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The safety and efficacy of dexamethasone in the perioperative management of glioma patients

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OBJECTIVE In this single-institution retrospective cohort study, the authors evaluated the effect of dexamethasone on postoperative complications and overall survival in patients with glioma undergoing resection.

METHODS A total of 435 patients who underwent resection of a primary glioma were included in this retrospective cohort study. The inclusion criterion was all patients who underwent resection of a primary glioma at a tertiary medical center between 2014 and 2019.

RESULTS The use of both pre- and postoperative dexamethasone demonstrated a trend toward the development of postoperative wound infections (3% vs 0% in single use or no use, p = 0.082). No association was detected between dexamethasone use and the development of new-onset hyperglycemia (p = 0.149). On multivariable Cox proportional hazards analysis, dexamethasone use was associated with a greater hazard of death (overall p = 0.017); this effect was most pronounced for preoperative (only) dexamethasone use (hazard ratio 3.0, p = 0.062).

CONCLUSIONS Combined pre- and postoperative dexamethasone use may increase the risk of postoperative wound infection, and dexamethasone use, specifically preoperative use, may negatively impact survival. These findings highlight the potential for serious negative consequences with dexamethasone use.

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KEYWORDS dexamethasone; primary glioma; steroids; perioperative; preoperative; postoperative; oncology

Gliomas are among the most common intracranial neoplasms and account for nearly 30% of all primary brain tumors.[1] There is significant heterogeneity among gliomas, leading to the WHO classification scheme of four grades based on histology and potential for malignancy.[2] Gliomas are generally associated with high morbidity and mortality, although there are significant differences among WHO grades I–IV.[3] Due to their location, gliomas are associated with significant mass effect, and cerebral edema is a common feature in many patients diagnosed with glioma.[4] Dexamethasone has historically been used for the management of cerebral edema in these patients.[5,6]

Dexamethasone is the steroid of choice for the management of cerebral edema given its high potency, long half-life, and lower mineralocorticoid side effects.[7] Although dexamethasone has been shown to alleviate cerebral edema, it is also associated with significant side effects, including immunosuppression, insulin resistance and hyperglycemia, venous thromboembolism, and poor wound healing.[7–9] Given these significant side effects, there is a need to balance the benefit of dexamethasone in treating cerebral edema with the morbidity and mortality associated with steroid-related complications. There are some guidelines for the use of dexamethasone in the general management of high-grade gliomas, although according to a recent 2014 review, most of these guidelines are based on studies in the 1990s and early 2000s.[7] There is sparse literature on the use of dexamethasone specifically in the pre- and postoperative setting. This perioperative interval is often associated with dexamethasone administration as patients can present with significant cerebral edema prompting resection, and patients can continue to have cerebral edema in the postoperative setting.[10]

ABBREVIATIONS CI = confidence interval; HR = hazard ratio; IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance Scale; MGMT = O^6-methylguanine-DNA methyltransferase; OS = overall survival.

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Given the lack of universal guidelines for dexamethasone use in the perioperative setting, there is significant variability in dexamethasone administration depending on clinician and institutional practice. In the present study, we evaluated whether pre- and postoperative dexamethasone administration affects the incidence of steroid-related complications, including postoperative wound infection and new-onset hyperglycemia. Furthermore, we determine the effect of dexamethasone administration on postoperative T2-weighted FLAIR volume. Finally, we assessed whether pre- or postoperative dexamethasone improves overall survival (OS) in patients with primary glioma undergoing resection.

Methods

Patient Population

A single-institution retrospective cohort study was conducted. This study was approved by the IRB and informed consent was not required because the data used in this study were gathered from routine clinical care. The inclusion criterion was all patients who underwent resection of a primary glioma at a tertiary medical center between 2014 and 2019. Patients who only underwent a core needle biopsy or open biopsy were excluded. Patients who only underwent resection of a recurrent glioma at this institution were excluded from the study. Patients lost to follow-up within 4 weeks of surgery were excluded as well. A total of 435 patients met the inclusion criteria for this study.

