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Collaboration in the presence of cerebral edema: The complications of steroids

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Abstract

Background: Brain tumor patients often present with neurological changes in the presence of cerebral edema. High-dose dexamethasone is often required for symptom management in brain tumor patients. There are limitations in the foundational research that support the recommendations for appropriate prescribing of dexamethasone. Understanding these limitations can help prescribers and care teams collaborate to better manage this unique patient population as well as identify areas for further research.

Methods: Evidence-based clinical practice guidelines for the management of adult brain tumor patients were reviewed from several certifying organizations. A complex database search and literature review was completed regarding relevant evidence used within these guidelines and for any supporting literature. The search was limited to MEDLINE, Cumulative Index to Nursing and Allied Health, Cochrane Library, and the National Guideline Clearinghouse using keywords. Each selected evidence-based guideline underwent appraisal using the Johns Hopkins Evidence-based Practice Model.

Results: All clinical practice guidelines identified recommendations for appropriate dosing and tapering of dexamethasone. The management of steroid-induced side effects was addressed in two of the reviewed guidelines. Only one guideline identified specific nursing interventions for monitoring steroid-related side effects. No guideline addressed interval timing of provider or nursing-based interventions as well as the role of collaboration between provider and nurse in monitoring for steroid toxicities.

Conclusions: More high-quality, well-controlled studies are needed around dexamethasone dosing for the management of cerebral edema. Clinical practice guidelines need to encompass both the prescriber and nursing-based interventions. Collaboration between disciplines is a necessity when monitoring and managing steroid-induced toxicities in brain tumor patients. Future evidence-based guidelines need recommendations for appropriate interval screening tests and quantifiable tools needed to aid in monitoring steroid-induced complications.

Key Words: Brain tumor, cerebral edema, dexamethasone, steroids, vasogenic edema

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BACKGROUND

Brain tumor patients often present with neurological changes in the presence of cerebral edema. Corticosteroids are a foundational component in the medical management of this patient population.[18] Dexamethasone is widely used and accepted by the medical community for the treatment and management of cerebral edema dating back to the 1960s.[7,15,16] Based on how frequently steroids are prescribed in brain tumor patients, neurooncology colleagues may assume that the available evidence provides a strong foundation for its clinical application. A thorough analysis of the literature reveals few high-quality, strongly controlled studies lacking consistent recommendations for the use of steroids in this population.[17] This creates great ambiguity in regards to prescribing. Understanding the available research can aid prescribers in their decision-making and assist care teams in their management of potential complications. The primary objective of this paper is to review the available evidence-based guidelines for the management of cerebral edema with dexamethasone in brain tumor patients, analyze the foundational evidence for these recommendations, and identify the need for any further research.

PATHOPHYSIOLOGY

Cerebral edema is the result of a disruption in the blood–brain barrier from tumor cells, allowing the accumulation of fluid in the extracellular space. Dexamethasone stabilizes the blood–brain barrier through the regulation of certain mediators found in tumors, ultimately decreasing vascular permeability, and reducing cerebral edema.[11,19,22,24] Dexamethasone is a type of synthetic glucocorticoid that controls many physiological functions.[9,13] Dexamethasone continues to be the glucocorticoid of choice for the management of cerebral edema in brain tumor patients due to its relatively long duration of action and its minimal mineralocorticoid effects.[8,17,25]

Many dexamethasone-related side effects are due to the inhibition of the hypothalamo-pituitary-adrenal axis and can exhibit effects on virtually every organ system in the body. See Table 1 for possible organ system-related side effects and management considerations.[8,12,25] Due to space limitations, a detailed review of the supporting evidence for the management of potential steroid-induced complications was omitted. Furthermore, dexamethasone is a CYP3A4 substrate and is therefore metabolized via the liver using the cytochrome P450 pathway. Commonly prescribed drugs for brain tumor patients such as phenytoin, carbamazepine, and many chemotherapeutic regimens may interfere with dexamethasone metabolism.[4-6,21] Careful prescribing is needed to limit these common drug interactions, and collaboration is essential to monitor many of the related complications.

Table 1: Organ system side effects of steroids

Organ system	Complication	Considerations
Cardiovascular/ renal	Hypertension Sodium and water retention Peripheral edema	Use with caution in heart failure and renal disease Electrolyte and BP* monitoring
Endocrine/ metabolic	Cushingoid appearance and weight gain Elevated serum glucose	Monitor for signs of adrenal insufficiency Monitor serum glucose Diet and exercise education
Gastrointestinal	Peptic ulcer Abdominal discomfort	H2 blocker of proton pump inhibitors
Infectious	Immunosuppression Suprainfection: Fungal, parasitic Reactivation of infection	Monitor for signs of infection Consider stress dosing
Integumentary	Impaired wound healing	Monitor for signs and symptoms of infection
Musculoskeletal	Myopathy Increased calcium excretion	Falls risk evaluation Oral supplements or possibly bisphosphonates with prolonged use and life expectancy
Ophthalmologic	Cataracts Glaucoma	Safety Ophthalmological evaluation
Psychiatric	Anxiety Depression Mood disorder	Appropriate screening tools Psychotherapy Pharmacotherapeutics

*BP: Blood pressure.

