Review Article:

Corticosteroid in various Oral lesions

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Abstract

Corticosteroids, since their introduction have become one of the most widely prescribed class of drugs. They belong to a class of chemicals that includes steroid hormones that are produced naturally in the adrenal cortex of vertebrates and analogous to those that are synthesized in laboratories. They have been used extensively in managing many oral lesions due to their excellent anti-inflammatory and immune-modulators effects. However, considering their potential and significant side effects, they are sometimes termed as the "double –edge sword" in the field of medicine. Their successful use depends upon the comprehension of the disease process. This includes an appropriate diagnosis, a clear view of the desirable treatment outcome and understanding of whether the treatment is aimed at the management of a chronic disease or enhanced resolution of a short – term condition. The possible side effects of systemic corticosteroids must be weighed against probable risks. This article is aimed at reviewing the use of corticosteroids in the treatment of various oral lesions, and deriving a certain protocol for the same.

Key words: Corticosteroids, Oral lesions

Introduction:

Corticosteroid have wide range of uses in dentistry. It is widely used in oral medicine, such as in vesiculo-bullous diseases, Potentially malignant lesions and conditions etc. It is not only the drug of diseases related oral medicine, but also used in endodontic treatment as an intra-canal medicaments, such as ledermix to reduce pulpal inflammation and prevent post operative pain and root resorption[1] , in oral surgical procedures, it is commonly used to limit post-operataive inflammation[2].

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Wide applications of corticosteroids in Dentistry can be mainly owed to their excellent anti-inflammatory and immune-modulator properties. It also carries the potential side effects, sometimes very severe.
The use of steroids should be viewed carefully in dentistry. Under following discussions this article try to organized a definite uses of corticosteroids in oral lesions with doses to minimizes the adverse drug reactions.

Physiology of corticosteroids:

Corticosteroids are group of hormones with similar chemical formulas which are secreted by adrenal cortex. The very slight differences in molecular structure of various corticosteroids give them very different functions. The hormonal steroids are classified according to their biologic effects as glucocorticoids, which

mainly affect intermediary metabolism and the immune system, and mineralocorticoids, which have principally a salt-retaining activity. Of large number of steroids released into the circulation by adrenal cortex, two are of greater importance – aldosterone, which is a mineralocorticoid, and cortisol, which is a glucocorticoid.

Mineralocorticoids promote sodium and water retention, and potassium loss by kidney, but have no anti-inflammatory or anti-allergic effect. Cortisol, also known as hydrocortisone, is the major glucocorticoid in humans. It is synthesized by the cells of the zona fasciculata and zona reticularis of adrenal cortex; its secretion is regulated by the adrenocorticotropic hormone (ACTH) from anterior pituitary gland. Cortisol has a wide range of physiologic actions such as influencing carbohydrate, protein, and fat metabolism; regulation of blood pressure and cardiovascular function; and affecting immune system.

Corticosteroid drugs are the synthetic analogs of cortisol hormone. They bind to specific intracellular receptors upon entering target tissues, and mimic the effects of the naturally occurring hormones; the main differences are the relative glucocorticoid versus mineralocorticoid potency and the long half-life that the synthetic analogs have.

Cortocosteroids are chemically similar to endogenous cortisol which is vital in protein, carbohydrate and fat metabolism, maintenance of vascular reactivity and body adaptation to stress [3,4]. Every day, the adrenal gland normally produces about 24-30 mg of cortisol, but may produce up to 300mg of cortisol in times of great stress. The secretion of cortisol is regulated by circadian rhythm, a stress-related response, and a negative feedback mechanism between the adrenals, hypothalamus, and pituitary. When supraphysiologic doses of corticosteroids(>30mg cotisol equivalent) are given for over 14 days, the hypothalamic –pitutary –adrenal axis may become suppressed and may even take up to 12 months to recover. A functional ability to respond to stress, however, has been shown to return within 2 weeks to 1 month.[5,6]

The normal secretion rate of the two principal corticoids in human is:

•Hydrocortisone:10-20 mg daily (nearly half of this is inthe few morning hours).
•Aldosterone: 0.125 mg daily.

