A Reduced Exogenous Steroid Taper for Postoperative Brain Tumor Patients—A Case-Control Study

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■ BACKGROUND: **Dexamethasone is a standard treatment for cerebral edema after brain tumor surgery. However, its side effects can negatively impact the quality and safety of care provided to patients. Sparse evidence exists in the literature regarding postoperative steroid dosing to guide clinicians. The objective of this study was to determine if a new reduced exogenous steroid taper (REST) protocol would effectively treat postoperative cerebral edema while reducing the incidence of steroid-related side effects including diabetes, hypertension, and insomnia.**

■ METHODS: **A REST protocol (dexamethasone 38.5 mg tapered over 10 days) was instituted for patients with postoperative brain tumor of a single surgeon. Historical controls treated with a high-dose taper (dexamethasone 117 mg taper over 17 days) were selected to match for baseline characteristics. Outcomes of new or worsened diabetes, hypertension, and insomnia, as well as length of stay (LOS) and 30-day readmission rates, were compared.**

■ RESULTS: **Twenty-five patients were included in each group. There were no significant differences in baseline characteristics. The REST group received a median of 34.5 mg (interquartile range, 32—41 mg) of dexamethasone, whereas controls received 43 mg (interquartile range, 16—91 mg) ($P = 0.04$). There was a significant reduction in the incidence of new or worsened hypertension in the REST group (0%) compared with controls (20%, $P = 0.02$). No difference was seen in the rates of diabetes mellitus, insomnia, LOS, or 30-day readmission rates.**

■ CONCLUSIONS: **A reduced steroid taper after brain tumor surgery significantly reduced the incidence of hypertension without increasing LOS or 30-day readmissions compared with controls treated with a high-dose taper.**

INTRODUCTION

The use of corticosteroid therapy for the treatment of patients with brain tumor has been a standard practice since the 1960s.[1-8] Dexamethasone in particular is favored given its potent anti-inflammatory properties, long half-life, and minimal sodium retaining potency.[2] Dexamethasone's mechanism of action is not fully elucidated, but it is thought to reduce cerebral edema through multiple sites of action including reduced tumor angiogenesis and vascular endothelial growth factor production, tumor growth, and neuronal cell death.[8,9] In addition to reducing peritumoral edema, dexamethasone is effective in the postoperative setting at treating the neurologic sequelae of brain retraction/manipulation that occurs during a tumor resection.[8-10]

The negative side effects of corticosteroids, including hyperglycemia, insomnia, hypertension, poor wound healing, psychosis/agitation, proximal myopathy, Cushingoid appearance, and gastrointestinal complaints, are known to be related to cumulative dose and duration of therapy.[11,12] In addition, recent animal studies suggest that steroids may increase invasion, proliferation, and angiogenesis in glioblastoma.[13] Complications from corticosteroid use can lead to longer hospital length of stay, hospital-acquired infections, and reduced patient satisfaction.

Key words
- Brain tumor
- Dexamethasone
- Postoperative cerebral edema
- Steroid taper

Abbreviations and Acronyms
DM: Diabetes mellitus
HTN: Hypertension
IQR: Interquartile range
LOS: Length of stay
REST: Reduced exogenous steroid taper

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Known predictors of developing side effects include the cumulative dose of corticosteroid given, as well as the duration of patient use.[11] A 1987 study in neuro-oncology patients indicated that patients who received a total of greater than 400 mg of dexamethasone had a 75% incidence of toxicity, whereas those who received a total of less than 400 mg had a 13% incidence of toxicity.[12] Reducing steroid doses to the lowest effective dose is a potential mechanism for improving the quality and safety of care provided to patients. Despite a need to balance the benefits and risks, there is a paucity of evidence regarding the optimal dosing of dexamethasone in postoperative neuro-oncology patients.[14] As a result, there is significant variability in treatment practices.[15]

At our institution, there is a longstanding practice of treating patients with postoperative intra- and extra-axial brain tumor with a 17-day, high-dose dexamethasone taper in the immediate postoperative setting. This taper is based on clinical experience and historical practice, but it is supported by little evidence from the literature.[10,16] In this study, we sought to determine if a shorter, lower dose dexamethasone taper would reduce the side effects of hyperglycemia, hypertension, and insomnia, while remaining effective in treating the symptoms of postoperative cerebral edema.

METHODS

Population and Study Design

This case-control study was approved by the institutional review board. Patient consent was not required for this minimal risk study, per institutional policy. Inclusion criteria were patients with brain tumor of a single surgeon (MWM) who underwent craniotomy for meningioma, glioma, or brain metastasis. Exclusion criteria included tumor pathology other than meningioma, glioma, or metastasis; preoperative use of dexamethasone for longer than 1 month; and implantation of brachytherapy seeds or Gliadel Wafer (Arbor Pharmaceuticals, Atlanta, Georgia, USA).

