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The Role of Corticosteroids in Today's Oral and Maxillofacial Surgery

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Additional information is available at the end of the chapter

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1. Introduction

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. The relative potencies and duration of action of representative corticosteroids are presented in Table 1.

Compound	Glucocorticoid potency	Mineralocorticoid potency	Duration of action
Cortisol	1	1	short
Cortisone	0.8	0.8	short
Fludrocortisone	10	125	Intermediate
Prednisone	4	0.8	Intermediate
Prednisolone	4	0.8	Intermediate
Methylprednisolone	5	0.5	Intermediate
Triamcinolone	5	0	Intermediate
Betamethasone	25	0	Long
Dexamethasone	25	0	Long

Short: 8-12 hours biologic half-life; Intermediate: 12-36 hours biologic half-life; Long: 36-72 hours biologic half-life. Adapted and modified from [1]

Table 1. Relative potencies and equivalent doses of representative corticosteroids

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.

2. Uses of corticosteroids in the treatment of oral and maxillofacial diseases

Corticosteroids are widely used in the treatment of diseases, disorders and conditions affecting the oral and maxillofacial area and the adjacent and associated structures. The diseases of the oral and maxillofacial region may be either local or the manifestation of a

systemic problem. Corticosteroids have their widest application in the management of acute and chronic conditions which have an allergic, immunologic, or inflammatory basis. Therefore, a group of corticosteroids which have predominantly a glucocorticoid activity and little or no mineralocorticoid action such as betamethasone, dexamethasone, triamcinolone, and prednisolone are used.

The following are the main therapeutic indications for glucocorticoids in oral and maxillofacial diseases.

2.1. Temporomandibular disorders (TMDs)

TMDs are clinical problems involving the temporomandibular joints (TMJs), the masticatory muscles, or both. TMDs affect a significant number of individuals, and are the most common musculoskeletal disorders that cause orofacial pain. [2] Trauma to the joint structures, especially microtrauma, accounts for the majority of patients who develop TMJ problems. However, a small number of joint diseases are caused by nontraumatic etiologic factors including benign and malignant neoplasms (osteoma, chondroma, and synovial sarcoma), congenital or developmental anomalies (condylar agenesis and hyperplasia), arthritides (rheumatoid arthritis), and systemic diseases. The most common signs and symptoms of TMDs are pain, altered mandibular movements, and the elicitation of joint noise.

Treatment of TMDs varies according to their etiologic basis. Conservative managements (splint therapy, thermal application, pharmacotherapy, and physiotherapy), surgical treatments, or a combination of them may be required. A variety of medications have been used to relieve pain, inflammation, muscle spasm and other signs and symptoms associated with TMDs. They include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, analgesics, and muscle relaxants.

Various glucocorticoids are used in the treatment of TMDs (Table 2). These drugs have dramatic effects on pain, hypomobility, and inflammation associated with acute TMJ problems. Oral corticosteroids are used mainly for treatment of acute TMJ discomforts or for diagnostic purposes. They should be used in a short term basis (tapering dose lasting 5 to 7 days), and repeated as infrequently as possible. Long term use of corticosteroids for the treatment of TMDs is contraindicated; it can result in a cushing's- like disease process, acute adrenal crisis, hypertension, electrolyte abnormalities, diabetes, and formation of osteoporosis including the TMJ. [2]

Drug	Alternative name	Usual dose
Hydrocortisone	Hydrocortone	20-240 mg/day
Prednisone	Deltasone, Orasone	5-60 mg/day
Prednisolone	Delta-Cortef	5-60 mg/day
Dexamethasone	Decadron	0.75-9.0 mg/day
Betamethasone	Celestone	0.6-7.2 mg/day

Adapted and modified from [2]

Table 2. Oral corticosteroids used in TMDs

Intracapsular injection of glucocorticoids has been reported to decrease pain in patients with both pain and limited mouth opening secondary to inflammatory disorders of the joint, such as arthritis and capsulitis. [3-5]

A number of mechanisms have been described for the anti-inflammatory actions of glucocorticoids. These drugs inhibit inflammatory mediator release from many cell types involved in inflammation such as macrophages, T-lymphocytes, mast cells, dendritic cells, and neutrophilic leukocytes. Glucocorticoids also reduce prostaglandin production by blocking the phospholipase A₂ enzyme.