Glucocorticoids are used, either singly or in combination with other drugs, in the treatment of a wide variety of medical disorders. Some therapeutic indications for these drugs are as follows:

- Musculoskeletal and connective tissue diseases (rheumatoid arthritis, polymyositis, systemic lupus erythematosus, and vasculitis)
- Respiratory diseases (sarcoidosis and chronic bronchitis)
- Gastrointestinal diseases (ulcerative colitis and crohn's disease)
- Allergic disorders (asthma, hay fever, and allergic rhinitis)
- Skin conditions (pemphigus, eczema, and dermatitis)
- Eye diseases (conjunctivitis, uveitis, and optic neuritis)
- Oral and maxillofacial diseases (lichen planus, keloid formation, and Bell's palsy)

Although corticosteroids are widely used for treatment of diseases and conditions affecting oral and maxillofacial region, the scientific literature on this topic is limited and scattered throughout numerous journals and books. By gathering this scattered information, this chapter presents a concise review of various uses of corticosteroid drugs in the treatment of diseases affecting oral and maxillofacial region, and the role they have in reducing post-operative morbidities such as pain, edema and trismus after various maxillofacial surgical procedures. The relation between maternal corticosteroid use and congenital maxillofacial deformities are explained. Also discussed is the perioperative management of patients receiving long-term therapeutic doses of corticosteroids.

Uses of corticosteroids in the treatment of different oral and maxillofacial diseases:

Recurrent Aphthous Ulcer

Hydrocortisone hemisuccinate (pellets of 2.5mg) and triamcinolone acetonide (adhesive paste containing 0.1% of the steroid) Gel, pellets and paste can be applied directly to the lesion after taking meals and during at bedtime twice or thrice in a day. It is commonly found mixed with adhesive such as orabase formulation.

If the ulcers are located in the inaccessible area topical dexamethasone elixir, 0.5mg/5ml held over the area or with a gauge, 4 times/day for 15 min, or betamethasone sodium phosphate rinse by dissolving 0.5mg in 5ml of water and asking the patient to rinse for 2-3 min, or beclometasonediproprionate in aerosol form could be use.[8]

Major aphthous ulcers commonly require systemic therapy. Prednison systemically is prescribed most commonly.It should begin at 1.0mg/kg a days a single dose in severe case and should tapered after 7-14 days.[9]

Oral Lichen Planus

The erosive, bullous or ulcerative lesions of lichen planus are treated with high potency topical steroids, such as 0.05% fluocinonide ointment (Lidex, three times a day). Lidex canalso be mixed 1:1 with carboxymethyl cellulose paste or otheradhesive ointments. A gingival tray can also be used to deliver0.05% clobetasol propionate with 1,00,000 IU/ml of Nystatin inorabase. Around 3 to 5 minute application of this mixture dailyappears to be effective in controlling erosive lichen planus.[10,11]In case of oral lichen planus (LP), anti-inflammatoryagents,such as the glucocorticosteroids (GC), e.g. hydrocortisoneplays a front-line role in the management of such conditions.[10,11] Intralesional injection of triamcinolone acetonide(10-20 mg) or short-term regimens of 40 mg of prednisone daily for 5 days, followed by 10 to 20 mg daily for an additional 2 weeks, have also been used in most severe cases.[12]

Oral Submucous Fibrosis

Oral submucousfibrosis(OSF) is an insidious, chronic , resistant disease involvning the mucosa, submucosa or any part of the oral cavity including the pharynx and esophagus. In this condition patient complain of difficulty in chewing, swallowing and restricted mouth opening in svere cases. Various treatment modalities are used for the treatment of OSF but topical application of corticosteroids helps in cases with ulcers and painful situation. Such application has therapeutic effects and mainly shows anti- inflammatory activity showing a direct healing action on the mucosal pathch.[13]

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid is a rare chronic blistering condition of the mouth, eyes and genitals and, rarely, the skin. The initial site of involvement is the oral mucosa. Many patients have mucous membrane pemphigoid affecting only the gums. Fluocinomide (0.05%) and clobetasol propionate
(0.05%) in an adhesive vehicle can be used three times a day for up to 6 months.[14] Systemic therapy of mucous membrane pemphigoid prednisone is usually given at a dose of 1 to 1.5 mg/kg/day, with appropriate monitoring for side effects.[15]

Pemphigus Vulgaris

It is severe in nature and also potentially life threatening vesiculobullous disease. Systemic corticosteroids will be administered with immunosuppressive agents, in order to achieve disease control with lower dose of steroids. Systemic administration of corticosteroids at doses of 1-2 mg/kg/day is effective for principal treatment of pemphigus vulgaris. Topical corticosteroids can be given to maintain remission.[16]

