days longer, $P=0.012$) (Table 2).

Predicting perioperative hyperglycemia Risk factors that predicted perioperative hyperglycemia ($P\leq0.2$) in a simple linear regression and were included in our final model are age ($P=0.113$), and diabetes diagnosis ($P<0.001$) (Table 3). For the multivariate linear regression model, only a diabetes diagnosis significantly predicted perioperative hyperglycemia (β, unstandardized = 21.212, $P<0.001$) (Table 3). The residual variance of the linear regression model via ANOVA sum of squares is 84.6% of total variance (267,814.601 of 316,609.508).

Association of pre-operative A1c with postoperative outcomes Pre-operative A1c was only available for 47 patients, of which 29 (61.7%) had good glycemic control and 18 (38.3%) had poor control. On univariate analysis an elevated hemoglobin A1c (≥6.5%) associates with significantly higher odds of all postoperative complications by 30 days (OR 5.56, $P=0.013$), infection at 30 days (OR 11.7, $P=0.012$) and LOS (24.1 days vs. 9.1 days, $P=0.027$) (Table 4). Neither group had a thrombotic event by 30 days.

Discussion

In this cohort of 199 patients undergoing first surgery for GBM, we observed that poor glycemic control and higher average daily dexamethasone use were associated with

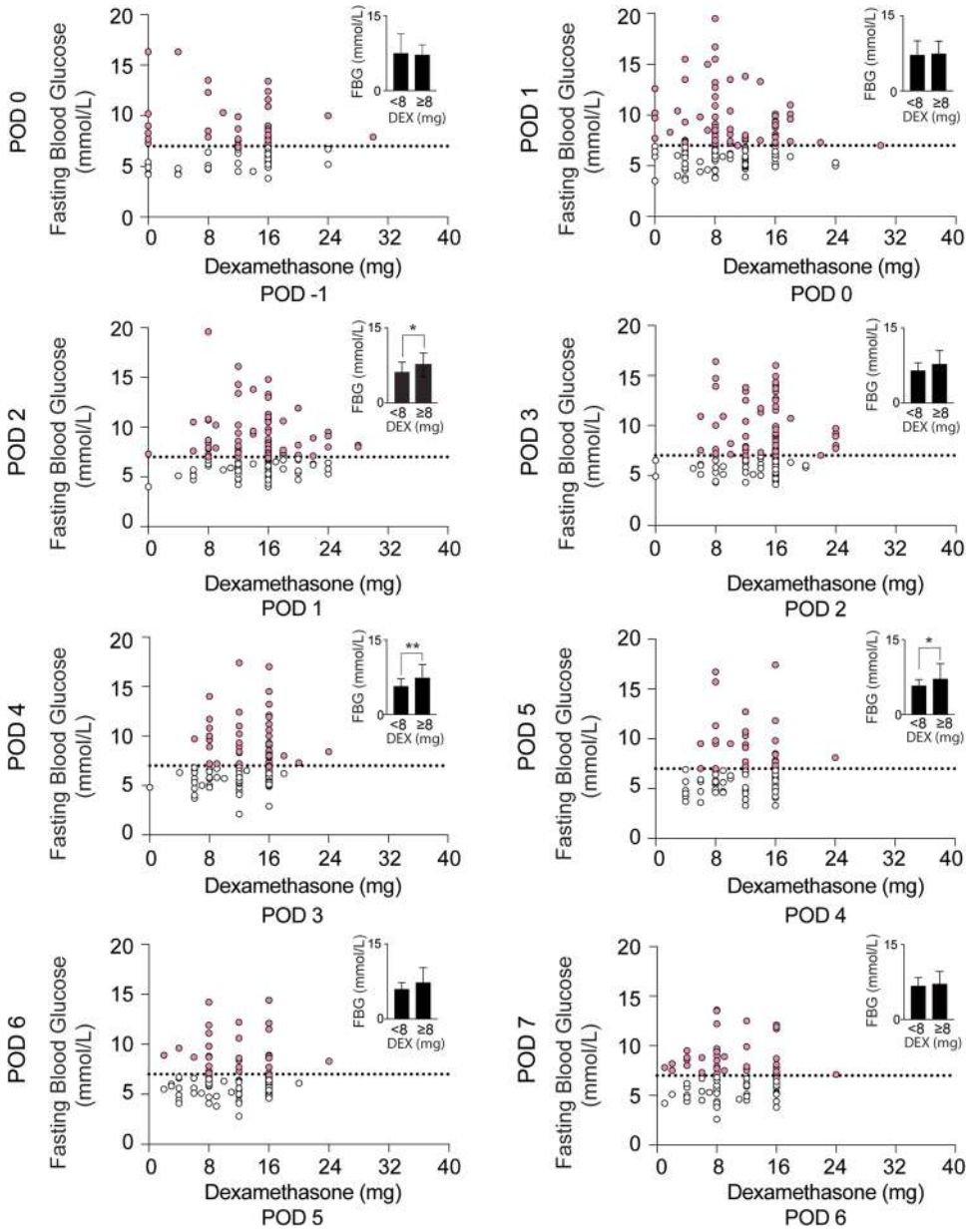

Fig. 2 Scatter plots showing the relationship between dose of dexamethasone administered and fasting blood glucose measurement the following day. Inset bar graphs show the proportion of patients with high FBG measurements according to dexamethasone dose (< 8 mg vs. ≥ 8 mg). Pink dots represent data points FBG ≥ 7 mmol/L. The *p*-values for the individual bar graphs from FBG POD0 to POD7 are 0.39, 0.63, 0.02, 0.05, 0.004, 0.02, 0.11, and 0.59, respectively. DEX, dexamethasone; FBG; fasting bloodglucose; POD, postoperative day