SEARCH STRATEGY

Understanding the underpinnings of evidence-based research is essential when completing successful database searches.[14] Multiple medical journal articles over the past decade, dated January 2005 through June 2015, were searched using MEDLINE, Cumulative Index to Nursing and Allied Health (CINAHL), Cochrane Library, and the National Guideline Clearinghouse. A variety of keywords were used to render the most results. Key terms searched included "brain tumor," "dexamethasone," "brain metastases," "glioma," and "cerebral edema." The exclusion of pediatric brain tumor patients was chosen to narrow the search results. Guidelines published in English were only considered.

Table 2 provides a summary of the database search results. MEDLINE was selected for the first database search due to its broad multidisciplinary nature. Publication types were limited to "guideline" and "practice guideline." Searches used isolated key terms with publication limitations as well as each isolated search term combined

Table 2: Database search results

Database	Number of searches	Number of title reviews	Number of full-text reviews	Number included in appraisal
MEDLINE	14	168	17	4
CINAHL	9	8	3	0
Cochrane Library	5	115	0	0
National Guideline Clearinghouse	5	228	3 (1 new)	1
Total	33	519	23	5

CINAHL: Cumulative Index to Nursing and Allied Health

with keyword "clinical practice guideline" and no publication limitation. CINAHL database searches used keywords limited to publication type "practice guidelines" as well as no publication limitations. CINAHL searches excluded articles found in MEDLINE. Finally, Cochrane Library and the National Guideline Clearinghouse were searched using isolated keywords. No new articles were rendered in CINAHL and Cochrane Library. The National Guideline Clearinghouse revealed one new guideline from the American Association of Neuroscience Nurses (AANN) and provided two full-text guidelines that were previously discovered in MEDLINE. Twenty-three articles underwent a full-text review for their content and inclusion of recommendations for the use of dexamethasone. A total of five evidence-based practice guidelines were selected to undergo evidence appraisal.

METHODOLOGY

Clinical practice guidelines are a review of research and nonresearch evidence to systematically develop recommendations that guide patient care. The Johns Hopkins Evidence-based Practice Model was used as a guide to appropriately appraise the evidence of each guideline using a quality rating range from high, good, to low. A high-quality rating has sufficient well-designed studies to support consistent and definitive recommendations. Good quality is based on fairly definitive conclusions with few well-designed studies while acknowledging the evidence limitations. Low quality supports insufficient evidence with inconsistent results.[14]

RESULTS

Ryken *et al*.,[17] developed guidelines for the role of steroids in the management of brain metastases. It was the only guideline given the appraisal rating of high due to the rigorous eligibility criteria for their study selections as well as their strict methodology for study quality assessment. It is important to acknowledge that their rigorous methodology limited the number of eligible studies to only two, one of which was omitted due to the lack of statistical analysis. Therefore, only one well-designed randomized control trial (RCT) was used to establish clinical recommendations.

Two evidence-based practice guidelines were appraised with a good grading. The AANN published guidelines for the adult brain tumor patient. The appraisal quality was good as the evidence was supported by RCTs lacking limitations and included observational studies.[1] The second was a guideline on the use of dexamethasone in patients with high-grade glioma from the Alberta Provincial Central Nervous System Tumor Team published by Kostaras *et al*.[12] Although this guideline had the largest number of total inclusion studies, the inclusion criterion was rather weak with many RCTs that lacked important limitations including prospective cohort studies, case–control studies, and case series.[12]

Finally, two of the five guidelines were given an appraisal grading of low. The European Federation of Neurological Societies published guidelines on the diagnosis and treatment of brain metastases by Soffietti *et al*.[20] Their evidence appraisal grading was low as their recommendations were based on the consensus of expert opinion labeled as "Good Practice Points."[3] Bhangoo *et al*.[2] published guidelines for the management of brain metastases. Their appraisal rating was also low as their recommendations were also based on evidence provided by expert opinion, case studies, case reports, and studies with historical controls.[2] There was also a lack of clarity in the total number of inclusion studies. Table 3 provides a summary of the clinical practice guidelines reviewed, their associated appraisal grading, and their recommendations.

DISCUSSION

All clinical practice guidelines agree that appropriate dosing is dependent on the severity of symptoms exhibited by the patient. Steroid use in the asymptomatic patient was difficult to determine based on the limited available evidence. Soffietti *et al*.[20] did not recommend the use of steroids in the asymptomatic patient based on expert opinion. Ryken *et al*.[17] could not draw any conclusions based on insufficient evidence. The general consensus for patients with mild to moderate symptoms was a dexamethasone starting dose of 4–8 mg/day in divided doses and up to 16 mg/day in patients with more severe symptoms such as those with impending brain herniation.[2,12,17,20]

The RCT by Vecht *et al*.[23] laid the foundation for these dosing recommendations. They found no difference in Karnofsky performance score between patients receiving dexamethasone 4 mg/day versus 16 mg/day, after 1 week of steroid treatment.[23] It is important to acknowledge that although this was a foundational study, there was a

