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Review Article

CORTICOSTEROIDS - ASSETS AND LIABILITIES ON PERIODONTIUM

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ABSTRACT

Corticosteroids are chemically similar to endogenous cortisol and are used fundamentally as replacement therapy in patients with adrenal insufficiency, and used as anti-inflammatory agents. They are widely used in systemic diseases such as rheumatoid arthritis, asthma, and connective tissue disorders. In dentistry primarily these are used to decrease post-operative pain and edema in inflammatory diseases such as oral lichen planus, pemphigus, and recurrent aphthous stomatitis. This action is predominantly due to eicosanoid formation that inhibits phospholipase A2 activity. Corticosteroids can be supplemented either topically systemically or as inhalational therapy. Research suggests that local application of corticosteroids shows favorable effect on the periodontal ligament and possesses antiresorptive effect, but long-term systemic therapy is a risk for periodontal diseases which may provoke attachment loss and disruption of transseptal fibers. Oral manifestations are common with the use of inhaled steroids and are dependent on dose, frequency, duration, and inhaler use. It is commonly associated with ulceration of tongue, buccal mucosa, and occasionally on the gingiva due to xerostomia and immune suppression. It also causes a decrease in bone mineral density. This review explains about various effects of different types of corticosteroids on periodontium used in dentistry.

Keywords: Corticosteroids, Topical, Systemic, Inhalational, Bone mineral density, Periodontium.

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INTRODUCTION

Physiologically steroids (cortisol and aldosterone) are produced by adrenal glands and help in various physiological functions such as metabolism of fats, proteins and carbohydrates, immune mechanism, and salt water balance [1,2]. Testosterone, estrogen, cortisol, and aldosterone are the steroid hormones produced by the body [3]. Corticosteroids are synthetic analogs of steroid hormones that are produced in the adrenal cortex of vertebrates [4]. In situations where the endogenous production of steroids are impaired, they are required to be supplemented externally, however at physiological doses [5,6]. They are available in different formulations such as ointments, gels, and tablets [7,8]. Steroids were first used clinically to treat dermatological diseases due to their anti-inflammatory action. Corticosteroids are commonly indicated in treating various types of inflammatory and immune-mediated disorders such as adrenocortical insufficiency, rheumatic diseases [9], asthma, and skin diseases [10]. In dentistry, they are generally used to relieve pain, anxiety and for the management of oral lesions that are manifestations of systemic disorders [11]. Evidence for the use of corticosteroids in periodontology, is limited to its use for periodontal manifestations of systemic disorders, and not as a mode of treatment of periodontal disease per se. Nevertheless it is necessary to know the uses of corticosteroids in dentistry as well as the effect of their use on the periodontium, and thus is the aim of the present review [12].

Uses of corticosteroids in dentistry

Corticosteroids are commonly administered in the topical, systemic, and inhalational form [13]. Of these, topical corticosteroids are the ones which are commonly used for the treatment of oral lesions [14,15]. They have in fact evolved and emerged as the mainstay of therapy for numerous oral lesions and conditions such as oral lichen planus [16], erythema multiforme [17], desquamative gingivitis [18], and major aphthous ulcers [16]. Their use is due to mainly their anti-inflammatory, immunosuppressive, and anti-proliferative property [19]. These properties/actions are expressed as a result of a process called as transactivation, which induces anti-inflammatory proteins and regulatory proteins [20]. This process is mediated by the nuclear glucocorticoid receptors which are present in the cytoplasm and modulate transcription of proteins. Corticosteroids displace proteins like heat-shock proteins from the inactive receptor site and bind to the receptor, and this corticosteroid-receptor complex then translocates to the nucleus and bind to a specific sequence of deoxyriboNucleic Acid [21] (Fig. 1). The metabolic effects and some of the adverse drug reactions may occur through this process.

Anti-inflammatory action

This action is mainly brought about by topical corticosteroids which mainly function by inhibiting the formation of eicosanoids. Corticosteroids stimulate the production of various polypeptides, collectively called lipocortin which has inhibitory effects on phospholipase A2 activity [22]. They are also known to block the action of vasodilators such as histamine and bradykinin and leading to vasoconstriction. This is clinically evident by a reduction in erythema [23,24].

Immunosuppressant action

This is brought about by suppression of cytokines namely interleukin 1 (IL - 1), IL- 2–6, IL-8, and tumor necrosis factor alpha, which results in a reduction of cell proliferation. They also affect the humoral immunity by reducing B cell expansion, antibody synthesis, and destruction of T lymphocytes [25].