important postoperative complications. On multivariate analysis, poor perioperative glycemic control was associated with increased odds of 30-day occurrence of any complication. Higher average dexamethasone daily dose was associated with increased odds of 30-day occurrence of any complication, 30-day infection, and a near significant association with 30-day thrombosis ($P = 0.072$). Furthermore, while daily average dexamethasone dose did not correlate with perioperative hyperglycemia on a linear regression model, doses ≥ 8 mg/day were associated with hyperglycemia on the following day on POD 2, 4 and 5. POD3 and POD6 demonstrated near significance at $P = 0.05$ and 0.11, respectively. We demonstrate that increased dexamethasone use can contribute to morbidity and mortality in GBM patients through augmenting the risk for postoperative complications, such as infections and thrombotic events.

Identifying factors that are associated with increased risk of complications can lead to improved care for GBM patients; specifically, avoiding hyperglycemia and utilizing the least possible dexamethasone dose that is effective for symptom control. Controlling perioperative hyperglycemia may decrease the risk of some of these complications, as supported by a meta-analysis of 5053 surgical patients showing tight glycemic control associated with lower infection rates [35]. In addition, optimizing glycemic index control can reduce postoperative LOS for GBM patients and lower associated burdensome costs on the healthcare system [15].

Table 2 Univariate and multivariate analysis of the association of perioperative glycemic control and high dexamethasone use with postoperative outcomes

Complication	Perioperative Glycemic Control						Average Dexamethasone Use	
	Good control $n=86$	Poor control $n=113$	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
30-day all complications	$n=86$ 17 (19.8%)	$n=110$ 43 (39.1%)	2.61 (1.35–5.01)	0.004	4.41 (1.89–10.27)	< 0.001	1.21 (1.07–1.37)	0.002
30-day thrombosis	$n=86$ 3 (3.5%)	$n=111$ 4 (3.6%)	1.04 (0.23–4.79)	0.956	2.55 (0.34–19.20)	0.365	1.34 (0.98–1.84)	0.072
30-day infection	$n=86$ 7 (8.1%)	$n=111$ 19 (17.1%)	2.33 (0.93–5.83)	0.065	2.69 (0.82–8.81)	0.102	1.28 (1.08–1.51)	0.004
	(mean ± SE)	(mean ± SE)		*p*-value	B ± SE	*p*-value	B ± SE	*p*-value
LOS (days)	$n=86$ 11.7 ± 1.7	$n=111$ 17.2 ± 3.5		0.566	11.3 ± 4.46	0.012	0.04 ± 0.64	0.948

