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Chapter

Corticosteroids in Neuro-Oncology: Management of Intracranial Tumors and Peritumoral Edema

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Abstract

Corticosteroids have been in use for decades and are one of the most prescribed drugs in all specialties of medicine. Jerome Posner, in his classic textbook "Neurological Complications of Cancer," refers to corticosteroids as widely used drugs in neuro-oncology leading to a remarkable decline in perioperative mortality and morbidity rates. Being the most powerful class of tumor-induced-edema reducing agents, they are adjuvant to chemotherapy and are also known to reduce the risk of encephalopathy and other associated neurological deficits in patients undergoing radiation therapy. They have been widely used in higher-than-normal doses in the management of pathologic, immunological, and inflammatory conditions and various other diseases. Novel insights into the mechanisms of action of corticosteroids and their effects on cancer patients are extensively being studied. While substantial clinical improvements can be seen in cancer patients, corticosteroids are also associated with adverse and well-characterized side effects leading to immediate as well as long-term complications in patients. This chapter reviews the clinical aspects of corticosteroid therapy used in neuro-oncological conditions and its effects on peritumoral edema. Although there is currently insufficient information on appropriate use, in most cases, corticosteroids are used in a supraphysiological and pharmacological manner to minimize the symptoms of cerebral edema. Due to limited clinical studies and evident side effects presenting synonymously with corticosteroid therapy, the emerging role of steroid-sparing drugs such as corticotrophin-releasing factors, tyrosine kinase inhibitors, and VEGF inhibitors will also be discussed.

Keywords: Neuro-oncology, brain tumor, cerebral edema, corticosteroid therapy, dexamethasone, bevacizumab

1. Introduction

Corticosteroids are synthetic analogs of a class of naturally synthesized hormone molecules in the adrenal cortex that act as biological mediators. These hormones play a vital role in regulating essential bodily processes such as metabolism, inflammation, response to stress, and electrolyte balance.

Corticosteroids have been classified based on major effects exhibited by them into glucocorticoids and mineralocorticoids. Glucocorticoids provide anti-inflammatory responses by suppressing inflammation and immunity, exert vasoconstrictive, and are responsible for the breakdown of fats, proteins, and

carbohydrates. Cortisol is a physiological mediator well-characterized to exhibit glucocorticoid effects in humans. Mineralocorticoids exhibit salt-retaining and electrolyte-balancing properties. A prominent hormone, aldosterone, projects the strongest mineralocorticoid activity. The pioneering of corticosteroids (such as dexamethasone, prednisolone, prednisone) has revolutionized the treatment approaches in the field of clinical oncology [1]. They mimic the action of naturally occurring hormones, are currently one of the most prescribed drugs worldwide, and can be used to treat several conditions such as infections, inflammatory disorders, allergic and autoimmune diseases, shock, lowering of excessive blood calcium levels, hypoglycemia, suppression of excess secretion from the adrenal cortex, prevention of graft rejection, neurological disorders, hematologic disorders, skin disorders, and corticosteroid replacement therapy [2, 3].

Steroids administered to brain tumor patients do not directly treat the tumor but are targeted to reduce edema surrounding the tumor (induced by the tumor itself or its treatment) thereby the mass effect and lymphoma in the central nervous system, prevent or alleviate the symptoms of nausea, vomiting and headache post-chemotherapy and temporarily improve other associated neurological symptoms [1]. They can cross the blood–brain barrier and act as analgesic agents by inhibiting the synthesis of prostaglandins thereby reducing inflammation and tissue edema is resolved by decreasing vascular permeability. Sustained use in high doses requires close monitoring to prevent and manage its side effects and intervene if other complications arise.

