



Corticosteroid Therapy for Brain Tumor Patients with Adrenal Insufficiency

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Abstract

The use of corticosteroids in cases of brain tumors has become common to reduce brain edema. However, the use can cause adrenal insufficiency (AI) if used long-term and in large doses and with rapid withdrawal. In cases of pituitary macroadenoma that has undergone surgery, AI may also occur. AI also affects the treatment of brain tumor patients. Hence, AI is an important problem in brain tumors because almost all patients with brain tumors receive corticosteroids at some point in the course of their disease. The management is similar to another AI with focus of hydrocortisone treatment. The adjustment of hydrocortisone dosage in patients whom undergo brain surgery is similar with another major surgery, whether the adjustment for pituitary adenoma patients whom undergo excision is more complicated and careful due to the high risk and incidence of AI in these patients.

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Introduction

The use of corticosteroids in cases of brain tumors has become common. In brain tumors, corticosteroid is primarily intended to reduce the tumor-surrounding edema, thus lessening the mass effect to the brain. Further, due to its glucocorticoid activity, corticosteroid can also be used to target lymphoma in the central nervous system, and also to prevent or treat chemotherapy-induced nausea and vomiting [1].

Although corticosteroid is widely used, however, there is a serious concern in the effect of steroid. Prolonged use with large dose and inappropriate withdrawal of corticosteroid tends to cause adrenal insufficiency (AI), which might cause morbidity and mortality to patients [2]. AI can also occur in cases of pituitary macroadenoma that has undergone surgery [3], [4]. The presence of AI, therefore, will affect the treatment of brain tumor patients [4]. This paper will discuss about corticosteroid management in brain tumor patients with AI.

Physiology of Cortisol in Brain Surgery

Corticotrophin-releasing hormone (CRH), released by the hypothalamus, stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. To complete the hypothalamic-pituitary (HPA) axis, cortisol (the stress hormone) is then produced by adrenal glands following ACTH stimulation. The HPA axis is regulated by a negative feedback mechanism in which cortisol suppresses the release of both CRH and ACTH. Cortisol is a catabolic glucocorticoid hormone that mobilizes energy stores to prepare the body for the fight or flight response to stressors. It promotes gluconeogenesis in the liver, leading to raised blood glucose levels. Hyperglycemia, however, reduces the rate of wound healing and is associated with an increase in infections and other comorbidities including ischemia, sepsis, and death [5]. Aside from its metabolic effect, cortisol is also a potent anti-inflammatory hormone capable of preventing the widespread tissues and nerve damage associated with inflammation [6]. Moreover, cortisol is also reported

to have an effect on the cardiovascular system, due to the contribution of endogenous cortisol secretion on the circadian rhythm of blood pressure [7], [8]. Dysregulation on HPA has also been suggested as one of the factors involved in the pathogenesis of essential hypertension [9], [10]. Exogenous corticosteroids are also known to have an effect on increased risk of cardiovascular and cerebrovascular diseases [11]. On the other hand, lack of cortisol, such as in AI, also has its own consequences. The most dangerous complication of AI is adrenal crisis, which can lead to death mostly due to hypoglycemic shock [12], [13].

Following surgical or accidental trauma, the nervous system activates the stress response by sending impulses from the injured site to the hypothalamus. The hypothalamus either removes its inhibitory tone on the pituitary or releases hormones which stimulate the production and/or release of pituitary hormones. Pituitary hormones act on their respective target organ causing the release of hormones such as the stress hormone and cortisol [14].

During and after surgery high levels of both ACTH and cortisol persist in the blood. Beside the grade of surgery, high cortisol level is also affected by anesthesia. The type of anesthesia also determines the effect on cortisol level, in which general anesthesia raises higher cortisol level right after the administration and returns back to normal level at after 24–48 h after uncomplicated surgery [15]. The time in which a surgery is performed also appears to have an effect on the cortisol level in a day. Cortisol level on surgery during later periods (i.e., afternoon) in a day is reported to result in earlier return to normal level compared to earlier periods (i.e., morning) [16]. In the presence of raised cortisol levels in a severe stress response, the rate of protein breakdown exceeds that of protein synthesis, resulting in the net catabolism of muscle proteins to provide substrates for gluconeogenesis. Further substrates for gluconeogenesis are provided through the breakdown of fat. Triglycerides are catabolized into fatty acids and glycerol, a gluconeogenic substrate [5], [14].

AI in Brain Tumor

AI is a serious concern in brain tumor patients. Almost all patients with brain tumors receive corticosteroids at some point in the course of their disease [17], [18]. The use of corticosteroids in brain tumor patients can cause AI if used in long-term with large doses and with rapid withdrawal, thus causing suppression of the HPA [2]. In prolonged suppression of HPA, adrenal glands eventually atrophy and take months to years to recover some degree of functioning [19]. The incidence of AI in cases of corticosteroid use in cases of brain tumors ranged from 1% to 2% [2].

