Effect of Long-term Use of Steroidal Anti-inflammatory Drugs on the Periodontal State: A Review

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Abstract

Corticosteroids are chemically similar to endogenous cortisol and mostly prescribed for their anti-inflammatory and immunosuppressive properties, which are due to the inhibition of phospholipase A2 activity. These drugs are extensively used in the treatment of a plethora of autoimmune disorders such as rheumatoid arthritis, various breathing disorders and also disorders of connective tissue. In the field of dentistry these drugs are prescribed in most of the mucocutaneous disorders such as they are mostly used in inflammatory diseases such as oral lichen planus, pemphigus, and oral stomatitis to alleviate post-operative discomfort and swelling. These drugs can be administered systemically,topically or asinhalational therapy. Evidence concludes that short term corticosteroids possess antiresorptive properties and its local application shows a favourable effect on the periodontal ligament, but when administered systemically for a long period could lead to periodontal diseases as it has shown to increase attachment with alveolar bone and destruction of transseptalfibers. Oral manifestations are dependent on duration,dose and frequency of use. It is commonly associated withmoniliasis, dental caries,altered taste sensation, ulceration of the tongue, buccal mucosa, and gingiva due to xerostomia,gingival inflammation, periodontal inflammation,and immune suppression. They can either cause dramatic improvement or dramatic adverse reactions which can lead to a considerable increase in the distributionof periodontal disorders. In patients on long-term corticosteroid therapy, oral health is generally not given importance during management. Hence this review explains about various effects of different types of corticosteroids on periodontium used in dentistry.

Keywords: *Corticosteroids, risk factors, mucocutaneous lesions, periodontitis, Bone mineral density.*

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 saltwater balance.[1,2] Testosterone, estrogen, cortisol and aldosterone are the steroid hormones produced by the body.Corticosteroids are synthetic analogues of steroid hormones that are produced in the adrenal cortex of vertebrates.[1] In 1940s glucocorticoids were first introduced and since then it has become an extensively prescribed class of drugs to manage various disorders such as adrenocortical insufficiency, rheumatic diseases, asthma, and skin diseases.[2] They are available in different formulations like ointments,gels and tablets.[3] Due to their anti-inflammatory action, steroids were first used clinically to treat dermatological diseases. Corticosteroids are commonly advised as replacement therapy in treating various types of inflammatory and immunosuppressive disorders.[4,5]

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Steroidal drugs are known to exert definite anti-allergic, anti-inflammatory and immunosuppressive effects.[1] However, despite these beneficial actions, corticosteroids are also known to cause adverse reactions likerashes, clouding of the lens, weakness in the muscles, GIT disorders and candidiasis. In dentistry, they are generally advised to reduce post-operative edema, postoperative pain, anxiety and for the management of oral inflammatory manifestations of systemic disorders like bullous pemphigoid, oral lichen planus, pemphigus, erythema multiforme, recurrent aphthous stomatitis, and hypersensitivity reactions.[2]

Research has proventhat the patients on corticosteroids often present with oligodontia or are characterized by dentition which is prone to dental caries.[6] Corticosteroids can cause osteoporotic changesin the alveolar bone due to the reduction of bone-forming cells and the amount of bone matrix. This results in a fibrous transformation of the periodontal ligament space and decrease of the alveolar bone height.[7] In periodontology, the use of corticosteroids is mostlyrestricted to its use for periodontal manifestations of systemic disorders, and not as a first-line treatment of periodontal disease per se. Nevertheless, it is necessary to know the uses and effects corticosteroids have, not only on oral diseases but also on the gingival and periodontal diseases and hence this review.[8,9]