Patients in the REST arm of the study were enrolled from mid-August through October 2017. The REST dosing schedule, involving a total of 38.5 mg of dexamethasone tapered over 10 days, is shown in Table 1 alongside the standard dexamethasone taper used for patients undergoing craniotomy for brain tumor before the institution of the REST protocol. Control patients received a total of 117 mg of dexamethasone over 17 days, according to this taper schedule. Although all patients were initially started on one of these 2 taper schedules, dose adjustments were made in some cases by the clinicians according to clinical circumstances. Patients were retrospectively analyzed by the assigned taper group (intention-to-treat) as well as by the total amount of steroid received (as treated).

The control arm of the study was retrospectively constructed from historical controls pseudorandomly selected from the preceding 1 year, before the launch of the REST protocol. The historical control group was matched to the REST group for several baseline characteristics including age, sex, tumor pathology, tumor size, presence of edema, prior treatments, preoperative symptoms (headache, seizure, and neurologic deficits), preoperative steroid use, and pre-existing diabetes mellitus (DM), hypertension (HTN), and insomnia. The primary outcomes included new or worsened HTN, DM, and insomnia requiring initialization or escalation of medical therapy after surgery. Antihypertensive medications were initiated and titrated to achieve a systolic blood pressure of less than 140 mm Hg. Pain was well controlled, per institutional protocol, before initiating new or additional antihypertensives. Similarly, insulin regimens were titrated to target a blood glucose level between 90 and 140 mg/dL. The diagnosis and treatment of insomnia was based on subjective patient reports. Secondary outcomes included length of stay (LOS) and 30-day readmission rate.

Statistical Analysis

Baseline characteristics were compared between the REST and control groups using univariate statistics. For categorical variables, a Pearson's χ^2 test, and for continuous variables, a 2-tailed Student's t-test was employed. To confirm that the REST group actually received a reduced overall steroid dose, the total dose, mean daily steroid dose, and taper duration were compared between groups. The outcomes of new or worsened DM, HTN, and insomnia; LOS; and 30-day readmissions were similarly compared between the REST and control groups, employing a Pearson's χ^2 test for categorical variables and a 2-tailed Student's t-test for continuous variables. The primary and secondary outcomes were also analyzed in an "as treated" fashion, according to the total

Table 1. Postoperative Dexamethasone Taper Schedule for the REST and Control Groups

Postoperative Day	REST	Control
1	4 mg BID	4 mg QID
2	4 mg BID	4 mg QID
3	4 mg BID	4 mg QID
4	2 mg BID	4 mg QID
5	2 mg BID	4 mg QID
6	1 mg BID	3 mg QID
7	1 mg BID	3 mg QID
8	1 mg in morning	3 mg BID
9	1 mg in morning	3 mg BID
10	0.5 mg in morning	2 mg BID
11	—	2 mg BID
12	—	1 mg BID
13	—	1 mg BID
14	—	1 mg in morning
15	—	1 mg in morning
16	—	0.5 mg in morning
17	—	0.5 mg in morning
Total steroid dose	38.5 mg	117 mg
Taper duration	10 days	17 days

BID, 2 times a day; QID, 4 times a day; REST, reduced exogenous steroid taper.

steroid dose (which included any preoperative steroids), mean daily steroid dose, and taper duration with logistic regression.

RESULTS

A total of 50 patients, 25 in each group, were included in the study. Eleven patients were excluded from the REST group over the 2.5-month study period because of nonincluded pathology (6), preoperative steroid use for longer than 1 month (2), and brachytherapy or Gliadel Wafer implantation (3). The same exclusion criteria were applied in selecting the historical control group. There were no significant differences in the baseline characteristics between the REST and control groups (Table 2). The REST group received a median of 34.5 mg (interquartile range [IQR], 32–41 mg) of dexamethasone over 10 days (IQR, 7–10 days), which was significantly less than the 43 mg (IQR, 16–91 mg)] received over 12 days (IQR, 7–17 days) by the historical control group ($P = 0.03$). The mean daily dose and taper durations had a nonsignificant trend toward higher mean dose and longer treatment in the control group (0.14 and 0.09, respectively).

Comparison of the incidence of new or worsened DM, HTN, and insomnia is shown in Table 3. There was a significant reduction in the incidence of new or worsened hypertension requiring antihypertensive medical therapy in the REST group (0%) compared with the control group (20%, $P = 0.02$). No difference was seen in the rates of DM or insomnia. Similarly, no difference was seen when comparing LOS and 30-day readmission rates. When analyzed on an "as treated" basis, logistic regression did not show a significant relationship between total steroid dose, mean dose, or taper duration and the primary and secondary outcomes.