Anti-proliferative action

This is seen as a result of a reduction in the mitosis in the epidermis which makes the basal cell layer thin, along with the stratum corneum and granulosum. Keratinocyte proliferation is seen to be affected, a decrease in the keratinocyte growth factor is noted, and also there is inhibition of fibroblast proliferation, migration, and chemotaxis. As these processes continue, abnormal aggregation of the elastin and collagen fibers becomes evident, thereby decreasing the synthesis of collagen and glycosaminoglycan's [26].

Topical corticosteroids are the most common form that is used for oral lesions, and hence it is important to know the factors that need to be taken into account when prescribing or using them. The effectiveness

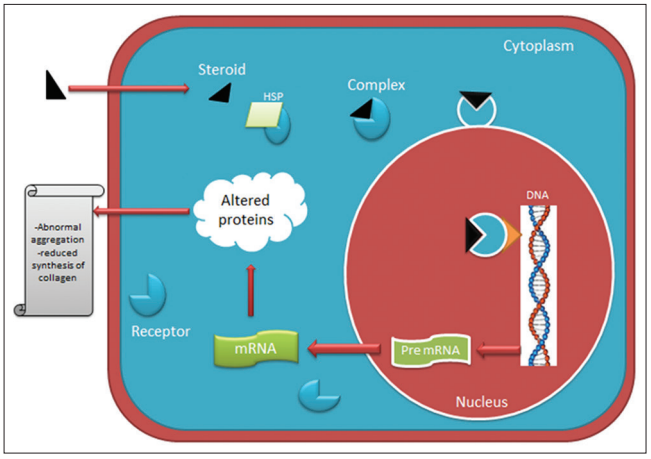

Fig. 1: Mechanism of action at molecular level (mRNA – messenger Ribose nucleic acid)

of treatment with topical corticosteroids depends on the halogenation of its main ingredient, i.e., cortisol. This halogenation leads to increased binding of cortisol to the glucocorticoid receptor. The penetration of the topical corticosteroid depends on the esterification of cortisol which increases the lipophilicity of the steroid [27]. Hence, the selection of corticosteroids should be based mainly on the potency of drug and area of application [28]. There are various classifications of topical corticosteroids based on their potency with or without using the vehicle. Among them, World health organization (WHO) classifies the topical corticosteroids into seven classes/groups, with Group 1 being the most potent and Group 7 being the least potent. In this system, potency is based on the activity of topical corticosteroid molecule, its concentration, and nature of vehicle [29]. The high potency formulations are recommended for short-term use only and are required for areas such as palms and soles and also for chronic or hyperkeratotic lesions. Low to medium potency topical corticosteroids are useful for acute inflammatory lesions on the face and can be used for a long-term [30]. Normally, high potency steroids for short-term duration are used for the oral application. Common corticosteroids used in dentistry based on their potency are listed in Table.1.

Topical corticosteroids are available in many formulations: Creams, ointments, lotions, and gel/hydrogel [31,32]. Vehicles function as a carrier for the active topical corticosteroid molecule, hydrate the skin and may help to increase the drug penetration. The absorption and potency of drug depend on the vehicle used, in addition to the chemical structure of the corticosteroid molecule [33]. Creams are water-based formulations and have a low occlusive ability. They spread easily, without a greasy feel, and is thus preferred by the patients [34]. Ointments are preferred for dry or scaly lesions and in highly keratinized areas. They increase hydration and provide good occlusion, thus improving drug penetration. Drug action can be enhanced further by the addition of propylene glycol, which increases the solubility of the drug in the vehicle. Among adhesive ointments, the orabase ointment (triamcinolone acetonide) is one of the most commonly used. It is a commercial formula that does not contain analgesics or antibiotics. Gels are formulated with a gelling agent and offer ease of application, but they are rarely used due to the possibility of causing pain after being applied. Conventionally, ointments have been considered to be more potent than the rest of the formulations [35].

The use of corticosteroids for treatment of periodontal disease is limited. Corticosteroids are known to have an effect on fibroblasts and bone remodeling [19], which may affect the periodontium and hence it is important to know about the uses and side effects of corticosteroids on the periodontium.

Effect of corticosteroids use on periodontium

The uses of corticosteroids solely for periodontal purposes are rare; hence, we have here tried to list out the possible effects of corticosteroid use on the periodontium (either in topical, inhalational or systemic form). The possible adverse effects of each type of corticosteroids are highlighted.