2. Traditional approaches to steroid therapy in brain tumor patients

The introduction of steroids, 50 years ago, revolutionized therapeutic approaches in Clinical oncology. The first use of cortisone to treat cerebral edema developed in patients post neurosurgery was accomplished by Ingraham in 1952 [4]. About five years later, Kofman pioneered the use of prednisone for peritumoral edema induced in patients with intracranial malignancies [5]. Dexamethasone, synthesized in 1958, is based on Galcich's experimental demonstration of brain tumor inhibition upon administering large doses of dexamethasone [6]. Its pioneering fundamentally changed the course of corticosteroid therapy in cancer patients and to date has been the most commendable drug due to its conducive effects in alleviating symptoms of tumor-induced cerebral edema and offers benefits of low sodium and water retention index thereby reducing the risk of electrolyte imbalance, low mineralocorticoid effect, and high glucocorticoid potency [1, 7, 8].

With further advancements, exhibited antineoplastic effects of dexamethasone, prednisone, prednisolone, and methylprednisolone against hematologic malignancies, their antiedema, and anti-lymphoma properties were known [9]. The administration of steroids has proved beneficial in rapidly relieving symptoms, minimizing tumor-associated pain, nausea, and vomiting, and ameliorate appetite in tumor patients [10]. Its advantageous characteristics have found immense clinical applications such as in treating patients with carcinomatous meningitis and lymphoma in the central nervous system [11].

3. Molecular mechanisms

Corticosteroids are the mainstay of treatment for neuro-oncological conditions, and they undergo various molecular mechanisms at the cellular level to give desired clinical results. These mechanisms are complex and distinct and with currently

limited evidence, are divided into genomic and non-genomic. The consensus is that the genetic level, effects such as an increased rate of transcription known as trans-activation, a transrepression-a process in which one protein represses the activity of the second protein, and post-translational regulation i.e., controlling the levels of active protein, can be seen, constituting the genomic mechanism, and producing anti-inflammatory effects. Activating a cascade of signaling pathways constitutes the non-genomic effects. These mechanisms mediate several side-effects, such as diabetes and glaucoma due to transactivation while suppression of hypothalamic–adrenal–pituitary axis due to transactivation. Both transactivation and transrepression seem to be involved in osteoporosis. Glucocorticoids bind to complementary cytoplasmic receptors upon diffusion through the plasma membrane. The binding of this free glucocorticoid receptor leads to the release of a heat-shock protein 90 kDa which in turn exposes two nuclear localization signals responsible for facilitating the movement of the glucocorticoid–receptor complex into the nucleus [12]. Specific DNA (deoxyribonucleic acid) elements called glucocorticoid response elements (GRE) regulate the transcription of nuclear DNA. Synthesis of several cytokines and chemokines involved in regulating inflammatory reactions such as *eotaxin* and *lipocortin 1* is suppressed by glucocorticoids at the level of transcription [13]. The interaction of glucocorticoids with other transcription factors such as p53 indirectly influences their activity on their target genes [14]. The production of proinflammatory cytokines and chemokines is controlled by transcription factors such as NF-KB, CRE-binding proteins, among others, and leads to activation of inflammatory pathways. Therefore, inhibiting these transcription factors induces anti-inflammatory responses [12, 15]. To summarize the mechanism: corticosteroids bind to intracellular cytoplasmic receptors upon crossing the plasma membrane and form the steroid–receptor complex. Consequently, the movement of the steroid-receptor complex into the nucleus directly influences the transcription of genes and upon interaction with other transcription factors, a non-transcriptional regulation of other signaling cascades is mediated.