AI in brain tumors can also be found in cases of pituitary macroadenoma that has undergone excision surgery. Manipulation and damage to the pituitary gland during surgery may prevent the proper secretion of ACTH, disrupting the HPA axis and secretion of the cortisol [20]. The incidence of AI in post-operative macroadenoma cases is about 5–10% [3], [21]. Pituitary hemorrhage or infarction (Sheehan syndrome) can also lead to secondary AI [12].

Management of Secondary AI in Brain Tumor Patients Whom Receives Long-term Corticosteroids

Determination of AI after long-term corticosteroid administration in brain tumor patients is carried out the same way as in other patients. Patients at high risk are patients with a prednisone dose of ≥ 20 mg/day, or equivalent treatment for more than 3 weeks, or; dose ≥ 5 mg of prednisone administered during the evening/night for more than 2 weeks, or; patients with clinical signs of Cushing syndrome [22].

Tests performed include the insulin hypoglycemia test, short stimulation test with synthetic ACTH at standard dose, short stimulation test with synthetic ACTH at low dose, metyrapone test, and glucagon test [23], [24], [25], [26], [27]. The determination of AI should be carried out in a multidisciplinary manner with an endocrinologist as the main determinant [4], [22].

Once established, AI must be managed immediately to prevent adrenal crisis. The management of secondary AI in brain tumor cases is based on glucocorticoid replacement. In secondary AI, mineralocorticoid production is preserved because aldosterone secretion is mainly regulated by the renin-angiotensin system with minimal dependence on ACTH; therefore, do not require mineralocorticoid replacement therapy [22].

Hydrocortisone is currently recommended as the glucocorticoid of choice in case of AI. The use of hydrocortisone allows for reaching optimum cortisol levels 30 min after oral intake [28]. Hydrocortisone has a mean plasma half-life of 95 min. Its high oral bioavailability and short half-life result in a profile with high peaks 1–2 h after administration, followed by a rapid decline after 5–7 h [29].

Although the current rapid release presentations of hydrocortisone are not able to mimic circadian rhythm of cortisol, an attempt is made to approximate this by giving divided doses. To avoid glucocorticoid overexposure, especially from midafternoon (because of its relationship to insulin resistance and the untoward metabolic consequences), various schemes have been

proposed. Recommended doses are 15–20 mg or 30 mg of oral hydrocortisone daily. Options of dividing the dosage include dividing the dose into two fractions (2/3 of the total dose in the morning upon awakening and 1/3 in midafternoon) or three fractions (1/2 of the total dose at 7 AM, 1/4 at 12 AM, and 1/4 mg at 4:30 PM) by avoiding administration later than 6 PM [4], [22]. Although there is no convincing evidence, three divided doses may partly correct the afternoon nadir in cortisol levels which occurs if two doses are administered [30], [31].

Monitoring of long-term glucocorticoid treatment in brain tumor patients is essential. The dose of glucocorticoid, if necessary, can be modified based on clinical symptoms and signs [29]. There are no objective parameters to assess the quality of replacement therapy. The lowest dose of glucocorticoid, based on weight calculation that relieves symptoms of glucocorticoid deficiency should be used to prevent overdosing [32], [33]. It is important to estimate daily dose of glucocorticoid and its distribution, and to adjust treatment to stress and intercurrent diseases [29].

The main clinical assessments for AI patients are weight control (measured and recorded periodically), clinical signs of AI, and signs of hypercortisolism/Cushing syndrome. Routine measurement of ACTH or cortisol curves is not required [22]. If patients have symptoms of glucocorticoid deficiency (fatigue, lack of energy, nausea, myalgia, and weight loss), dosage should be increased. However, if symptoms do not improve, treatment should be resumed at the previous dose and other potentially responsible causes should be assessed [32]. Dose will be excessive if symptoms or signs of Cushing syndrome occur (weight increase, central obesity, striae, osteoporosis, insomnia, edema, HBP, and impaired glucose metabolism) [22].

Management of Secondary AI in Brain Tumor Patients Whom Undergo Brain Surgery

Insufficient cortisol production during a surgical stress response leads to adrenal crisis. This condition is marked by progressive loss of vasomotor tone and impaired alpha-adrenergic receptor responses to noradrenaline. Ongoing reductions in vascular tone lead to orthostatic hypotension followed by supine hypotension and finally shock, which will be fatal if not rapidly corrected. A tendency on water retention and hyponatremia induced by antidiuretic hormone is very common after surgery. Thus, patients with insufficient aldosterone production will be particularly susceptible to hyponatremia [34].

Surgical stress is not an all or nothing phenomenon. The level of surgical stress is varied for

each patient. Patient-specific, surgical, and anesthetic procedures are factors that determine the level of surgical stress, as well as its pre-operative and post-operative care. In a recent systematic review and meta-analysis by Prete *et al.*, perioperative cortisol concentrations in 2953 patients were escalated and more prominent in older subjects and woman with procedures involving open surgery and general anesthesia [35].