Data Collection

Patient demographics were collected from the patient clinic notes. Tumor characteristics such as O^6-methylguanine-DNA methyltransferase (MGMT) methylation status, isocitrate dehydrogenase (IDH) mutation status, and WHO grade were determined from the pathology note on the resected tissue sample. Furthermore, length of surgery, pre- and postoperative dexamethasone use, pre- and 3-month postoperative Karnofsky Performance Scale (KPS) score, immediate and 3-month postoperative complications, and postoperative chemotherapy and radiation therapy were determined from patient clinical notes. Tumor location, preoperative tumor volume, and preoperative T2-weighted FLAIR volume were manually determined by 4 authors from MR images in the patients' charts using the software program Carestream Vue PACS. An immediate postoperative complication was defined as a venous thrombosis, stroke, hemiparesis, seizure, or aphasia that was documented between the date of surgery and date of discharge from the hospital. A 3-month postoperative complication was defined as a documented complication between postoperative hospital discharge and 3-month clinic follow-up visit. Neurological deficits were defined as hemiparesis, aphasia, visual field deficit, or ataxia. A postoperative wound infection was defined as a surgical site infection between the date of surgery and the date of the 3-month clinic follow-up evaluation. New-onset hyperglycemia was defined as clinically documented hyperglycemia between the date of surgery and the date of the 3-month clinic follow-up evaluation in a patient who did not previously have diabetes mellitus. Furthermore, OS was defined as the time from the date of surgery to the date of death or last known follow-up evaluation.

Statistical Analysis

Baseline patient characteristics were compared between cohorts of steroid use (none, preoperative only, postoperative only, or both) using an ANOVA test for continuous variables and a chi-square or Fisher's exact test for categorical variables. A Kaplan-Meier curve was constructed to compare the univariable association between dexamethasone use and OS. A multivariable Cox regression analysis evaluating the association between dexamethasone use and OS was performed after adjusting for variables with p values < 0.05 on univariable analysis of factors associated with dexamethasone use. This ensured that variables that may affect the propensity to receive steroids were controlled for and that the independent effect of various steroid regimens was evaluated. A sensitivity analysis utilizing a more parsimonious stepwise multivariable Cox regression was also performed. Schoenfeld residuals were used to check for the proportional hazards assumption in both models.[11] Collinearity was evaluated using a correlation matrix (correlation coefficient ≥ 0.7 selected as a cutoff for collinearity).[12] All statistical analyses were performed on STATA SE (version 15, StataCorp) and R (version 4.0.2, R Foundation for Statistical Computing) software. The cutoff for statistical significance was $p \leq 0.05$.

Results

Baseline Characteristics

The baseline patient characteristics for the 435 patients who met the inclusion criteria for this study are presented in Table 1. The mean age of the patients in this study was 54 years. Females accounted for 40% of the patients. The MGMT promoter was methylated in 34% of patients. An IDH mutation was present in 34% of patients. Twenty-eight percent of patients reported frequent alcohol consumption and 34% were either former or current smokers. Thirteen percent of patients had a history of diabetes, 9.2% of patients had a history of hypothyroidism, and 1.6% of patients had a history of hyperthyroidism. One patient had a WHO grade I tumor, 19% had a grade II tumor, 9.6% a grade III tumor, and 72% a grade IV tumor.

Thirty-four patients (7.8%) did not receive dexamethasone, 16 (3.7%) received only preoperative dexamethasone, 199 (46%) received only postoperative dexamethasone, and 186 (43%) received both pre- and postoperative dexamethasone. The mean postoperative dexamethasone taper length was 9.3 days. We found that 5.3% of patients had their operation shifted to an earlier date than initially planned due to worsening symptoms. The mean length of surgery was 5 hours. The mean preoperative KPS score was 81 and the mean postoperative KPS score was 77. With respect to immediate postoperative complications, 2.3% of patients had a venous thrombosis, 5.0% had a seizure, 1.2% had a stroke, 1.2% had aphasia, and 19% had hemiparesis. With respect to 3-month postoperative complications, 7.4% of patients had hemiparesis, 1.8% had ataxia, 6.0% had aphasia, and 3.2% had a visual deficit. A