4. Vasogenic edema and Antiedema property of corticosteroids

The use of corticosteroids for the management of malignant brain tumors and symptomatic peritumoral edema was recognized several decades ago [3]. They are frequently prescribed to reduce the increased intracranial pressure caused due to peritumoral fluid accumulation. Although edema occurs in patients with malignant lesions but is also evident in cases of benign tumors such as meningiomas [16, 17]. A disruption in the blood–brain barrier leads to the flow of fluid into extracellular spaces of brain parenchyma resulting in vasogenic edema. This disruption results in increased permeability of the BBB primarily due to the opening of the inter-endothelial tight junctions and increased endothelial pinocytosis and endothelial fenestrations [18, 19]. An insufficient number of normal astrocytes, responsible for producing factors that are required for the formation of normal BBB, results in defects in endothelial tight junctions, production of cytokines such as vascular endothelial growth factor (VEGF) [20], and hepatocyte growth factor [21] by both benign and malignant brain tumors and increase tumor vessel permeability [22]. The suggested mechanism of corticosteroids is a reduction in permeability of tumor vessels by upregulation of genes and molecules such as occludin, a tight junction component in endothelial cells [23], and by dephosphorylating occludin and another TJ component, zona occludens (ZO1) [24]. Another mechanism of influencing the endothelial permeability is by non-transcriptional regulation of capillaries that involves rearranging and attachment of vascular endothelial (VE)-cadherin

to the cytoskeleton [25]. The permeability of the blood–brain barrier is decreased upon steroid administration and this limits the extravasation of fluids [26, 27].

5. Treatment of Lymphomatous neoplasms

Steroids are frequently prescribed in patients with primary lymphoma in the central nervous system or in cases of secondary lymphomatous neoplasms where they rapidly respond by promoting cell cycle arrest and cell death by the mechanism of apoptosis in a p38 mitogen-activated protein kinase (MAPK) dependent manner in B and T cells [27–29]. Steroids are administered during the initial stages along with chemotherapy and the clinical and radiographic response can be rapid in cases of lymphoma and inflammatory conditions. Some preclinical studies suggest that proliferation of some glioma cells may reduce upon dexamethasone exposure [30]. On the other hand, certain reports suggest that steroids have no effect or stimulate the growth of glioma cells [31, 32]. Effects of steroids can be transient and require chemotherapy or irradiation to prevent the recurrence of the tumor [33]. Furthermore, there is no significant clinical evidence so far that proves the role of steroids in the growth inhibition of gliomas or metastasis in humans.

6. Anti-emetic properties

Steroids are administered either singly or in combination with 5HT-3 receptor antagonists, neurokinin-1 receptor antagonists, and aprepitant for the prophylaxis and the treatment of chemotherapy-induced nausea and vomiting and to manage subsequent symptoms of dehydration and electrolyte imbalance [34]. Steroid administration leads to a reduced release of serotonin from hematocytes and this directly affects the cellular expression of its receptors, thereby preventing nausea and vomiting [35, 36]. The most favorable corticosteroids are methylprednisolone and dexamethasone in patients with moderate to high emetogenic chemotherapy.

7. Dosing and tapering

Steroid administration is adjuvant to chemotherapy and all cancer patients will receive steroid therapy at some point in their cancer treatment and may continue to receive them through surgery, chemotherapy, radiation, and prolonged use may be needed because of its benefits of symptomatic relief. Despite its extensive use, there is a lack of significant clinical evidence about the choice of drug, dose, duration, and tapering schemes.

Various clinical trials have been conducted that aim to assess the effects of doses of 8 mg versus 16 mg dexamethasone and 4 mg versus 16 mg in patients with peritumoral edema. Significant clinical improvement among all groups administered with dexamethasone can be seen on the Karnofsky performance scale. Low doses of dexamethasone (4-8 mg/day) are recommended to avoid developing serious complications but they may require reinstitution after cessation of steroid therapy [37]. Whereas higher doses of dexamethasone (16 mg/day) along with osmotherapy (mannitol, glycerol) or surgery, may be required in adverse conditions [38]. In some cases, higher than usual doses may be required for headaches. Current evidence has a lack of information about the correlation between dose and body weight or dose and age. Attempts to standardize the steroid therapy regimen have remained unsuccessful and it is suggested that the dosage must be altered according to the specific needs of

the patient depending on the size of the lesion, location, mass effect, and presenting symptoms. It is recommended that for successful results and for preventing steroid-associated toxicity, tapering should be considered as soon as clinically acceptable [39]. Interestingly, a longer duration of 23 weeks of steroid therapy is required for patients with a primary brain tumor as opposed to 7 weeks that is required for secondary brain tumors. Steroid therapy can be stopped quickly in patients that have been receiving it for a shorter duration, usually 10–14 days. On the other hand, careful and closely monitored tapering is required for patients with prolonged steroid use to avoid declination of their medical state and/or dependency or withdrawal effects and evident hypercortisolism. Hydrocortisone, which is commonly prescribed in 2 doses per day to mimic the physiological action of cortisol in patients with its deficient levels. 20 mg and 10 mg dose administration in the morning and afternoon, respectively, are suggested for patients with remarkably high cortisol insufficiency [40].