Table 2. Univariate Comparison of Baseline Characteristics Between the REST and Control Groups

Characteristic	REST (n = 25)	Control (n = 25)	*P* Value
Age (years)	58 [48–67]	61 [56–73]	0.1
Sex (% female)	18 (72%)	12 (48%)	0.08
Pathology			0.46
Low-grade glioma	3 (12%)	1 (4%)	
High-grade glioma	2 (8%)	5 (20%)	
Meningioma	18 (72%)	16 (64%)	
Metastasis	2 (8%)	3 (12%)	
Maximal tumor dimension (mm)	34 [20–43]	40 [29–51]	0.18
Edema/increased T2 signal	13 (52%)	15 (60%)	0.57
Prior treatments			0.27
Surgery	4 (16%)	1 (4%)	
Radiation	0 (0%)	1 (4%)	
Surgery + radiation	4 (16%)	2 (8%)	
Headaches	12 (48%)	13 (52%)	0.77
Seizures	8 (32%)	7 (28%)	0.76
Neurologic deficits (vision, motor, cranial nerve)	13 (52%)	14 (56%)	0.78
Prior DM	2 (8%)	3 (12%)	0.64
Prior HTN	9 (36%)	14 (56%)	0.16
Prior insomnia	5 (20%)	3 (12%)	0.44
Preoperative steroids	5 (20%)	7 (28%)	0.5
Total preoperative dose (mg)	34 [23–74]	64 [40–104]	0.24
Total amount of steroid (mg)	34.5 [32–41]	43 [16–91]	0.04*
Steroid taper duration (days)	10 [7–10]	12 [7–17]	0.14
Mean daily steroid dose (mg/day)	3.45 [3.4–4.6]	4.3 [3–6.4]	0.09

DM, diabetes mellitus; HTN, hypertension; REST, reduced exogenous steroid taper.
*Statistically significant with $P \leq 0.05$, [ ] denotes 25% to 75% interquartile range.

DISCUSSION

Corticosteroids are very effective at treating peritumoral edema and the transient neurologic sequelae of brain retraction/manipulation after surgery due to their effects on the blood-brain barrier.[5,6,14] However, numerous deleterious steroid-related side effects have a significant negative impact on the quality of care provided to neurosurgical patients. Furthermore, recent work by Luedi et al[13] has shown that dexamethasone increases proliferation, invasion, and angiogenesis in an orthotopic glioblastoma multiforme mouse model, and thus may potentially worsen the prognosis for patients with glioblastoma multiforme. Despite its widespread use in patients with neurosurgical tumor, very little data exist to guide clinicians when trying to optimize dosing for maximal benefit and minimal risk in the postoperative setting. A 2-week high-dose dexamethasone taper after craniotomy for brain tumors has been a longstanding practice at our institution. However, a literature review revealed no evidence to support this taper schedule. In this study, we sought to determine if a new reduced dexamethasone taper would improve the quality of care by decreasing the incidence of new and/or worsened DM, HTN, and insomnia, while still effectively

Table 3. Univariate Comparison of DM, HTN, and Insomnia Outcomes Between the REST and Control Groups

Outcome	REST (n = 25)	Control (n = 25)	*P* Value
New/worsened DM requiring insulin	0	2 (8%)	0.15
New HTN requiring medication	0	5 (20%)	0.02*
New insomnia requiring medication	6 (24%)	8 (32%)	0.53
Length of stay (days)	2 [2–4]	3 [2–4]	0.24
30-day readmission	2 (8%)	1 (4%)	0.55

DM, diabetes mellitus; HTN, hypertension; REST, reduced exogenous steroid taper.
*Statistically significant with $P \leq 0.05$, [ ] denotes 25% to 75% interquartile range.

treating the cerebral edema after surgery. We found a significant reduction in hypertension that required patients to start new antihypertensive medications after surgery. There was no significant impact on the incidence of diabetes, insomnia, LOS, or 30-day readmission rate.

The initiation of a new medication postoperatively for hypertension can lead to medication side effects such as electrolyte abnormalities and renal failure, excessive reduction in blood pressure values, and the unnecessary continuation of an antihypertensive medication on discharge, which can potentially lead to hypotension at home. Decreasing the incidence of postoperative hypertension is important to enhancing patient safety and improving overall quality of postoperative care.