TABLE 1. Baseline patient characteristics (n = 435)

Variable	Value
Mean age (SD), yrs	54 (16.6)
Females, n (%)	173 (40)
MGMT methylation status, n (%)	104 (34)
IDH mutation status, n (%)	87 (34)
Alcohol consumption, n (%)	121 (28)
History of diabetes, n (%)	56 (13)
History of hypothyroidism, n (%)	40 (9.2)
History of hyperthyroidism, n (%)	7 (1.6)
Smoking status, n (%)	
Never smoker	284 (65)
Former smoker	133 (31)
Current smoker	17 (3.1)
WHO grade, n (%)	
I	1 (0.2)
II	77 (19)
III	40 (9.6)
IV	298 (72)
Dexamethasone use, n (%)	
None	34 (7.8)
Preop only	16 (3.7)
Postop only	199 (46)
Pre- & postop	186 (43)
Mean postop dexamethasone taper length (SD), days	9.3 (5.5)
Operation shifted earlier, n (%)	23 (5.3)
Mean length of surgery (SD), hrs	5.0 (1.5)
Mean preop KPS score (SD)	81 (11.6)
Mean postop KPS score (SD)	77 (15.9)
Immediate postop complications, n (%)	
Venous thrombosis	9 (2.3)
Seizure	21 (5.0)
Stroke	5 (1.2)
Aphasia	5 (1.2)
Hemiparesis	81 (19)
3-mo neurological deficit, n (%)	
Hemiparesis	32 (7.4)
Ataxia	8 (1.8)
Aphasia	26 (6.0)
Visual deficit	14 (3.2)
Postop wound infection, n (%)	5 (1.2)
New-onset hyperglycemia, n (%)	24 (5.5)
Postop chemotherapy, n (%)	320 (74)
Postop radiation, n (%)	322 (74)
Tumor location, n (%)	
Frontal	153 (40)
Temporal	113 (30)
Parietal	64 (17)
Occipital	20 (5.3)
Cerebellar	3 (0.8)
Subcortical	15 (3.9)
Other	12 (3.3)
Mean preop imaging characteristics (SD), cm^3	
Tumor volume	31 (87.5)
T2-weighted FLAIR	43 (52.1)

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TABLE 1. Baseline patient characteristics (n = 435)

Data were not accurately charted for some patients, thus percentages were calculated based on the number of patients with available data.

postoperative wound infection was noted in 1.2% of patients. New-onset hyperglycemia was documented in 5.5% of patients. We found that 74% of patients received postoperative chemotherapy and postoperative radiation therapy for their brain tumor.

The most common tumor location was frontal (40%), followed by temporal (30%), parietal (17%), occipital (5.3%), subcortical (3.9%), other (3.2%), and cerebellar (0.8%). The mean preoperative tumor volume as measured on T1-weighted MRI with contrast enhancement was 31 cm^3. The mean preoperative T2-weighted FLAIR volume was 43 cm^3.

Univariate Analysis

Univariate analysis of baseline patient characteristics was performed after stratifying by the four cohorts of dexamethasone use (none, preoperative only, postoperative only, and both; Table 2). There was a significant difference in age between these four cohorts (47.9 vs 60.7 vs 50.7 vs 57.2 years, respectively, for the four cohorts as described above; $p < 0.001$). There was also a significant difference in IDH mutation status among the four cohorts (22% vs 29% vs 27% vs 15%, $p = 0.046$). Univariate analysis also showed differences for WHO grade II and IV tumors. The distribution of WHO grade II tumors was 35%, 6%, 24%, and 9% ($p < 0.001$) for the four cohorts. The distribution of WHO grade IV tumors was 50%, 75%, 56%, and 84%, respectively ($p < 0.001$). Likewise, there were differences in postoperative chemotherapy and radiation between the four cohorts. Postoperative chemotherapy was performed in 59%, 56%, 68%, and 84% of patients ($p < 0.001$). Postoperative radiation therapy was performed in 65%, 63%, 66%, and 86% of patients ($p < 0.001$). Finally, univariate analysis found significant differences in the preoperative imaging characteristics among these four cohorts. Preoperative tumor volume was 83.1, 34.9, 18.0, and 36.4 cm^3, respectively ($p = 0.004$), and preoperative T2-weighted FLAIR volume was 20.6, 54.5, 34.9, and 52.2 cm^3, respectively ($p = 0.002$).