Uses of steroidal anti-inflammatory (corticosteroids) in oral diseases: Corticosteroids are commonly administered in the topical, systemic, and inhalational form.[10] of these, topical corticosteroids are the ones that are commonly used for the treatment of oral lesions.[11] They have evolved and emerged as the mainstay of therapy for numerous oral lesions and conditions such as oral lichen planus, erythema multiforme, desquamative gingivitis and major aphthous ulcers.[12,13] Their use is mainly due to the anti-inflammatory, immunosuppressive, and anti-proliferative properties of corticosteroids.[14] These properties/actions are expressed as a result of a process called transactivation. It is mediated by the nuclear glucocorticoid receptors which arepresent in the cytoplasm which regulates the protein transcriptiontoinduce anti-inflammatory proteins and regulatory proteins.[15] Corticosteroids displace proteins like heat shock proteins from the inactive receptor site and bind to the receptor, and this corticosteroid-receptor complex then getstranslocated to the nucleus and binds to a specific sequence of deoxyribonucleic acid. The metabolic effects and some of the adverse reactions could be occurring through this process.[14,15]

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.[16] They are also known to block the action of vasodilators such as histamine and bradykinin leading to vasoconstriction. This is clinically evident by a reduction in erythema.[17]

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, leading to a reduction of cell proliferation. They also affect the humoral immunity by reducing B cell expansion,destruction of T lymphocytes and antibody synthesis.[18]

Anti-proliferative action: This is seen as a result of a reduction in the mitosis in the epidermis which makes the basal cell layer, as well as the corneum and granulosumlayer of the keratinized epithelium thinner. The proliferation of keratinocytes is affected, there is a decrease in the keratinocyte growth factor, and inhibition of fibroblast proliferation, migration, and chemotaxis. This is followed by abnormal aggregation of the elastin and collagen fibers,which decreases the synthesis of collagen and glycosaminoglycans. For oral lesions,topical corticosteroids are most commonly advised and hence it is important to know the factors that need to be taken into consideration when prescribing or using them. The effectiveness of treatment with topical corticosteroids depends on the halogenation of its 6main ingredient, i.e., cortisol. This halogenation leads to an 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.[17]Hence, the corticosteroids should be selected based mainly on their potency and the area of application.[19]

There are various classifications of topical corticosteroids based on their potency with or without using the vehicle. Among them, the World health organization (WHO) classifies the topically administered steroids into seven groups, with Group 1 which is the most potent and Group 7 being the least potent. Potency is determined based on the activity of the corticosteroid molecule, its concentration, and the nature of the

vehicle.[20] Highly potent concoctions are meant to used for a brief period only and are topically applied on the soles of the foot, and palms of the hands. It can also be used for the management of hyper keratinized lesions. For the management of the lesions on the face caused due to various acute inflammations low to medium potency formulations are used. They can be used for a longer period. Normally, high potency steroids are used for oral application for a short duration.[17]

Since the adventmany different delivery systems of these topically applied steroids have been developed such as Creams, ointments, lotions, and gel/hydrogel.[20,21] Vehicles are nothing but carriers. They carry the active steroid molecule which keeps the skin hydrated and moisturized and enhances the penetrative capacity of the drug. Creams are the vehicles that aremost preferred by the patients. Their occluding capability is less due to their water-based preparation. Hence, they spread easily, without anoily and sticky feeling.[21]Ointments are preferredin highly keratinized areas and for dry or scaly lesions. They enhance moisture-holding capacity and possess a good occluding ability. This aids in the penetrating capacity of the drug. Gels are prepared using a gelling agent.This makes the application of the dug more convenient. The shortcoming of using gels is that they have the possibility of inflicting pain and discomfort after the application. Conventionally, ointments have been considered to be more potent than the rest of the formulations.[22] The use of corticosteroids for treatment of periodontal disease is however limited. Corticosteroids are known to affect fibroblasts and bone remodeling, which may affect the periodontium and hence it is important to have a thorough knowledge regarding its application and the drawbacks of using these steroids on the periodontium.[23]

Effects of corticosteroids on the periodontium: Corticosteroids, when topically applied to the erythematous marginal gingiva suppresses the inflammatory process and masks the rate at which the bleeding should be occurring blinding the clinician with the false picture. It has been observed that,in cases where steroid anti-inflammatory drugs are administered topically or injected in the gingival tissues, there is a disturbance in the ability to percolate into the capillaries and formation of collagen, decrease in the b lymphocytes and granulation tissue.[24]

Researchers have established that a high dosage of hydrocortisone brings about an increase in the activity of various enzymes that help in the degradation of the collagen and enhance the fibro lysis.One of the major classes of enzymes is matrix metalloproteinases (MMPs). Marked increase is seen in the subtypes 1, 2,7 and 11, while low levelsthis steroid reduced the expression of the same.[22]