Table 3: Evidence-based practice guidelines for steroids in the management of brain tumors

Study/guideline	Number of inclusion studies	Appraisal grading	Dosing recommendations	Taper/monitoring recommendations
AANN[1]	4	Good	-	Nurses should be aware of side effects and provide ongoing assessment Nurses should work with the team to manage
Bhangoo *et al*.[2]	Unknown	Low	Mild-moderate symptoms 4-8 mg/day Severe: Up to 16 mg/day	Taper over 2 weeks
Kostaras *et al*.[12]	8	Good	Postoperative maximum dose 16 mg/day	Individualized tapers Careful monitoring of organ system side effects
Ryken *et al*.[17]	2	High	Starting dose 4-8 mg/day Severe symptoms: 16 mg/day or more	Taper over 2 weeks
Soffietti *et al*.[20]	Unknown	Low	Starting dose 4-8 mg/day Severe symptoms: 16 mg/day or more	Reduce dose in 1 week Wean off in 2 weeks

AANN: American Association of Neuroscience Nurses

relatively small sample size, the statistical analysis lacked clarity, and the results may be inconsistent.[17]

Doses >16 mg/day have not been well researched and careful consideration is warranted in those with severe symptoms associated with increased intracranial pressure.[17,20] Tapering over 2 weeks was the general consensus,[2,17,20] but individualized tapered dosing schedules may need to be considered.[12] Recommendations for glucocorticoid stress dosing in the acutely ill brain tumor patient was not addressed in any of the reviewed guidelines.

One retrospective study analyzed 138 brain tumor patients who received dexamethasone during their radiation treatment.[10] They found that the most frequent side effect reported was a rise in serum glucose >100 mg/dl (47% of brain metastases vs. 72% of primary brain tumors). Other common side effects reported were peripheral edema (11% of metastases), psychiatric disorders (9.9% of metastases vs. 10.6% of primary brain tumors), and Cushing's syndrome (14.9% of malignant gliomas). Life-threatening complications were rare.[10] It is important to recognize this study did have many limitations, as there was no fixed protocol for dexamethasone dosing and a lack of study controls.

Recommendations for monitoring steroid-induced side effects were addressed by two clinical practice guidelines reviewed, Kostaras *et al*.,[12] and the AANN.[1] Kostaras *et al*.[12] gave very detailed recommendations for the prevention and treatment of common complications of dexamethasone use based on organ system. For example, they recommend the use of prophylactic proton pump inhibitors for patients with a prior history of peptic ulcer and the use of psychotherapy plus an antidepressant, with or without the use of an anxiolytic for the treatment of anxiety or mood disorder.[12] Recommendations for appropriate monitoring parameters or screening tools to assess for steroid-induced complications were not addressed.

AANN was the only clinical practice guideline reviewed that addressed specific recommendations regarding appropriate nursing interventions related to corticosteroid potential side effects. AANN recommends that nurses should administer steroids as ordered by the provider and are responsible for monitoring drug-related side effects. Furthermore, nurses should work with their health care team to manage these side effects. AANN made several broad recommendations, including but not limited to monitoring blood glucose levels, hyperglycemia education, assessing for signs of opportunistic infection and muscle weakness, and monitoring for behavioral changes.[1] In reviewing the foundational evidence, there was no mention of appropriate screening interval frequencies or any additional quantitative tools that would better assist nursing to monitor for steroid-induced toxicities.

CONCLUSION

Dexamethasone has been used for many decades in the management of cerebral edema in the brain tumor patient. Multiple evidence-based practice guidelines have been published on the appropriate dosing and tapering of dexamethasone to ultimately reduce the risk of steroid toxicities. As discovered, more high-quality, well-controlled, and statistically analyzed research is needed around dexamethasone dosing in the management of cerebral edema in the brain tumor patient. Many of the published guidelines are based on foundational evidence that lack these important qualities.

Furthermore, prevention of steroid-induced complications needs to be encompassed in evidence-based guidelines. Although it is important to know how to treat steroid induce complications, knowing how to screen in order to prevent or limit their toxic effects is crucial. For example, when and how often should fasting plasma glucose be checked? This becomes even more complex in the outpatient setting. Guidelines should also address specific, quantifiable tools that are essential in prevention, such as

a baseline depression and/or anxiety screen prior to the initiation of high-dose steroids. Future evidence-based guidelines should provide recommendations for appropriate interval screening tests and quantifiable tools needed to aid in monitoring complications.

Finally, collaboration between disciplines is a necessity when monitoring and managing steroid-induced toxicities in brain tumor patients. Each discipline is being guided by the foundational research of their practice. Care teams need to collaborate to bring the knowledge and evidence that support each discipline. It is essential for evidence-based guidelines to address both nursing and provider interventions. Future guidelines need to be developed in a multidisciplinary fashion bringing the experts from different disciplines together to manage the complex brain tumor patient. Although it is important for nursing to understand and monitor for possible side effects exhibited by their patient, the providers who are prescribing need to collaborate with nursing to manage these complications.

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Conflicts of interest
There are no conflicts of interest.

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