8. Side effects

Depending on the type of drug and prescribed dose, a wide spectrum of systemic and neurological side effects can occur in response to corticosteroid therapy. While manifestations of some side effects can be seen immediately upon administration of corticosteroids, others may develop over time and may persist even after steroid therapy has been terminated, such as cataract formation and osteoporosis [1]. Most side effects are easily manageable, but some can be fatal. Patients considered at substantial risk have impaired immune systems either due to organ transplantation or upon undergoing chemotherapy or radiotherapy.

8.1 Systemic

Systemic side effects include a cushingoid appearance, truncal obesity, hirsutism, acne, impaired wound healing, striae, nausea, anorexia, easy bruising and capillary fragility, immunosuppression, hypertension, increased risk of infections, respiratory muscle weakness, glucose intolerance, electrolyte disturbance, fluid retention, peripheral edema, increased appetite, gastrointestinal bleeding, growth retardation, cataracts, glaucoma, and visual blurring [41].

Arterial hypertension, considered as the most common side effect, occurs in 20% of the patients. It is usually reversible and blood pressure values attain a normal value upon cessation of steroid intake. For patients whose steroid therapy cannot be discontinued, hypertension requires symptomatic treatment. Since the main cause of hypertension is an abnormal increase in the volume of blood plasma by steroids, the preferred line of treatment is the use of diuretics [42].

8.2 Gastrointestinal

Although, no significant correlation between steroid usage and gastrointestinal bleeding has been found in clinical studies, yet histamine H2 antagonists and proton pump inhibitors are commonly prescribed to minimize the risk of gastric ulcers, hemorrhage, and other rare gastrointestinal problems such as pancreatitis, colon perforation, and fatty liver disease [43–45].

8.3 Osteoporosis

An increase in cases of developing osteoporosis and avascular necrosis is seen in patients receiving steroid therapy evident from the lumbar spine and hip

fractures [46, 47]. Although several factors can contribute to the occurrence of osteoporosis, yet the suggested mechanism is that due to skeletal muscles getting directly affected by the glucocorticoids, calcium absorption is reduced leading to hyperparathyroidism and a decrease in gonadal hormones. Molecular studies suggest a decrease in IGH-1 and prostaglandin E2, which are responsible for stimulating bone growth [48]. Administration of phenytoin and valproic acid also promote osteoporosis [49–51]. To prevent/manage the symptoms of osteoporosis calcium supplements (1500 mg/day), Vitamin D (800 international units/day) [48], and bisphosphonates such as alendronate and zoledronate are commonly prescribed [52]. Kyphoplasty may be required in patients with severe pain from compression fractions.

8.4 Neurological and neuropsychiatric

Common neurological side effects of corticosteroids are myopathy, visual blurring, tremor, behavioral changes, headache, reduced taste and smell, and cerebral atrophy while rare complications include psychosis, hallucinations, neck flexors, dementia, seizures, dependency, epidural lipomatosis, and neuropathy.