Intralesional corticosteroids in this situation could be given also, this accelerate the scarring

process of a lesion. It may be used to treat persistent lesions. This treatment , which does not give consistent result, involves intralesional injections given every 1-2 weeks; treatment is often seen along with cuteneous or mucosal atrophy, which is the main drawback of this treatment.[17]

Systemic lupus Erythematosus

Lesions that are symptomatic can be managed with high-potency topical corticoids or injections of Intralesional steroids. Systemically low dose prednisone 10-20 mg/day or a dose of 20-40 mg every alternate day may be required in some cases.
Potent topical steroids and antimalarials are the prime drugs to treat systemic lupus erythematosus. Patients commonly begin with a topical steroid (e.g., betamethasone or clobetasol) applied 2 times a day, and then shift to a lower-potency steroid as soon as possible. Intralesionalcorticosteroid injection is useful as a supportive therapy for individual lesions.[18]

Erythema multiforme

Erythema multiforme is a blistering, ulcerative mucocutaneous condition of uncertain etiopathogenesis. The most common etiologic association with erythema multiforme is herpes simplex virus infection, which is frequently associated with the erythema multiforme flare.[19]It
displays a wide range of clinical disease. In mild cases, ulcerations develop, affecting the oral mucosa. In severe cases, diffuse sloughing and ulceration of the entire skin and mucosal surfaces are seen. Early therapy begins with systemic prednisone (0.5to1.0 mg/kg/day) or pulse methylprednisolone (1 mg/kg/day for 3 days) has shown to be very effective.23 Intravenous (IV) pulsed dose methylprednisolone (3 consecutive daily infusions of 20 to 30 mg/kg to a maximum of 500 mg given over 2 to 3 hours) is reported, with the suggestion that this approach is superior to oral prednisone because it imparts the benefit when treatment is administered as early as possible in the progression of the cutaneous insult.[20]

Central Giant Cell Granuloma

Intralesional corticosteroids are used in the treatment of central giant cell granuloma. In the treatment of central giant cell granuloma. In one of the study , equal parts of triamcinoleacetonide (10mg) and lidocain (0.5%) were mixed. Approximately 3, ml of solution was injected into the lesion by multiple penetrations with a needle of 0.5 mm in diameter. The injections were done weekly. In 6th week, if penetration of the cortex overlying the osteocytic zone was no longer visible; this determined the nd of the treatment. Three weeks after termination of the intralesional injection bony regenartion could be observed radiologically.[21]

Contraindications of corticosteroids:

It is usually contraindicated in the treatment of primary bacterial infections and in patients with hypersensitivity and systemic corticosteroids are contraindicated in peptic ulcers, diabetes mellitus, hypertension, pregnancy, tuberculosis and other infections, osteoporosis, herpes simplex virus, psychosis, epilepsy, congestive heart failure and renal failure.[22]

Limitation of Corticosteroids therapy:

Although the benefits of glucocorticoid therapy are derived from short-term vascular changes and limited immunosuppression, prolonged or highdose glucocorticoid therapy has multiple side effects (Table 1). [23]
For instance, extended glucocorticoid treatment can cause hypertension by two distinct mechanisms:
one involves renal sodium retention and the ensuing increase in blood volume;
a second results from potentiation of vasopressor responses to angiotensin II and catecholamines.[24]
Inhaled glucocorticoids are absorbed by the circulatory system and still cause side effects such as a decreased growth rate in children.[25,26]
sustained treatment with substantive amounts of glucocorticoids during childhood is often associated with decreased adult stature.69 Glucocorticoids also have damaging effects on

bone in adults. Osteoporosis and an increased risk of fractures are the main side effects of glucocorticoid therapy.[23] Osteoporosis is mediated in part by the binding of glucocorticoid receptors to negative glucocorticoid-responsive elements that inhibit transcription of osteocalcin in osteoblasts; osteocalcin is an important extracellular matrix protein that promotes bone mineralization.[28,29] Several other side effects of glucocorticoids, including the inhibition of corticotropin-releasing hormone and the expression of pro-opiomelanocortin, are also mediated by negative glucocorticoid-responsive elements . The repair of aseptic wounds is also inhibited by glucocorticoids. For example, fractures trigger inflammation and the production of cytokines crucial for the healing and remodeling of bone.[30-32]

Table: 1: Tissue –Specific Side Effects of High –Dose or prolong corticosteroid therapy.