In chronic periodontitis patients, also diagnosed with asthma and under long-term inhalational steroid therapy pathological migration and loss of teeth (mostly mandibular anterior teeth) have been observed.[23,24] Research has proven that patients under the inhalational therapy are more prone to the diseases of the periodontium more prevalent in the mandibular jaw. It is more likely to be seen in the cases which are further influence by other debilitating diseases such as osteoporosis.[25] In the adolescent age group who are on long-term steroid anti-inflammatory drugs there is an increased risk of gingivitis and tooth decay due to xerostomia. Mouth breathers and those taking inhalers that have these steroidal formulations are associated with drastic variations in salivary pH, decreased salivary flow, increased accumulation of the dental plaque which further creates a cascade mechanism causing an increase in the rate of caries initiation and progress.[26]

Safkan et alconcluded that those who were under steroidal anti-inflammatory drugs are often predisposed to gingivitis.[27] It further evidenced that using corticosteroids for a longer duration (one year or more)led to a marked increase in the presentation of the clinical symptoms of periodontal inflammation.

Markitziu et al carried out a study to assess the periodontal changes in patients of pemphigus vulgaris undergoing corticosteroid therapy.[28] The results of the study have shown statistically significant differences in bleeding on probing and in gingival recession but no significant changes in alveolar bone height.

Despite their strong anti-inflammatory and immunosuppressive effects, long term application of corticosteroids can cause enhanced deterioration of dental health and hygiene. Misuse or overuse of steroidal anti-inflammatory drugs must also be taken into account as they may affect not only the teeth, but also the soft tissues and alveolar bone.[29] It has also been found that prolonged application of corticosteroids adversely affects the osseous metabolism, along with a notable decrease in the density of the inorganic component of the mandibular jaw.

Inhaled corticosteroids, sodium cromoglycate, anticholinergic bronchodilators, β-2 agonists are frequently administered alone or in combination in the form of inhalation therapy for the treatment of asthma and chronic obstructive pulmonary disease.[26] The dosage, duration and frequency of application of steroid anti-inflammatory drugs directly correlate to the severity of adverse effects seen in the oral cavity in general and the periodontium in particular. Several adverse reactions affecting the oral cavity due to long term inhalational Corticosteroid therapy include not only severelyaltered taste perception, ulceration, moniliasis, demineralization of the tooth and dry mouthbut also severe gingivitis and periodontitis.

Aggregation of plaque deposited on the tooth is directly proportional to the reduced rate in salivation. The unbalanced buffering capacity of saliva and constant low pH scores provides a conducive condition for the growth of acidogenic and acidophilic caries causing microbes such as *Streptococcus mutans and Streptococcus sobrinus*.

The adverse habit of breathing through mouth in the patients with long term corticosteroid therapy, contributes to the aggravation of gingival inflammation due to the loss of water from the alveolar mucosa. The disturbance in the pathophysiology along with disturbance in local and systemic immunity, provoked by long term corticosteroid therapy, has shown to considerably increase the distribution of periodontal disorders.[24] Taking into account the fact that saliva acts as a reservoir of the necessary factors required for protection against gingivitis and periodontitis, drugs affecting the qualitative and quantitative properties of saliva directly influence the severity of periodontitis.[23]

Conclusion

This review concludes that long-term corticosteroid therapy directly influences the oral cavity. It further leads to several adverse reactions from moniliasisto gingivitis and periodontitis to impairedosseous metabolism. Furthermore, a significant amount of reduction in the Bone Mineral Density (BMD) of the mandible. Therefore, patients receiving this treatment for a longer duration (oral, topical, inhalational) should undergo a thorough dental check-up, and regular follow-up. This is to check and prevent any disturbance in the dental health and to estimate the risk factors for gingivitis and periodontitis. However, it is still taxing to come to a definite conclusion on the relation of oral Corticosteroids with the loss of tooth and the status of the periodontium. More number of studies on the effect of the different forms of corticosteroids on the gingival and periodontal state are required to draw more definitive conclusions.

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