In periodontology, topical and systemic steroids have been indicated for patients with dermatologic disorders, such as pemphigus, erythema multiforme, and systemic lupus erythematoses which have shown any gingival or periodontal manifestation.

Topical corticosteroids

Corticosteroids, when applied topically on inflamed marginal gingiva with periodontal disease, have shown a reduction of bleeding and inflammation without affecting the periodontal disease progression [36]. Histologically, reduction in capillary permeability, a decrease in plasma cells and granulation tissue, and inhibition of collagen formation is noted when corticosteroids are injected into the gingiva [36-38]. Although not conclusive, reports exist, which indicate the antiresorptive action of corticosteroids [39]. In an *in vitro* study, when the effect of dexamethasone (Dex) on osteoblasts was studied for 21 days, it was noted that Dex affects directly the formation of osteoclasts by altering the proliferation and differentiation of osteoclasts precursors and inhibiting bone resorption in mature osteoclasts. It also helps in osteoblastic differentiation from gingival fibroblasts by regulating the expression of Runt-related transcription factor 2 (Runx2) [40,41]. Runx2 also known as core-binding factor subunit alpha-1 is a protein that in humans is encoded by the Runx2 gene and is a key transcription factor associated with osteoblast differentiation [42]. Studies have also demonstrated a concentration-dependent effect of corticosteroids. It was shown that hydrocortisone at high concentration (10^{7}) increase matrix metalloproteinases (MMP) levels (MMP1, MMP2, MMP7, and MMP11), whereas at low concentration (10^{9}) it downregulates their expression. Hence, studies using different doses of drugs and their effects on periodontal tissue are required to prove the clinical efficacy of these drugs [43].

Furthermore, the oral lesions that are treated by corticosteroids being chronic in nature, requires the drug to be in constant contact with the area being targeted for treatment. The use of a tray designed for the same, allows for the drug to be secure and also provides for an occlusive therapy [44,45].

Systemic corticosteroids

Animal studies have shown that systemic steroids have adverse effects on the periodontium and its response to bacterial plaque. These studies have reported a change in response of plaque after steroid supplementation [46]. However, studies done on humans have shown that the reaction on gingival tissues was more related to the oral hygiene status and the age of the individual than to "whether or not the patient had been receiving steroids." This observation was further validated by experimental studies which have reported that use of systemic corticosteroids for more than 6 months can affect the periodontium [47]. It is initially seen as gingival ulceration, which may progress to the apical migration of the epithelium, leading to loss of transseptal fibers and attachment loss [48,49]. Data from animal experiments and observations in humans have demonstrated that the systemic corticosteroids may result in increased osteoporosis of alveolar bone due to increase in serum levels of corticosteroids, which may be a risk factor of periodontal disease [50-52]. Corticosteroids have a significant effect on bone metabolism. They increase bone resorption, inhibit bone formation, decrease the intestinal absorption of calcium ions and modify Vitamin D metabolism [53]. Olgaard *et al.*, in 1992, have stated that although significant reductions of the bone mineral content were observed in corticosteroid treated-nephrotic patients and that the bone decay rates were significantly different at the mandible, forearm, and lumbar spine [54]. A study comparing the

Table 1: Commonly used corticosteroids in dentistry

Potency	Examples	Concentration	Lesions
Ultrahigh	Clobetasol propionate	Cream, 0.05%	Oral lesions of psoriasis (rare), vesiculobullous lesions, desquamative gingivitis
High	Betamethasone dipropionate fluocinonide triamcinolone acetonide	Ointment, 0.05% cream, or gel, 0.05% ointment, 0.1%	Oral lichen planus aphthous ulcers lichen planus, traumatic ulcers
Moderate	Fluocinolone acetonide triamcinolone acetonide	Ointment, 0.025% cream, 0.1%	Pemphigus lichen planus
Low	Dex sodium phosphate methylprednisolone	Oral Oral	Perioperative use in dentoalveolar surgeries