Most pervasive yet mild neuropsychiatric effects such as anxiety, insomnia, irritability, euphoria, and mood disturbances may develop in response to corticosteroid therapy. Adverse effects include euphoria, steroid-induced dementia, cortical atrophy, cognitive dysfunction, memory loss, and psychotic episodes that may occur but are more likely in patients with a history of psychiatric disorders. Episodes of seizures may relapse in patients with a history of seizure disorder. Impairment in physiology during the development of the brain such as hippocampal neurogenesis is seen in animal models administered with corticosteroids. Similarly, prednisolone has been shown to negatively affect verbal memory function in humans and long-term cognitive dysfunction is evident in children if taken in combination with dexamethasone. However, it can be challenging to differentiate between the manifestations of radiation therapy, gliomas, and the increase in levels of intracranial pressure with complications occurring due to corticosteroid use. Discontinuation or tapering is recommended for managing steroid-induced neuropsychiatric effects as soon as clinically acceptable. Prednisone dose must be kept lower than 40 mg/day. The use of Neuroleptics, valproic acid, and lithium can be considered but tricyclic antidepressants should be avoided as they can worsen the condition [53–57].

8.5 Myopathy

Although the pathophysiology of steroid myopathy remains unknown, yet it has been shown to negatively affect the quality of life in patients. Clinical studies suggest that steroid myopathy occurs more commonly (almost 10%) in patients with primary brain tumors administered with fluorinated glucocorticoids such as dexamethasone over the ones administered with non-fluorinated glucocorticoids, such as hydrocortisone or prednisone (which may not have proven to be highly effective in controlling cerebral edema) [58–60]. Common symptoms associated with steroid myopathy are a proximal weakness with normal sensation and deep tendon reflexes intact. Detection is made using electromyography. The probable mechanism of steroid myopathy can be protein synthesis inhibition, increased protein catabolism, and induction of the activity of glutamine synthetase [61, 62]. Development of muscle weakness may develop even upon administration of low doses over a shorter duration and may not occur in patients even with high doses and prolonged duration of application. Individuals without symptoms of myopathy may also be considered at minimal risk for developing cushingoid features and fluid

retention. In patients with steroid myopathy, the accepted standard of management is the cessation of steroids, but it may still require months for recovery to take place. Steroid-induced muscle wasting is demonstrated to be reduced by muscle activity and hence exercise and muscle therapy are recommended to alleviate the symptoms or reduce the risk of developing steroid myopathy [63].

8.6 Adrenal insufficiency (AI)

About 1% of patients receiving steroid therapy for the treatment of brain tumors develop steroid adrenal insufficiency upon sudden glucocorticoid withdrawal. The presenting symptoms of AI are like those of increased intracranial pressure and side effects of antineoplastic treatment. Management of AI is focused on hydrocortisone treatment and dosage is similar to that recommended for other major surgeries [64].

8.7 Diabetes

Diabetes occurs in up to 50% of steroid-treated patients and is the most common form of drug-induced diabetes mellitus [65]. It is already well known that corticosteroids, such as dexamethasone, prednisone, and hydrocortisone, cause elevations in blood glucose levels in both patients regardless of pre-existing diabetes. Severe hyperglycemia may lead to acute or severe complications, such as dehydration, impaired immune system and wound healing, increased risk of infection, ketoacidosis, and acute hyperglycemic syndrome. According to the Joint British Diabetes Association (JBDA), the predisposing factors for steroid-induced hyperglycemia as pre-existing type 1 or 2 diabetes, obesity, family history of diabetes, among others. Management of steroid-induced diabetes is similar to that of regular type 2 diabetes, and patients consistently showing high blood sugar levels should be treated to prevent long-term complications including cardiovascular and renal damage.

8.8 Steroid withdrawal

Continued corticosteroid therapy can be recommended for patients with advanced or terminal diseases or those in hospice care to prevent withdrawal symptoms including those of steroid-pseudo rheumatism, myalgia, abdominal pain, nausea, arthralgia, and acute adrenal insufficiency (highest risk with more than 6 weeks of administration). The occurrence of these complications with corticosteroid discontinuation would require further medication and treatment, aggravating the symptoms of restlessness, excessive sleepiness and can act as contributing factors in relapsing of masked symptoms. It must be noted that continued corticosteroid administration would still require managing its side effects such as insomnia, hypertension, hyperglycemia, and psychotic episodes.