95% CI 95% confidence interval; *aOR* adjusted odds ratio; *B* β coefficient unstandardized; *BMI* body mass index; *LOS* length of stay; *OR* odds ratio; *SE* standard error

Table 3 Simple and multiple linear regression to identify risk factors associated with perioperative glycemic control

Variable	% days high FBG					
	Univariate analysis			Multivariate analysis		
	B ± SE	β	*p*-value	B ± SE	β	*p*-value
BMI	0.374 ± 0.0.537	0.051	0.487			
Age	0.410 ± 0.258	0.113	0.113	0.119 ± 0.244	0.032	0.628
Sex (female)	-0.114 ± 5.828	-0.001	0.984			
Type 2 diabetes mellitus	21.528 ± 3.617	0.391	< 0.001	21.212 ± 3.682	0.386	< 0.001
KPS	1.350 ± 1.654	0.058	0.415			
Residual tumor volume	0.196 ± 0.292	0.048	0.503			
Average dexamethasone use perioperatively	-0.384 ± 0.861	-0.032	0.656			

FBG fasting blood glucose; *B* β coefficient unstandardized; *β* β coefficient standardized; *BMI* body mass index; *KPS* Karnofsky performance status; *SE* standard error

Table 4 Univariate analysis of the association of pre-operative hemoglobin A1c with postoperative complications

Complication	Good control $n=29$	Poor control $n=18$	OR	95% CI	*p*-value
30-day all complications	$n=29$ 4 (13.8%)	$n=17$ 8 (47.1%)	5.56	1.34–23.0	0.013
30-day thrombosis	$n=29$ 0 (0%)	$n=17$ 0 (0%)	-	-	-
30-day infection	$n=29$ 1 (3.4%)	$n=17$ 5 (29.4%)	11.67	1.23–110.80	0.012
LOS (days, mean ± SE)	$n=29$ 9.1 ± 1.79	$n=18$ 24.1 ± 6.64	-	-	0.027

OR odds ratio; *95% CI* 95% confidence interval; *LOS* length of stay; *SE* standard error

We also found that a pre-operative finding of elevated hemoglobin A1c was associated with increased odds of 30-day occurrence of any complication, 30-day infection, development of T2DM, and LOS on univariate analysis. Preoperative workup which includes hemoglobin A1c may identify patients who are at a higher risk of experiencing postoperative complications.

The current state of literature suggests worse outcomes for neurosurgical patients with perioperative hyperglycemia but data for GBM patients is scarce. High perioperative hemoglobin A1c is associated with increased complications in patients undergoing spine surgery [18] and perioperative hyperglycemia worsens complications for patients with acute stroke undergoing thrombectomy [3]. Previous GBM

findings examined associations between complication rate and perioperative glycemic control, with different definitions of poor glycemic control [4, 19]. Link et al. assessed postoperative function loss in patients with primary eloquent GBM [19]. Decker et al. examined any complication, including seizure, respiratory failure, pneumonia, fever, sepsis, return to operating room, 30-day mortality, 30-day readmission, or mortality [4]. The studies found no significant correlations between hyperglycemia and pneumonia, fever, or sepsis events. However, the definitions used to denote hyperglycemia in these two studies may not be clinically relevant. Link et al. used the threshold of 8.88 mM random blood glucose (RBG), while Decker et al. used a definition of "doubling of median glucose" for odds ratios and RBG cut-off points of 9.0—9.3 mM for their receiver operating curves. Our study confirms the association between postoperative complications and poor glycemic control while using a clinically applicable definition of hyperglycemia (i.e., hyperglycemia defined as FBG ≥ 7.0 mM).