Postoperative Outcomes and Dexamethasone Use

We studied the effect of dexamethasone administration (none, preoperative only, postoperative only, and both) on postoperative outcomes (Table 3). There was no difference among the cohorts with respect to postoperative KPS score ($p = 0.109$). There was a significant difference

TABLE 2. Univariate analysis of baseline patient characteristics stratified by dexamethasone use

Variable	Dexamethasone				p Value
	None	Preop	Postop	Both	
No. of pts	34	16	199	186	
Mean age (SD), yrs	47.9 (17.3)	60.7 (17.1)	50.7 (17.4)	57.2 (14.7)	**<0.001**
Females, n (%)	20 (59)	8 (50)	119 (60)	115 (62)	0.801
Mean BMI (SD), kg/m^2	27.5 (5.3)	28.2 (8.4)	27.4 (5.7)	27.4 (5.3)	0.954
MGMT methylation status, n (%)	8 (44)	5 (42)	46 (29)	45 (27)	0.311
IDH mutation status, n (%)	7 (22)	4 (29)	49 (27)	27 (15)	**0.046**
Alcohol consumption, n (%)	15 (44)	4 (25)	60 (30)	42 (23)	0.057
History of diabetes, n (%)	1 (3)	4 (25)	22 (11)	29 (16)	0.063
History of hypothyroidism, n (%)	3 (9)	3 (19)	16 (8)	18 (10)	0.458
History of hyperthyroidism, n (%)	2 (6)	0 (0)	4 (2)	1 (1)	0.127
Smoking status, n (%)					
Never smoker	25 (74)	10 (63)	134 (67)	115 (62)	0.489
Former smoker	7 (21)	6 (38)	59 (30)	62 (33)	0.445
Current smoker	2 (6)	0 (0)	6 (3)	9 (5)	0.635
WHO grade, n (%)					
I	0 (0)	0 (0)	0 (0)	1 (1)	0.543
II	12 (35)	1 (6)	48 (24)	16 (9)	**<0.001**
III	2 (6)	3 (19)	24 (12)	11 (6)	0.069
IV	17 (50)	12 (75)	112 (56)	157 (84)	**<0.001**
Operation shifted earlier, n (%)	2 (6)	0 (0)	12 (6)	9 (5)	0.840
Mean length of surgery (SD), hrs	3.7 (5.7)	3.3 (3.1)	6.3 (10.3)	4.4 (6.2)	0.063
Mean preop KPS score (SD)	80.3 (12.1)	77.5 (13.4)	81.7 (12.4)	80.6 (10.4)	0.480
Postop chemotherapy, n (%)	20 (59)	9 (56)	135 (68)	156 (84)	**<0.001**
Postop radiation, n (%)	22 (65)	10 (63)	131 (66)	159 (86)	**<0.001**
Tumor location, n (%)					
Frontal	13 (38)	6 (38)	68 (34)	66 (35)	0.945
Parietal	4 (12)	1 (6)	22 (11)	37 (20)	0.074
Temporal	4 (12)	3 (19)	53 (27)	53 (28)	0.198
Occipital	1 (3)	0 (0)	6 (3)	13 (7)	0.286
Cerebellar	1 (3)	0 (0)	2 (1)	0 (0)	0.215
Subcortical	1 (3)	2 (13)	8 (4)	4 (2)	0.140
Other	1 (3)	0 (0)	7 (4)	4 (2)	0.789
Mean preop imaging characteristics (SD), cm^3					
Tumor volume	83.1 (321.9)	34.9 (40.6)	18.0 (23.6)	36.4 (31.8)	**0.004**
Preop T2-weighted FLAIR	20.6 (26.5)	54.5 (43.3)	34.9 (61.8)	52.2 (42.5)	**0.002**

pt = patient.
Boldface type indicates statistical significance.