The recommendations of hydrocortisone adjusting dosage for brain tumor patients whom undergo brain surgery are divided into pre-operative, intraoperative, and post-operative adjustment. The recommendation of pre-operative adjustment is the administration of 100 mg of hydrocortisone intravenously right before the anesthesia followed by continuous infusion of 200 mg of hydrocortisone in 24 h. For post-operative treatment, continuous infusion of 200 mg of hydrocortisone in 24 h or 50 mg of hydrocortisone intramuscularly per 6 h can be given if enteral administration is not possible. If enteral administration is possible, hydrocortisone dose can be doubled for 48 h before continue with usual treatment dose. In patients whom receive hydrocortisone treatment for more than 4 weeks before surgery, double dose of hydrocortisone can be given for 48 h up to 1 week after surgery followed with usual treatment dose [34].

Management of AI in Pituitary Adenomas Patient Whom Undergo Tumor Removal Surgery

Management of AI in pituitary adenomas patient is different and more complex, especially for post-operative requirements. The pre-operative and intraoperative requirements are nearly same as other brain tumor patients with AI whom undergo brain surgery. Another strategy is by giving hydrocortisone sodium succinate can be given 50 mg intramuscularly at 11 PM and 6 AM (before surgery) and right before surgery 50 mg of hydrocortisone mixed with 1000 ml of D5LR + 20 mEq KCl/l are given at the rate of 75 ml/h. During surgery, intravenous administration of 100 mg of hydrocortisone can be given every 8 h [4].

Post-operative management of steroid is trickier in these patients. For the patients with adequate level of cortisol before surgery and low suspicious of ACTH deficiency after surgery, the 50 mg of hydrocortisone can be given intramuscularly or by intravenous infusion every 6 h for 24 h after surgery. On day 2 after surgery, the steroid regiment is then changed to enteral prednisone with the dose of 5 mg every 6 h, followed by 5 mg of prednisone every 12 h. The steroids can be discontinued after 5 days [4].

However, if there is hypocortisolemic condition before surgery or there is a suspicious of possibility

of ACTH deficiency in the patient after surgery, the approach is very different. The 50 mg of hydrocortisone can be given intramuscularly or by intravenous infusion every 6–12 h and taper and stopped after 24–48 h postoperatively. After 24 h of discontinuation, check the 6 AM cortisol level. If the cortisol level is >9 mcg/dl, then no further tests or treatment required. However, if the cortisol level is lower than 9 mcg/dl, there is a possibility of ACTH deficiency that is harmful to the patient. If adrenal reserve can be formally assessed, patient can be discharged on 50 mg of hydrocortisone every AM and 25 mg every 4 PM usually until 1 month after surgery [4].

The hydrocortisone then tapered at home 10 mg/doses daily for 2–3 weeks down to 20 mg every AM and 10 mg every 4 PM and it holds for several days, usually until 1 month after surgery as mentioned above. The patient was then asked to hold the PM dose and check an 8 AM serum cortisol the next day before taking the AM dosage. To avoid AI in patients with incompetent reserve, as soon as the blood is drawn have the patient take their morning cortisol dose and resume regular dosing until the test results are available. If 8 AM cortisol test shows any significant adrenal function (>9 mcg/dl), then taper the patient off hydrocortisone [4], [36].

The problem is when the patient's 8 AM cortisol test is under 9 mcg/dl. The guideline suggests the use of metyrapone test. This test more accurately assesses the HPA-adrenal axis and is useful if there is suspicion of reduced reserve of pituitary ACTH production. Metyrapone inhibits 11- β -hydroxylation in the adrenal cortex, reducing production of cortisol and corticosterone with concomitant increase of serum 11-deoxycortisol precursors and its 17-OHCS metabolites which appear in the urine. In response, a normal pituitary increases ACTH production. First of all, the patients should have a synthetic ACTH stimulation test first to rule out primary AI. This test is forbidden if there is known primary AI and the patient must be tested as an inpatient. The patient will be given 2–3 g metyrapone at midnight. On the next morning, the serum 11-deoxycortisol level will be checked. Normal response is a 11-deoxycortisol level >7 mcg/dl. If the level is below 7 mcg/dl, the ACTH deficiency can be ruled in and the permanent hydrocortisone treatment, as in other AI patients must be given [4].

Summary

AI is one of serious and problematic concern in brain tumor patients who receive steroid therapy or after pituitary macroadenoma surgery. Improper steroid management in these patients can lead to morbidity and even mortality. Therefore, exact diagnosis and appropriate steroid therapy in brain tumor patients with AI is essential, particularly those who undergo surgery.

Dosage of steroid can be adjusted depends on surgical stress and patient's condition after surgery in collaboration with anesthesiologist and endocrinologist [1].

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