9. Immunological response to corticosteroids

Immunosuppression is common in response to dexamethasone causing inhibition of immune nend inflammatory responses and therefore, posing a challenge for the development of immunotherapeutic approaches in late-stage cancer treatment. Risk of life-threatening fungal infections such as *Pneumocystis jirovecii* is elevated with administration of moderate to high doses [66].

While the exact mechanism is unknown, dexamethasone has been shown to promote apoptosis in T-lymphocytes [67], suggesting directive nature of T-cell positive and negative selection in the thymus by glucocorticoids, limiting the

activation-induced cell death during the contraction phase of an adaptive immune response and induction of generalized thymocyte apoptosis after polyclonal T-cell activation [68]. A shift in immune response towards a Th2 humoral response from a Th1 cellular response is induced by influencing the levels of cytokines produced by the lymphocytes [69]. Moreover, dexamethasone causes a reduction in the number of splenic and lymph node B-cells and attenuation of early B-cell progenitor proliferation. Glucocorticoids also enhance the activity of macrophages and promote tolerance in dendritic cells thereby, exerting a potent anti-inflammatory effect [70]. The risk for infection may increase by steroid-induced lymphopenia but it also limits the number of treatment strategies applied for activating the immune system and boosting anti-tumor responses.

10. Immunotherapy

Novel immunotherapeutic agents such as ipilimumab are proving their potential efficacy in the treatment of malignant gliomas. A studied mechanism is that it targets cytotoxic T lymphocyte-associated antigen 4 and interferes with the inhibition of T-cell function, which subsequently translates into enhanced antitumor activity.

Current clinical developments are focusing on programmed cell death of immune cell receptor. Hence, clinical trials are being conducted on ipilimumab, that contains anti-programmed cell death-1 antibody, nivolumab for the treatment of glioblastoma [71, 72]. Steroids may interfere with boosting immune response and therefore can be counterproductive for patients delivered with vaccines. Accordingly, several vaccination trials restrict the use of steroids at the time of enrollment to select only patients with a suitable immunological profile.

11. Dexamethasone and phenytoin interactions

Phenytoin is prescribed prophylactically before surgery and in combination with dexamethasone during the initial stages of primary and secondary metastatic brain tumors. Phenytoin may exert protective effects in reducing the risk of steroid-induced myopathy, but the mechanism remains unclear. It is suggested that an increase in the rate of metabolic clearance of cortisol and dexamethasone by phenytoin and decrease in half-life of dexamethasone by 50% and its metabolic conversion to hydroxyl metabolite by the action of CYP3A4, a liver enzyme could be the probable mechanism [73–76]. Levels of phenytoin are contrastingly altered upon co-administration with dexamethasone [77–79]. Hence it is difficult to measure levels of phenytoin in patients taking dexamethasone. Therefore, it also becomes extremely important to carefully monitor levels of phenytoin and tapering should be done as soon as the edema is successfully controlled [80].

12. Dexamethasone and chemotherapy

Administration of glucocorticoids may significantly contribute to altering the pharmacokinetics and may restrict the action of chemotherapeutic drugs from exerting the blood–brain barrier, therefore, limiting the desired effects. It was hypothesized by Duan et al., that hyperglycemia (occurring in response to corticosteroid therapy) inhibits apoptosis and therefore promotes malignant growth, causing proliferation of cells, speeding up the process of metastasis, and aiding resistance to chemotherapy. Dexamethasone exerts protective effects against apoptotic action of

temozolomide in glioma cells in vitro [81]. Ongoing experiments aim to determine the antagonizing or synergizing action of dexamethasone with chemotherapeutic drugs such as rapamycin and apoptotic drugs like staurosporine. Pretreatment and subsequent cotreatment strategies for experiments have indicated an additive effect of dexamethasone in combination with growth factor signaling inhibitors.