in the immediate postoperative hemiparesis complication among the four cohorts (26% vs 44% vs 23% vs 10%, respectively; $p < 0.001$). There was also a significant difference in the 3-month neurological deficit of ataxia among the four cohorts (0% vs 6% vs 0% vs 4%, respectively; $p = 0.010$). The use of both pre- and postoperative dexamethasone demonstrated a trend toward the development of postoperative wound infections (3% vs 0% in single use or no use, $p = 0.082$). No association was detected between dexamethasone use and the development of new-onset hyperglycemia ($p = 0.149$). We also found that there was no difference in postoperative dexamethasone taper length between the patients who had a postoperative wound infection within 3 months of surgery and those who did not (12.7 vs 9.3 days, $p = 0.14$). Likewise, there was no significant difference in postoperative dexamethasone taper length for patients who had new-onset hyperglycemia (11.2 vs 9.3 days, $p = 0.24$).

We found that patients who received preoperative dexamethasone had a significantly higher preoperative T2-weighted FLAIR volume than patients who did not (52.3 vs 33.0 cm^3, $p = 0.0003$). However, there was no significant

TABLE 3. Univariate analysis of patient outcomes stratified by dexamethasone use

Variable	Dexamethasone				p Value
	None	Preop	Postop	Both	
Mean postop KPS score (SD)	76.5 (18.9)	67.3 (16.7)	77.5 (15.5)	77.7 (15.5)	0.109
Immediate postop complications, n (%)					
Venous thrombosis	0 (0)	1 (7)	4 (2)	4 (2)	0.502
Seizure	0 (0)	1 (7)	12 (6)	8 (4)	0.419
Stroke	0 (0)	1 (7)	1 (1)	3 (2)	0.205
Aphasia	1 (3)	0 (0)	1 (1)	3 (2)	0.337
Hemiparesis	9 (26)	7 (44)	46 (23)	19 (10)	**<0.001**
3-mo neurological deficit, n (%)					
Hemiparesis	0 (0)	2 (13)	13 (7)	17 (9)	0.160
Ataxia	0 (0)	1 (6)	0 (0)	7 (4)	**0.010**
Aphasia	0 (0)	1 (6)	11 (6)	14 (8)	0.346
Visual deficit	1 (3)	0 (0)	7 (4)	6 (3)	0.999
Postop wound infection, n (%)	0 (0)	0 (0)	0 (0)	5 (3)	0.082
New-onset hyperglycemia, n (%)	0 (0)	1 (6)	8 (4)	15 (8)	0.149

Boldface type indicates statistical significance.

difference between patients who did and did not receive preoperative dexamethasone in the mean change in T2-weighted FLAIR volume between preoperative and immediate postoperative MRI (–2.0 vs –3.77 cm^3, p = 0.44). When stratified by WHO grade (Table 4), patients with a WHO grade II glioma who received preoperative dexamethasone did have a more significant decrease in T2-weighted FLAIR volume between preoperative and immediate postoperative MRI (–16.0 vs –1.4 cm^3, p = 0.02). Patients with a WHO grade III or IV glioma who received preoperative dexamethasone did not have a significant change in T2-weighted FLAIR volume between preoperative and immediate postoperative MRI (p = 0.39 and p = 0.90, respectively).