Furthermore, our study corroborates with previous findings that link increased infection rates with higher daily dexamethasone dose in GBM patients [22], while also demonstrating increased odds of longer LOS and other complications, such as 30-day thrombosis. This study is also the first to assess the association between pre-operative hemoglobin A1C and post-operative complications in GBM patients. Poor pre-operative glycemic control defined as hemoglobin A1C ≥ 6.5% aligned with a diagnosis of T2DM and was associated with infectious and thrombotic complications as well as increased length of stay.

The strengths of our study include a large sample size and ample data points for statistical analyses. Most patients had appropriate follow up to identify complications by 30 days. Our patient population is also similar to that reported in the literature with comparable median overall survival, which was longer for MGMT promoter methylated tumors [12, 33]. Patients with gross total resection had longer median overall survival compared to patients with partial resection, as shown in previous studies [23, 28]. There was a longer time to tumor growth in patients who had gross total versus partial resection. This effect was more prominent in MGMT promoter methylated tumors in concordance with the literature [13, 32]. Furthermore, the frequency and timing of postoperative thrombosis observed in our study was similar to that reported in the literature for neurosurgical oncology patients [27]. Our 30-day rate of venous thromboembolism (3.6%) was similar to the reported 3.5% rate in Senders et al. [31]. Further our rates of surgical site infection (1.5%) and CNS infection (1.5%) are similar to the infection rate previously published in a systematic review (3.25%) [29], and the CNS infection rate reported in a retrospective cohort study (0.8%) [21].

The limitations of our study include the absence of preoperative hemoglobin A1c of all patients and insufficient information on dexamethasone use after discharge. Furthermore, other co-morbidities that could contribute to complication risk were not evaluated, which would likely lead to an over-fitted model. Instead, we used KPS, residual tumor volume, preoperative T2DM diagnosis, and BMI to assess for patient functional status and baseline comorbidity. Our analysis revealed that KPS was independently associated with complications at 30 days; infection at 30 days; and prolonged length of stay as would be expected for dependent and immobile patients. Our study was not able to consider the effect of postoperative stress hyperglycemia isolated from the effects of dexamethasone. In one study, postoperative stress hyperglycemia incidence was 47.7% in neurosurgical non-diabetic critical care and 45.9% in cranial tumor patients [36]. If we define postoperative stress hyperglycemia as FBG ≥ 7.0 mM on POD1 or POD2, our incidence is similar at 55.8% (82/147). Notably, the association between high dexamethasone dose and poor perioperative glycemic control in our study was less prominent on POD 0 and POD 1, possibly due to the confounding effect of postoperative stress hyperglycemia. Also, this is an observational study and can only show correlation, not causation.

Future studies such as a prospective study comparing standard-of-care to increased scrutiny over perioperative hyperglycemia would add to the findings of this study. It would also be of interest to explore the minimal dexamethasone dose associated with a biologically significant effect on blood–brain barrier stabilization in patients with GBM since our study would support a "less is more" strategy when using dexamethasone in the perioperative period after GBM surgery.

Conclusions

Perioperative hyperglycemia and elevated pre-operative hemoglobin A1c are associated with increased risk of important postoperative complications in GBM patients. Higher average daily dexamethasone in the postoperative period is associated with hyperglycemia and an increased risk of complications. Thus, hyperglycemia and dexamethasone dose in the postoperative period are two modifiable factors that could be targeted to reduce the postoperative complication risk in GBM patients. Furthermore, preoperative hemoglobin A1c measurement may help to predict an increased risk of postoperative complications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00701-023-05541-6.

Acknowledgements We would like to thank Dr. Kevin Petrecca, Dr. David Sinclair, and Dr. Abbas Sadikot for their comments. We also acknowledge Dr. Marie-Christine Guiot for assistance in identifying GBM patients from the neuropathology register. We also extend our gratitude to all the members of the healthcare team involved in brain tumor patient care at the MNH, including the neurosurgeons, nursing team, occupational therapists, physiotherapists, respiratory therapists and social workers.