13. Alternatives to corticosteroids

Steroids have been shown to have limited effects of clinical significance and there are several side effects associated with it. Therefore, a need for novel anti-angiogenic alternatives such as Bevacizumab with strong steroid-sparing, more effective, and less toxic characteristics, arises. It is a neutralizing antibody that targets a specific protein called VEGF, responsible for promoting the growth and spread of tumor blood vessels, therefore reducing peritumoral edema. A major challenge in the action of anti-VEGF is the inhibition of the action of other drugs administered to target the tumor since drugs similar to bevacizumab also affect normal blood vessels. An approval for bevacizumab is still lacking and the cost is a barrier. Other similar drugs are VEGF -receptor inhibitors such as cediranib, sorafenib, sunitinib. In the same way, tyrosine kinase inhibitors (TKIs) such as cediranib and cabozantinib, target vascular endothelial growth factor receptor 2 (VEGFR-2). Similarly, drugs such as corticorelin acetate, a synthetic analog of corticotropin-releasing factor have been proved to reduce edema by directly acting on CR1 and CR2 receptors in animal models and allows higher maximal reduction of the dexamethasone dose compared with control-treated brain tumor patients in a randomized trial [82–84]. Also, patients receiving corticorelin acetate are less likely to be affected by myopathy or cushingoid appearance. There are still undergoing trials to determine its efficacy in acute and chronic peritumoral edema. The effects of other drugs such as boswellic acids, cyclooxygenase (COX)-2 inhibitors, and angiotensin-II inhibitors on brain tumors is still uncertain [85–87].

14. Glucose levels in patients administered with corticosteroids

Corticosteroid use may cause hyperglycemia in almost 20–50% of patients, therefore negatively affecting patient outcomes. A study conducted in Sunnybrook Odette Cancer Centre in Toronto and published in Annals of Palliative Medicine, upon categorizing patients with and without pre-existing diabetes according to the Canadian Diabetes Association (CDA) criterion for diagnosis of diabetes, concluded that the effects of corticosteroids are dose-dependent and tend to impact random plasma glucose (RPG) levels more than fasting plasma glucose (FPG) levels. In a screening conducted by Harris et al., no correlation between risk factors for diabetes and the patients with hyperglycemia was found, thus recommending that all cancer patients must be screened 4–6 hours post-administration of steroids and additional monitoring may not be required if normal results are obtained on individual tests after initial dosing. Therefore, it seems challenging to determine patients that are at substantial risk for developing corticosteroid-induced hyperglycemia (C-IH) and to prevent it if typical risk factors for diabetes do not show consistency with the development of C-IH. Previously conducted studies concluded that C-IH is common in both patients with and without diabetes [odds ratio of 1.5 to 2.5 and 1.36 to 2.31 for developing glucocorticoid-induced hyperglycemia (GC-IH) in patients treated with a glucocorticoid (GC), respectively] and were strongly influenced by total GC dose, duration of use, age, and BMI (Body Mass Index) [88, 89]. Also, steroids even leading to acute

elevations in blood glucose levels can have significant clinical implications demanding early identification and management in patients both with and without diabetes.

An extensive baseline examination including medical history, body weight, height, and blood pressure for all patients is recommended by Liu et al., to determine risk factors or conditions that may be influenced by corticosteroid use. Before the commencement of corticosteroid therapy, a blood glucose test should be conducted and if the initial results deviate at baseline, then home glucose monitoring is suggested [90]. The CDA recommends subsequent 48 hours monitoring for all individuals starting corticosteroid therapy and maintenance of glycemic control irrespective of the patient having pre-existing diabetes or not [91]. Interventions and continued screening may be required if the individual test results show values above the normal range (6–10 mmol/L). Therefore, it is extremely essential to monitor patients receiving corticosteroids to prevent adverse clinical implications and complications that may occur in the long term in non-palliative patients. Thorough assessment and blood-sugar-lowering medications are recommended for patients with corticosteroid-induced diabetes. Whereas patients with pre-existing diabetes may require modifying their diabetes management regimen and consideration of benefits and pitfalls before moving forward with corticosteroid therapy. Monitoring guidelines for steroid-induced diabetes recommended by the Joint British Diabetes include once-a-day monitoring for patients without diabetes and the frequency of testing should depend on the glucose level measured. Whereas diabetic patients should be tested 4 times a day. Although the guideline provides a well-structured monitoring regime, yet extensive patient education and resources to supply all patients taking steroid therapy with home capillary glucose monitoring kits are required. A study by Zanders et al. showed that adherence to glucose-lowering drug treatment declines following a cancer diagnosis [92]. Introducing different forms of medications and treatment regimens may result in overall lower effectiveness to drug treatment. To summarize, it is important to note that corticosteroids are an essential component of standard cancer treatment, but the chronic use of corticosteroids may strongly influence diabetic status and negatively affect patient outcomes. Patients prescribed corticosteroids should be closely monitored to prevent adverse effects and to effectively manage in case of their occurrence. To optimize patient care and outcomes, it is recommended that patients receive support and monitoring to prevent corticosteroid-induced diabetes and complications associated with it.