Dex: Dexamethasone

use of two different corticosteroid drugs and their effect on bone has shown that the detrimental effect of long-term steroid treatment on the skeleton may not be abolished, but it can be reduced significantly by using deflazacort when compared to prednisone [55]. A recent *in vitro* study showed the effect of Dex on periodontal ligament stem cells (PDLSCs), induces many genes, including dickkopf-1 (DKK-1) in PDLSCs. Enzyme-linked immunosorbent assay showed that DKK-1 is secreted from PDLSCs in response to dexamethasone (Dex) treatment in human PLDSCs this induced DKK-1 wingless-type MMTV (mouse mammary tumor virus) integration site (Wnt) - mediated activation of β-catenin signaling and inhibits the growth of PDLSCs thereby causing increase in periodontal breakdown [56]. In contrast, few studies have shown no significant difference in periodontal parameters with the long-term use of corticosteroids [57]. In a study done in patients having neurological disorders who were on corticosteroid therapy had, no difference in periodontal parameters in follow-up period of 1–4 years was observed [58,59]. It has been shown that long-term administration of systemic corticosteroids may lead to adrenal suppression, immunosuppression, central obesity, hyperglycemia, and increased susceptibility to infection, reduction of bone mineral density (BMD), and increased risk of osteoporosis [60-62].

Inhalational corticosteroids

Inhalational corticosteroids are not used for the treatment for oral lesions; however, their use for the treatment of respiratory diseases is not without side effects. Although these medications, are generally, considered safer when compared to oral and systemic corticosteroids, they also have adverse effects [63]. Inhalational corticosteroids are generally prescribed in asthmatic patients. In this group of patients, the salivary flow and the concentration of immunoglobulin A is reduced; there is dehydration of alveolar mucosa due to mouth breathing, alteration of immune response and an increase in the concentration of immunoglobulin E in gingival tissue. A higher incidence of calculus formation in these patients is observed, due to increased levels of calcium and phosphorous in saliva, contributing to the poor periodontal health in these patients [64,65]. When inhalational corticosteroids are administered to these patients, in addition to the above-mentioned effects, an increase in periodontal destruction is observed, and also changes in the BMD are noted. Current evidence suggests that in adults, systemic effects of inhalational corticosteroids do not lead to adverse effects at doses of 400 μg or less of budesonide [66].

It has been suggested that the type of inhaler used for administering corticosteroids should also be taken into consideration [67,68]. Inhalers are available with or without a spacer attached, and it is reported that spacer devices attached to inhalers can reduce the local effects of the steroids when compared to those without spacers [69,70]. Literature presents with systematic reviews and meta-analyses which have examined the effect of inhaled corticosteroids on BMD, the conclusions derived however differed considerably [71]. For example, Leone *et al*., in 2003, concluded that adult asthma patients generally do not sustain a significant reduction in BMD in response to inhaled corticosteroid treatment [72], whereas Richy *et al*. 2003 concluded that all inhaled corticosteroids affect BMD. It is also unclear, whether a threshold dose for adverse effects exists [73]. The main effects are seen with doses above 1600 g [74]. Tooth loss as a result of decreased BMD has been observed in asthmatic patients undergoing long-term inhalational steroid therapy [75,76]. This reduced BMD was evident in the mandible, and it could be because of fractions of drug remaining in the oral cavity [77]. It is thus suggested that patients on inhalational corticosteroids should have their mandibular BMD checked regularly, especially if they have any risk factors for osteoporosis [78,79]. A reduction of the dose of inhalational corticosteroids has also been suggested in these patients. An increase in the risk of caries, gingival inflammation and reduced salivary secretion is also seen in young adult patients on long-term steroid therapy. The severity and incidence of severe gingivitis are more in patients using inhalational corticosteroids than other forms of steroids. It has been suggested that the inhalers used and mouth breathing may lead to decreased saliva production, changes in pH, and increased risk of plaque and caries [80,81]. However, animal studies have shown that inhaled budesonide does not modulate periodontal breakdown. This might be due to inappropriate formulation and dosage. Additional studies are needed to estimate the effects of budesonide on the oral mucosa and the periodontium.

CONCLUSION

Wide applications of corticosteroids in dentistry can be mainly owed to their excellent anti-inflammatory and immunomodulatory properties. Patients with gingival lesions of vesiculobullous diseases require interdisciplinary care, and the form of application will be depended on various factors that have to be considered. Along with the important role in the management of lesions affecting the oral mucosa and skin, these agents also carries the potential side effects that are sometimes very severe. One question that remains is whether the risk of adverse effects on bone differs among the different corticosteroids. The reasons for these inconsistent findings may be due to insufficient dosage and inadequate interactions among the combination of drugs taken by the patient. Although these drugs have good anti-inflammatory and immunosuppressive properties, corticosteroids are less used in the management of periodontal diseases.

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CONFLICTS OF INTEREST

Nil.

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