The mean postoperative follow-up duration was 1.6 ± 1.3 years (median 1.3 years). On Kaplan-Meier analysis, dexamethasone use was significantly associated with mortality (p < 0.001, log-rank test; Fig. 1), with the poorest survival in patients with isolated preoperative dexamethasone use. A Cox regression analysis was performed (Table 5) following a univariate analysis (Tables 2 and 3) to determine the effect of dexamethasone use on OS. When adjusting for age, IDH status, WHO grade II, WHO grade IV, postoperative hemiparesis, postoperative ataxia within 3 months, postoperative chemotherapy, postoperative radiotherapy, preoperative tumor volume, and preoperative T2-weighted FLAIR MRI, dexamethasone use was significantly associated with a greater hazard of death (p = 0.017). This effect was particularly pronounced in the case of isolated preoperative dexamethasone use (hazard ratio [HR] 3.0, 95% confidence interval [CI] 0.9–9.4, p = 0.062). On sensitivity analysis utilizing a parsimonious stepwise model, similar results were obtained (Table 6). Dexamethasone use, age, WHO grade II, WHO grade IV, postoperative hemiparesis, and ataxia were all important independent predictors of mortality. In both models, the proportional hazards assumption was met (nonsignificant p values for weighted residuals), and no collinearity was detected (Supplemental Table 1).

TABLE 4. Change in FLAIR volume between preoperative and immediate postoperative MRI stratified by preoperative dexamethasone administration and WHO grade

WHO Grade	Dexamethasone (mean ± SD), cm^3		p Value
	Preop	No Preop	
II	–16 ± 10	–1.4 ± 34	**0.02**
III	–6.8 ± 12	–0.70 ± 22	0.39
IV	–2.2 ± 25	–2.5 ± 21	0.90

Boldface type indicates statistical significance.

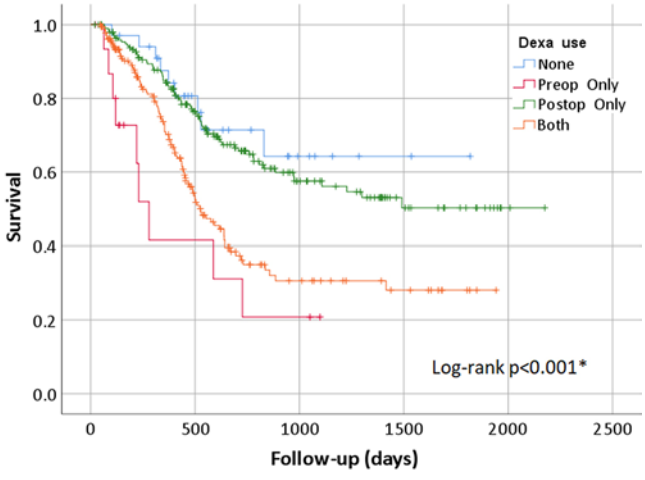

FIG. 1. Kaplan-Meier survival analysis of patients undergoing primary glioma resection stratified by dexamethasone (Dexa) usage (n = 435). Figure is available in color online only.

TABLE 5. Multivariable Cox regression analysis of dexamethasone use (n = 339)

Characteristic	HR (95% CI)	p Value
Dexamethasone use		**0.017**
None	Reference	—
Preop only	3.0 (0.9–9.4)	0.062
Postop only	1.2 (0.5–2.7)	0.742
Both	1.9 (0.8–4.4)	0.135
Age, per yr	1.013 (1.010–1.026)	**0.049**
IDH	0.6 (0.3–1.2)	0.181
WHO grade II	0.3 (0.1–0.8)	**0.014**
WHO grade IV	2.6 (1.3–5.3)	**0.008**
Postop hemiparesis	1.9 (1.3–2.8)	**0.002**
Ataxia w/in 3 mos	7.2 (2.8–18.6)	**<0.001**
Postop chemotherapy	0.9 (0.4–1.9)	0.764
Postop radiotherapy	0.7 (0.4–1.5)	0.419
Preop tumor volume	1.001 (1.000–1.003)	0.075
Preop T2-weighted FLAIR	0.996 (0.992–1.001)	0.151

Boldface type indicates statistical significance.