15. Neuroimaging

Dramatic outcomes are seen in clinical results of over 70% of patients receiving steroid therapy for metastatic intracranial diseases with improvement in the enhancement of the tumor, peritumoral edema, and mass effect. Computed Tomography results show a linear decrease in edema volume with measure volume of edema reduced to one-fourth times in 2 weeks of 4 mg/day steroid administration [93]. Magnetic resonance imaging shows a decrease in 10% edema volume just within a week with an average reduction in the mean volume of 4.5% within 24 hours of administering the first dose [94]. A decreased contrast enhancement with tumor is seen, suggesting partial restoration of the blood–brain barrier.

16. Drug of choice and recommendations

With the currently available evidence, dexamethasone is the most preferred drug due to its lack of mineralocorticoid activity and with its half-life being

36–54 hours provides longer duration relief from symptoms. There is currently insufficient evidence to recommend a treatment for patients with asymptomatic brain tumors without mass effect. Level 3 corticosteroids are recommended for patients with starting dose of 4–8 mg/day dexamethasone to temporarily relieve mild symptoms of increased ICP and edema related to mass effect and higher doses of 16 mg/day in divided doses, may be considered for patients with moderate to severe symptoms of increased ICP due to mass effect. A one-time trial of corticosteroid must be conducted for a duration of less than a week and results should be monitored against specific goals in particular time duration and should be discontinued if the desired results are not achieved in that duration (for example- 1 week). If the therapy is well suited and well-tolerated, it can be prescribed up to a dose of 16 mg/day (starting with minimum dose possible) for 2–3 weeks. If longer administration is required, then slow and carefully monitored tapering is required to prevent withdrawal symptoms and relapsing of initial symptoms [95–97].

17. For future investigations

Currently, there is limited information in detail about the proper use of steroids in neuro-oncology. Although a significant clinical improvement is seen in patients, an urgent need for studies addressing its dosage and toxicity exists. Future studies should focus on dosing and risk factors while limiting the side effects to potentially optimize the benefits of corticosteroid therapy.

18. Summary and discussion

Since their discovery, decades ago corticosteroids have been widely used for the treatment of brain tumors and have been considered one of the most powerful classes of tumor-induced edema reducing agents and contribute to minimizing associated neurological side effects. They are prescribed to temporarily relieve symptoms of metastatic brain tumors and only the lowest grade of recommendation can be made for mild to moderate symptoms. Higher doses may be recommended for patients with adverse symptoms tapered slowly over two weeks or longer. Sustained corticosteroid administration for long durations requires close monitoring to prevent associated immediate side effects and complications occurring in the long term. Due to well-characterized complications developing in response to steroid therapy, a need for steroid-sparing drugs such as Bevacizumab arises, but it has its limitations. Currently, there is no standard dosing regimen recommended for corticosteroids and they are prescribed depending on individual needs to maximize symptomatic relief and minimize side effects. Therefore, to bring about positive patient outcomes and to potentially optimize the benefits of corticosteroid therapy, it is suggested that future studies should focus on appropriate dosing regimens and approaches to minimize the occurrence of side effects taking into consideration the risk factors that may negatively influence the medical state.

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