Funding This study recognizes funding from McGill University Health Centre Department of Neurosurgery Foundation, granted to Dr. Roberto Jose Diaz. All authors of this study have no relevant financial or non-financial interests to disclose.

Data Availability Data available on request from the authors, contingent on approval from local ethics board.

References

1. American Diabetes Association Professional Practice C (2022) 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care 45:S17-S38. https://doi.org/10.2337/dc22-S002
2. Bae SH, Park MJ, Lee MM, Kim TM, Lee SH, Cho SY, Kim YH, Kim YJ, Park CK, Kim CY (2014) Toxicity profile of temozolomide in the treatment of 300 malignant glioma patients in Korea. J Korean Med Sci 29:980–984. https://doi.org/10.3346/jkms.2014.29.7.980
3. Cannarsa GJ, Wessell AP, Chryssikos T, Stokum JA, Kim K, De Paula CH, Miller TR, Morris N, Badjatia N, Chaturvedi S, Gandhi D, Simard JM, Jindal G (2022) Initial Stress Hyperglycemia Is Associated With Malignant Cerebral Edema, Hemorrhage, and Poor Functional Outcome After Mechanical Thrombectomy. Neurosurgery 90:66–71. https://doi.org/10.1227/neu.0000000000001735
4. Decker M, Sacks P, Abbatematteo J, De Leo E, Brennan M, Rahman M (2019) The effects of hyperglycemia on outcomes in surgical high-grade glioma patients. Clin Neurol Neurosurg 179:9–13. https://doi.org/10.1016/j.clineuro.2019.02.011
5. Diabetes Canada Clinical Practice Guidelines Expert C, Punthakee Z, Goldenberg R, Katz P (2018) Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes 42 Suppl 1:S10-S15. https://doi.org/10.1016/j.jcjd.2017.10.003
6. Ferroni P, Roselli M, Riondino S, Cavaliere F, Guadagni F (2016) Insulin resistance as a predictor of venous thromboembolism in breast cancer. Endocr Relat Cancer 23:L25-28. https://doi.org/10.1530/ERC-16-0187
7. Fong AC, Cheung NW (2013) The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract 99:277–280. https://doi.org/10.1016/j.diabres.2012.12.023
8. Grabowski MM, Recinos PF, Nowacki AS, Schroeder JL, Angelov L, Barnett GH, Vogelbaum MA (2014) Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg 121:1115–1123. https://doi.org/10.3171/2014.7.JNS132449
9. Guadagni F, Riondino S, Formica V, Del Monte G, Morelli AM, Lucchetti J, Spila A, D'Alessandro R, Della-Morte D, Ferroni P, Roselli M (2017) Clinical significance of glycemic parameters on venous thromboembolism risk prediction in gastrointestinal cancer. World J Gastroenterol 23:5187–5195. https://doi.org/10.3748/wjg.v23.i28.5187
10. Hagan K, Bhavsar S, Arunkumar R, Grasu R, Dang A, Carlson R, Cowles C, Arnold B, Potylchansky Y, Rahlfs TF, Lipski I, Walsh C, Jimenez F, Nguyen AT, Feng L, Cata JP (2017) Association Between Perioperative Hyperglycemia and Survival in Patients With Glioblastoma. J Neurosurg Anesthesiol 29:21–29. https://doi.org/10.1097/ANA.0000000000000339
11. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee ShU (2017) Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. Asian Pac J Cancer Prev 18:3–9. https://doi.org/10.22034/APJCP.2017.18.1.3
12. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997–1003. https://doi.org/10.1056/NEJMoa043331
13. Incekara F, Smits M, van der Voort SR, Dubbink HJ, Atmodimedjo PN, Kros JM, Vincent A, van den Bent M (2020) The Association Between the Extent of Glioblastoma Resection and Survival in Light of MGMT Promoter Methylation in 326 Patients With Newly Diagnosed IDH-Wildtype Glioblastoma. Front Oncol 10:1087. https://doi.org/10.3389/fonc.2020.01087
14. Jafar N, Edriss H, Nugent K (2016) The Effect of Short-Term Hyperglycemia on the Innate Immune System. Am J Med Sci 351:201–211. https://doi.org/10.1016/j.amjms.2015.11.011
15. Jiang SHK, Patel D, Waldeck AR, Botteman M, Aly A, Norden AD (2017) Direct medical costs of treatment in newly-diagnosed high-grade glioma among commercially insured US patients. J Med Econ 20:1237–1243. https://doi.org/10.1080/13696998.2017.1364258
16. Kostaras X, Cusano F, Kline GA, Roa W, Easaw J (2014) Use of dexamethasone in patients with high-grade glioma: a clinical practice guideline. Curr Oncol 21:e493-503. https://doi.org/10.3747/co.21.1769
17. Lieber BA, Han J, Appelboom G, Taylor BE, Han B, Agarwal N, Connolly ES Jr (2016) Association of Steroid Use with Deep Venous Thrombosis and Pulmonary Embolism in Neurosurgical Patients: A National Database Analysis. World Neurosurg 89:126–132. https://doi.org/10.1016/j.wneu.2016.01.033
18. Lim S, Yeh HH, Macki M, Mansour T, Schultz L, Telemi E, Haider S, Nerenz DR, Schwalb JM, Abdulhak M, Park P, Aleem I, Easton R, Khalil J, Perez-Cruet M, Chang V (2021) Preoperative HbA1c > 8% Is Associated With Poor Outcomes in Lumbar Spine Surgery: A Michigan Spine Surgery Improvement Collaborative Study. Neurosurgery 89:819–826. https://doi.org/10.1093/neuros/nyab294
19. Link TW, Woodworth GF, Chaichana KL, Grossman SA, Mayer RS, Brem H, Weingart JD, Quinones-Hinojosa A (2012) Hyperglycemia is independently associated with post-operative function loss in patients with primary eloquent glioblastoma. J Clin Neurosci 19:996–1000. https://doi.org/10.1016/j.jocn.2011.09.031
20. Liu H, Liu Z, Jiang B, Ding X, Huo L, Wan X, Liu J, Xia Z (2016) Prognostic Significance of Hyperglycemia in Patients with Brain Tumors: a Meta-Analysis. Mol Neurobiol 53:1654–1660. https://doi.org/10.1007/s12035-015-9115-4
21. McClelland S 3rd, Hall WA (2007) Postoperative central nervous system infection: incidence and associated factors in 2111 neurosurgical procedures. Clin Infect Dis 45:55–59. https://doi.org/10.1086/518580
22. Mistry AM, Jonathan SV, Monsour MA, Mobley BC, Clark SW, Moots PL (2021) Impact of postoperative dexamethasone on survival, steroid dependency, and infections in newly diagnosed glioblastoma patients. Neurooncol Pract 8:589–600. https://doi.org/10.1093/nop/npab039