TABLE 6. Sensitivity analysis: parsimonious stepwise multivariable Cox regression analysis of dexamethasone use (n = 417)

Characteristic	HR (95% CI)	p Value
Dexamethasone use		**0.003**
None	Reference	—
Preop only	2.7 (1.1–6.9)	**0.044**
Postop only	1.1 (0.5–2.2)	0.829
Both	1.9 (0.9–3.7)	0.081
Age, per yr	1.015 (1.004–1.026)	**0.006**
WHO grade II	0.3 (0.1–0.6)	**0.002**
WHO grade IV	2.3 (1.4–3.9)	**0.001**
Postop hemiparesis	2.2 (1.6–3.1)	**<0.001**
Ataxia w/in 3 mos	6.3 (2.7–14.6)	**<0.001**

Boldface type indicates statistical significance.

Discussion

The current standard of care for gliomas includes a combination of resection, radiation therapy, and chemotherapy.[13,14] Despite these interventions, the prognosis for glioma is poor, especially WHO grade IV glioblastoma.[15] Dexamethasone, commonly used in patients with glioma for the management of cerebral edema, may not synergize well with this current standard of care.[7,16] Pitter et al. found that corticosteroid use during radiation therapy in patients with glioblastoma was an independent predictor of decreased survival in three independent patient cohorts.[23] Wong et al. found that dexamethasone-induced immunosuppression reduced the efficacy of tumor-treating electric field therapy and chemotherapy in patients with glioblastoma.[17] Reardon et al. found that dexamethasone therapy reduced the efficacy of neoantigen-targeting vaccine immunotherapy for glioblastoma.[18] These studies suggest that dexamethasone may not synergize with radiation therapy, chemotherapy, or even immunotherapy. However, there is sparse literature on the role of steroids in the immediate pre- and postoperative setting, and it is unclear whether dexamethasone in these settings improves OS. In this study, we retrospectively evaluated the effect of pre- and postoperative dexamethasone use on the incidence of steroid-related complications and OS in patients with glioma.

It was found that most patients undergoing resection of a glioma are administered either postoperative dexamethasone only (46%) or both pre- and postoperative dexamethasone (43%). Dexamethasone is typically administered to patients pre- and postoperatively for glioma resection as these patients often present with symptoms of cerebral edema.[6,19] In this study, patients who received both pre- and postoperative dexamethasone showed a trend toward a higher incidence of postoperative wound infection within 3 months of surgery (3.0% vs 0%, p = 0.08). Of note, the incidence of new-onset hyperglycemia was not significantly higher in patients who received both pre- and postoperative steroids (p = 0.15). These findings suggest that patients who receive both pre- and postoperative dexamethasone may not have a significantly higher risk for the common steroid-related complications of wound infection and hyperglycemia.

Next, we evaluated whether the patients who received preoperative dexamethasone presented with more cerebral edema, as measured by T2-weighted FLAIR volume. We found that, indeed, patients receiving preoperative dexamethasone had a significantly higher preoperative T2-weighted FLAIR volume than the patients who did not receive preoperative dexamethasone (52 vs 33 cm^3, p = 0.0003). This result suggests there was a clinical indication for prescribing preoperative dexamethasone in these patients, i.e., management of the increased cerebral edema. In cases of severe edema and mass effect, steroids should be given as a lifesaving measure. However, patients who received preoperative dexamethasone did not have a larger reduction in FLAIR volume when comparing the preoperative and immediate postoperative MRI (–2.0 vs –3.77 cm^3, p = 0.44). When stratified by WHO grade, it was found that patients with a WHO grade II tumor did have a significantly larger reduction in FLAIR volume between the preoperative and immediate postoperative MRI (–16 vs –1.4 cm^3, p = 0.02). These data suggest that preoperative dexamethasone may provide a greater benefit in patients with a lower-grade glioma than in patients with a higher-grade glioma.