Tissue	Side Effects
Adrenal gland	Adrenal atrophy, Cushing's syndrome
Cardiovascular system	Dyslipidemia, Hypertension, Thrombosis, Vasculitis
Central nervous system	Changes in behavior, Cognition, Memory and mood
Gatsrointestinal tract	Gatrointesinal bleeding, Pancreatitis, Peptic ulcer
Immune system	Broad immunosuppression, activation of latent viruses
Integument	Atrophy, delayed wound healing, erythema, hypertrichosis, perioral dermatitis, petechiae, glucocorticoids-induced acne, striae rubrae distenses, telangiectasis
Musculoskelital system	Bone necrosis, Muscle atrophy, Osteopororosi, retardation of longitudinal bone growth
Eye	Ctataracts, glaucoma
Kidney	Increase sodium retention and potassium ex-creation
Reproductive system	Delayed puberty, fetal growth retardation, hypogonadism

In addition to blocking cytokine signaling, glucocorticoids inhibit the synthesis of matrix metalloproteinases and collagen, which are important factors in wound repair.[33-36] Glucocorticoids also promote gluconeogenesis in the liver, the degradation of proteins to free amino acids in muscle (and muscle atrophy), and lipolysis,[37-39] ultimately producing hyperglycemia. There are currently no means of ameliorating the side effects of prolonged glucocorticoid therapy that function at the level of the glucocorticoid receptor or the glucocorticoidresponsive elements; rather, treatments such as insulin (or its analogues) for glucocorticoid-induced diabetes, bisphosphonates for osteoporosis, and standard lipid regulators for dyslipidemia are oftenused.[40] This problem has led to research that has identified potentially selective glucocorticoids.

Conclusion:

The usage of corticosteroids is vast, yet crucial. No wonder, cortisol (hydrocortisone) is called the "life-protectinghormone" and aldosterone, the "life-saving hormone."

Corticosteroids used in different forms canbe givenintralesionally, topically, and even systemically. Sometimes it may be given to control edema, whereas, in some situations, it is given because of its immunosuppressive properties. Even though corticosteroids have adverse effects, their anti-inflammatory and immuno-modulatory properties are very beneficiary and supersede them.

It can be said in conclusion that corticosteroids play an important role in the management of lesions affecting the oral mucosa and skin. In addition, its importance in medical emergencies cannot be neglected.

References:

1. Sunil R Panat, Nitin Upadhaya, Mobeen Khan, Md Asad Iqubal, Corticosteroids used in Deentistry: An Update,Journal od Dental Sciences and Oral Rehabilitation, April-June 2014; 5(2): 89-92
2. Holley JR, Hohl TH, Use of steroids in the prevention of some complications after traumatic oral surgery, J Oral MaxillafacSurg, 58, 2000, 531-537.
3. Jatan Sanghavi, Amita Aditya, Applications of corticosteroids in Dentistry. J Dent Allied Sci 2015;4:19-24
4. Kehrl JH, Fauci AS. The Clinical use of glucocorticoids. Ann Allergy 1983;50:2-8
5. Glick M. Glucocorticosteroid replacement therapy: A literature review and suggested eplacement therapy. Oral Surg Oral Med Oral Pathol 1989;67:614-20.
6. Wynn RL, Meiller TF, Crossley HL. Drug Information Handbook for Dentistry. 5th ed. leveland: Lexi-Comp; 1999.
7. Tripathi DK. Corticosteroids. In: Essentials of Medical Pharmacology.5th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2003. p. 254-65.
8. Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Hayrinen-Immonen R. Recurrent aphthous ulcers today, A review of the growing knowledge. Int J Oral MaxillafacSurg 2004;33:221-34.
9. Field EA, Allan RB. Review article: Oral ulceration-Aetiopathogenesis, Clinical diagnosis and management in the gastrointestinal clinic. Aliment PharmacolTher 2003;18: 949-62
10. Gonzalez-Moles MA, Ruiz-Avila. Treatment of severe gingival lesion by topical application of clobetasol propionate in the custom tray. Oral Surg Oral Pathol Oral Endo 2003;95:688-692.
11. Bernard P, Chaneux J. Bullous pemphigoid: a review. Ann DermtolVererol March 2011;138(3):173-181.
12. Nisengard R, Levine R. Diagnosis and management of desquamative gingivitis. Periodontal Insights 1995;2:4-9.
13. Borle RM, Borle SR. Management of oral submucous fibrosis; a conservative approach. J Oral Maxillofac Sur 1991;49:788-791.
14. Scully C, Carrozo M. Update on mucous membrane pemphegoid: A heterogenousimmunemediatedsubepithelial blistering entitiy.OralSurg Oral Pathol Oral Endo 1999;88:56-68.
15. Neff AG, Turner M, Mutasim DF. Treatment strategies in mucous membrane pemphigoid. TherClin Risk Manag 2008;4(3):617-626.
16. Glick MS, Greenberg M, Ship JA, Burket's Oral Medicine, XI Edition: Hamilton, BC Decker Inc, 2008
17. Fellner MJ, Sapadin AN, Current therapy of pemhigus vulgaris. Mt Sinai J Med 2001;68:268-78
18. Panjwani S. Early diagnosis and treatment of discoid lupus erythematosus. J Am Board Fam Med 2009;22:206-13.
19. French L, Prins C. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. 2nd ed. Philadelphia PA: Elsevier: 2008;287-300
20. Martinez AE, Atherton DJ. High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. PediatrDermatol 2000;17(2):87-90.
21. Kermer C, Miller W, Local injection of corticosteroids for central giant cell granuloma: A case report IJOMS 1994;23:366-68
22. Tripathi KD. Essential of medical pharmacology. 4th ed. Jaypee Brothers Medical Publishers Pvt Ltd 1999. p. 285-287.
23. Schacke H, Docke WD, Asadullah K.Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002;96:23-43.
24. Ullian ME. The role of corticosteroids in the regulation of vascular tone. Cardiovasc Res 1999;41:55-64.

25. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol 2003;112:Suppl 3: S1-S40.
26. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999;159:941-55.
27. van der Eerden BC, Karperien M, Wit JM. Systemic and local regulation of the growth plate. Endocr Rev 2003;24:782-801.
28. Dostert A, Heinzel T. Negative glucocorticoid receptor response elements and their role in glucocorticoid action. Curr Pharm Des 2004;10:2807-16.
29. Iwamoto J, Takeda T, Sato Y. Effects of vitamin K2 on osteoporosis. Curr Pharm Des 2004;10:2557-76.
30. Sato S, Kim T, Arai T, Maruyama S, Tajima M, Utsumi N. Comparison between the effects of dexamethasone and indomethacin on bone wound healing. Jpn J Pharmacol 1986;42:71-8.
31. Seidenberg AB, An YH. Is there an inhibitory effect of COX-2 inhibitors on bone healing? Pharmacol Res 2004;50:151-6.
32. Beer HD, Fassler R, Werner S. Glucocorticoid-regulated gene expression during cutaneous wound repair. Vitam Horm 2000; 59:217-39.
33. Chakraborti S, Mandal M, Das S, Mandal A, Chakraborti T. Regulation of matrix metalloproteinases: an overview. Mol Cell Biochem 2003;253:269-85.
34. Richardson DW, Dodge GR. Dosedependent effects of corticosteroids on the expression of matrix-related genes in normal and cytokine-treated articular chondrocytes. Inflamm Res 2003;52:39-49.
35. Cutroneo KR. How is Type I procollagen synthesis regulated at the gene level during tissue fibrosis. J Cell Biochem 2003;90:1-5.
36. Nuutinen P, Riekki R, Parikka M, et al. Modulation of collagen synthesis and mRNA by continuous and intermittent use of topical hydrocortisone in human skin. Br J Dermatol 2003;148:39-45.
37. Dallman MF, Strack AM, Akana SF, et al. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front Neuroendocrinol 1993;14:303-47.
38. Mitch WE. Mechanisms accelerating muscle atrophy in catabolic diseases. Trans Am Clin Climatol Assoc 2000;111:258-69.
39. Leal-Cerro A, Soto A, Martinez MA, Dieguez C, Casanueva FF. Influence of cortisol status on leptin secretion. Pituitary 2001;4: 111-6.
40. Trence DL. Management of patients on chronic glucocorticoid therapy: an endocrine perspective. Prim Care 2003;30:593-605.