23. Molinaro AM, Hervey-Jumper S, Morshed RA, Young J, Han SJ, Chunduru P, Zhang Y, Phillips JJ, Shai A, Lafontaine M, Crane J, Chandra A, Flanigan P, Jahangiri A, Cioffi G, Ostrom Q, Anderson JE, Badve C, Barnholtz-Sloan J, Sloan AE, Erickson BJ, Decker PA, Kosel ML, LaChance D, Eckel-Passow J, Jenkins R, Villanueva-Meyer J, Rice T, Wrensch M, Wiencke JK, Oberheim Bush NA, Taylor J, Butowski N, Prados M, Clarke J, Chang S, Chang E, Aghi M, Theodosopoulos P, McDermott M, Berger MS (2020) Association of Maximal Extent of Resection of Contrast-Enhanced and Non-Contrast-Enhanced Tumor With Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma. JAMA Oncol 6:495–503. https://doi.org/10.1001/jamaoncol.2019.6143
24. Mor V, Laliberte L, Morris JN, Wiemann M (1984) The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 53:2002–2007. https://doi.org/10.1002/1097-0142(19840501)53:9<2002::aid-cncr2820530933>3.0.co;2-w
25. Nazar CE, Lacassie HJ, Lopez RA, Munoz HR (2009) Dexamethasone for postoperative nausea and vomiting prophylaxis: effect on glycaemia in obese patients with impaired glucose tolerance. Eur J Anaesthesiol 26:318–321. https://doi.org/10.1097/EJA.0b013e328319c09b
26. Oppenlander ME, Wolf AB, Snyder LA, Bina R, Wilson JR, Coons SW, Ashby LS, Brachman D, Nakaji P, Porter RW, Smith KA, Spetzler RF, Sanai N (2014) An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 120:846–853. https://doi.org/10.3171/2013.12.JNS13184
27. Rethinasamy R, Alias A, Kandasamy R, Raffiq A, Looi MC, Hillda T (2019) Deep Vein Thrombosis and the Neurosurgical Patient. Malays J Med Sci 26:139–147. https://doi.org/10.21315/mjms2019.26.5.13
28. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS (2011) An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115:3–8. https://doi.org/10.3171/2011.2.JNS10998
29. Schipmann S, Akalin E, Doods J, Ewelt C, Stummer W, Suero Molina E (2016) When the Infection Hits the Wound: Matched Case-Control Study in a Neurosurgical Patient Collective Including Systematic Literature Review and Risk Factors Analysis. World Neurosurg 95:178–189. https://doi.org/10.1016/j.wneu.2016.07.093
30. Schultz H, Rasmussen BK, Kristensen PL, Jensen AK, Pedersen-Bjergaard U (2018) Early incidence of glucocorticoid-induced diabetes in patients with brain tumors: a retrospective study of the first 7 days of treatment. Neurooncol Pract 5:170–175. https://doi.org/10.1093/nop/npx027
31. Senders JT, Goldhaber NH, Cote DJ, Muskens IS, Dawood HY, De Vos F, Gormley WB, Smith TR, Broekman MLD (2018) Venous thromboembolism and intracranial hemorrhage after craniotomy for primary malignant brain tumors: a National Surgical Quality Improvement Program analysis. J Neurooncol 136:135–145. https://doi.org/10.1007/s11060-017-2631-5
32. Sharma M, Bellamkonda S, Mohapatra S, Meola A, Jia X, Mohammadi A, Angelov L, Barnett GH, Vogelbaum M, Ahluwalia MS (2018) Correlation Between the Residual Tumor Volume, Extent of Tumor Resection, and O(6)-Methylguanine DNA Methyltransferase Status in Patients with Glioblastoma. World Neurosurg 116:e147–e161. https://doi.org/10.1016/j.wneu.2018.04.134
33. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL (2014) Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol Biomarkers Prev 23:1985–1996. https://doi.org/10.1158/1055-9965.EPI-14-0275
34. von Kanel R, Mills PJ, Dimsdale JE (2001) Short-term hyperglycemia induces lymphopenia and lymphocyte subset redistribution. Life Sci 69:255–262. https://doi.org/10.1016/s0024-3205(01)01127-4
35. Wang YY, Hu SF, Ying HM, Chen L, Li HL, Tian F, Zhou ZF (2018) Postoperative tight glycemic control significantly reduces postoperative infection rates in patients undergoing surgery: a meta-analysis. BMC Endocr Disord 18:42. https://doi.org/10.1186/s12902-018-0268-9
36. Yuksel S, Ugras GA, Sirin K, Turan Y, Kurucu S (2020) Stress hyperglycemia and glycemic control in critical neurosurgical patients: A retrospective study. Ann Med Res 27:2298–2305. https://doi.org/10.5455/annalsmedres.2020.05.451