Finally, our Cox regression analysis found that dexamethasone usage was associated with an increased hazard of death. More specifically, the greatest effect appears to be with the preoperative dexamethasone-only cohort (HR 3.0, 95% CI 0.9–9.4, p = 0.062). Although the patients who were administered preoperative dexamethasone presented with a significantly higher T2-weighted FLAIR volume, our Cox model did not find preoperative T2-weighted FLAIR volume to be a significant independent predictor of OS. The literature suggests that hyperglycemia is independently associated with increased incidence of postop-

erative neurological deficits in patients with glioblastoma, and postoperative neurological deficits are associated with worsened prognosis and OS.[20–22] Finally, our finding that preoperative dexamethasone administration does not significantly decrease postoperative T2-weighted FLAIR volume suggests that there may not be a correlation between preoperative dexamethasone and postoperative edema associated with glioma resection. Thus, we conclude that dexamethasone is important for the management of preoperative cerebral edema, but it must be administered with caution as patients without significant preoperative cerebral edema may not benefit and may experience steroid-related complications. Indeed, the morbidity and mortality associated with steroid-related complications must be weighed against the potentially lifesaving effects of dexamethasone in glioma patients with cerebral edema. Given the dual effect of dexamethasone on improving survival but also potentially increasing morbidity, careful selection of patients with a clinical indication for dexamethasone is important to minimize the increased hazard of death associated with dexamethasone usage in this patient population.

Limitations

This study is limited by its inherently retrospective design. The KPS score had to be calculated manually by the authors because it was not present in the patient charts. Furthermore, all of the patients in this study were treated at a single institution, potentially reducing the generalizability of these results. The presence of multiple measured and unmeasured confounders that impact survival and steroid use also affects the results. We performed a multivariable Cox regression to control for these confounders. Missing data also presents a limitation, so a parsimonious stepwise model was utilized to select the most important confounders affecting survival, thereby increasing sample size.

Conclusions

In this study, we evaluated the incidence of steroid-related complications with dexamethasone usage in patients undergoing glioma resection. Furthermore, we identified the effect of dexamethasone administration on T2-weighted FLAIR volume and OS in these patients. Our findings suggest that combined pre- and postoperative dexamethasone use may trend toward increasing the risk of postoperative wound infection. Furthermore, dexamethasone use pre- and postoperatively may negatively impact survival, with the most pronounced effect observed in patients receiving only preoperative dexamethasone. Based on these findings, clinicians should be aware of the significant risks associated with dexamethasone use in patients undergoing glioma resection. It is important to note that dexamethasone should, of course, be administered in patients with life-threatening and/or impending cerebral edema, but in patients without significant cerebral edema, dexamethasone has the potential to adversely affect patient outcomes. Furthermore, these conclusions suggest that the effects of dexamethasone on survival and morbidity are complicated, and further studies including randomized controlled trials are necessary to further elucidate the role of dexamethasone in patients undergoing glioma resection. Indeed, the immunosuppressive effects of dexamethasone may have implications for novel strategies currently under investigation such as immunotherapy. Because all patients in this study had a primary glioma that underwent resection, our conclusions may not apply to patients with meningiomas or metastatic tumors, given that they were excluded from the study.

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Author Contributions

Conception and design: Lim, Medikonda, C Jackson. Acquisition of data: Medikonda, Patel, C Jackson, Saleh, Srivastava. Analysis and interpretation of data: Medikonda, C Jackson. Drafting the article: Lim, Medikonda, Patel. Critically revising the article: Lim, Medikonda, C Jackson. Reviewed submitted version of manuscript: Lim, Medikonda, C Jackson. Approved the final version of the manuscript on behalf of all authors: Lim. Statistical analysis: Medikonda, Feghali, Mohan, Pant. Study supervision: Lim, CM Jackson, Weingart, Mukherjee, Bettegowda, Gallia, Brem.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Table 1. https://thejns.org/doi/suppl/10.3171/2021.4.JNS204127.

Previous Presentations

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