The risk of a reduced corticosteroid dose is the possibility of undertreating the neurologic symptoms after surgery including headaches, nausea, malaise, weakness, aphasia, and so on. These neurologic symptoms, seen commonly in the postoperative setting after brain tumor resection, increase morbidity, lengthen hospital stays, and prolong recovery from surgery. Although the retrospective review of patient records did not allow for direct comparison of these symptoms, secondary outcomes of LOS and 30-day readmission rates were assessed as surrogates for the effective treatment of neurologic symptoms after surgery. No difference was seen in LOS or 30-day readmission rates. This supports that a reduced taper improved rates of HTN while still adequately treating the sequelae of cerebral edema.

There are several important limitations to this study. Although the study population was heterogeneous (including both intra- and extra-axial, supra- and infratentorial tumors), the majority (68%) of the study population consisted of patients with meningioma, thus limiting the generalizability of the findings to other pathologies. The exclusion of patients on longstanding preoperative dexamethasone (>1 month) further limits the applicability of our findings to a large group of neuro-oncology patients for whom steroid treatment is necessary. Further work is needed to optimize postoperative dosing regimens for intra-axial tumors (32% of our study population) and those requiring preoperative steroids. Although the REST arm of the study was prospectively enrolled, the control arm consisted of historical cases for which data were retrospectively extracted from the medical record. These controls were randomly selected from a 1-year period just before the start of the REST protocol to minimize any possible differences in practice of the surgeon or clinical team. Randomization of a larger sample size to REST or control steroid tapers would strengthen the findings. Finally, further work should also evaluate rates of delirium/psychosis, another steroid-induced side effect with a significant negative impact on the quality of care for neurosurgical patients.

CONCLUSIONS

A reduced steroid taper for patients after brain tumor surgery was effective in reducing the incidence of hypertension while adequately treating neurologic symptoms when compared with historical controls treated with a longer, high-dose taper. Continual efforts to evaluate longstanding, specialty specific practices, such as high-dose steroids after brain tumor surgery, will lead to incremental improvements in the quality of care for patients.

REFERENCES

1. Kaal EC, Vecht CJ. The management of brain edema in brain tumors. *Curr Opin Oncol*. 2004;16:593-600.
2. Ryan R, Booth S, Price S. Corticosteroid-use in primary and secondary brain tumour patients: a review. *J Neurooncol*. 2012;106:449-459.
3. McClelland S III, Long DM. Genesis of the use of corticosteroids in the treatment and prevention of brain edema. *Neurosurgery*. 2008;62:965-968.
4. Ruderman NB, Hall TC. Use of glucocorticoids in the palliative treatment of metastatic brain tumors. *Cancer*. 1965;18:298-306.
5. Galicich J, French L. Use of dexamethasone in the treatment of cerebral edema resulting from brain tumors and brain surgery. *Am Pract Dig Treat*. 1961;12:169-174.
6. Galicich JH, French L, Melby JC. Use of dexamethasone in treatment of cerebral edema associated with brain tumors. *J Lancet*. 1961;81:46-53.
7. Long DM, Hartmann JF, French LA. The response of experimental cerebral edema to glucosteroid administration. *J Neurosurg*. 1966;24:843-854.
8. Fan Z, Sehm T, Rauh M, Buchfelder M, Eyupoglu IY, Savaskan NE. Dexamethasone alleviates tumor-associated brain damage and angiogenesis. *PLoS One*. 2014;9:e93264.
9. Kim H, Lee JM, Park JS, et al. Dexamethasone coordinately regulates angiopoietin-1 and VEGF: a mechanism of glucocorticoid-induced stabilization of blood-brain barrier. *Biochem Biophys Res Commun*. 2008;372:243-248.
10. Tommasino C. Postoperative cerebral edema. Physiopathology of the edema and medical therapy. *Minerva Anestesiol*. 1992;58(suppl 1):35-42.
11. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med*. 2009;103:975-994.
12. Weissman DE, Dufer D, Vogel V, Abeloff MD. Corticosteroid toxicity in neuro-oncology patients. *J Neurooncol*. 1987;5:125-128.
13. Luedi MM, Singh SK, Mosley JC, et al. Dexamethasone-mediated oncogenicity in vitro and in an animal model of glioblastoma. *J Neurosurg*. 2018;129:1-10.
14. Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: benefits and pitfalls. *Expert Rev Clin Pharmacol*. 2011;4:233-242.
15. Sturdza A, Millar B-A, Bana N, et al. The use and toxicity of steroids in the management of patients with brain metastases. *Support Care Cancer*. 2008;16:1041-1048.
16. Gomes JA, Stevens RD, Lewin JJ III, Mirski MA, Bhardwaj A. Glucocorticoid therapy in neurologic critical care. *Crit Care Med*. 2005;33:1214-1224.

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