The most striking effect of glucocorticoids is to inhibit the expression of multiple inflammatory genes encoding cytokines, chemokines, inflammatory enzymes, receptors and adhesion molecules. [6] Changes in gene transcription are regulated by proinflammatory transcription factors, such as nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1). These proinflammatory transcription factors switch on inflammatory genes via a process involving recruitment of transcriptional coactivator proteins and changes in chromatin modifications such as histone acetylation. Glucocorticoids exert their anti-inflammatory effect on responsive cells by binding and activating a cytoplasmic glucocorticoid receptor. The interaction between the activated glucocorticoid receptor and proinflammatory transcription factors may result in deacetylation of histones and repression of inflammatory genes. [7]

In chronic inflammatory disorders of TMJ, macrophages, T-lymphocytes, and other cell types involved in inflammation release many cytokines and chemokines which will induce expression of adhesion molecules, release of variable enzymes from fibroblasts and osteoclasts and result in bone erosion. IL-8, which is a chemokine, is known to cause the infiltration of neutrophils into synovial fluid and promote joint inflammation. It was detected in 80% of the synovial tissue specimens taken from the TMJs with internal derangement. Similarly, IL-11 has been involved in the pathogenesis of osteoarthritis and rheumatoid arthritis. It has been found in synovial fluids of diseased temporomandibular joint and other joints. [8]

Cytokines participate in various inflammatory processes and induce protease synthesis; their effects can be either synergic or inhibitory. In synovial joints, IL-1 α , IL-1 β and TNF- α induce synovitis and promote the production of proteinases resulting in degradation of cartilage, while IL-1ra works to block IL-1 α and IL-1 β from binding to other cell receptors and has many beneficial effects on inflammatory diseases. [9] In a study by Nordahl et al. it was found that the local production of tumor necrosis factor-*alpha* (TNF- α) occurred in the TMJ synovium of patients with chronic inflammatory connective tissue disease, and the severity of pain and tenderness of the TMJ was related to the level of TNF- α . [10] In a study by Fredriksson et al., it was shown that the presence of TNF- α in the synovial fluid of TMJ predicted a positive treatment response to intra-articular glucocorticoid injection in patients with chronic TMJ inflammatory disorders. [11]

Long-term complications associated with intra-articular glucocorticoid injection cannot be determined from the limited investigations done to date and thus remained unclear. Wenneberg et al. in a study evaluating the long-term prognosis of intra-articular

glucocorticoid injections for TMJ arthritis observed that this treatment modality was helpful, and there were no radiographically demonstrable side effects of the treatment. [12] In contrast, Haddad IK showed that intra-articular injections of corticosteroids (triamcinolone acetonide) cause damage to fibrous layer, cartilage, and bone of TMJ. [13]

Juvenile idiopathic arthritis (JIA) is a chronic rheumatologic disease of children which may involve TMJ region, and cause significant craniofacial growth disturbances. The treatment of TMJ arthritis is controversial. It has been shown that glucocorticoid injection of the TMJ reduces pain and inflammation, and improves the function of TMJ in children with JIA. [14] Other studies also confirmed that corticosteroid injection of the TMJ can be safely performed in children with JIA, and is effective. [15-18] Few studies have evaluated TMJ corticosteroid injection in JIA. In these studies the volume of corticosteroid injected was chosen empirically. Treatment protocols such as injection of 1 cc (40 mg) of triamcinolone acetonide, 1 cc (20 mg) of triamcinolone hexacetonidein, and 0.5 to 1 cc of the diluted (with 1% lidocaine HCL) triamcinolone hexacetonidein into each of the involved TMJs, all have been used in previous studies. [14-16] The peak effect occurs after approximately 6 weeks of treatment, and the expected duration is 6-17 months. The children may receive a second injection approximately 6 months after the first. [16]

Side effects of intra-articular steroid injection in children include immediate reactions, such as pain and headache, or delayed side effects, such as joint infection and loss of subcutaneous fat. [16] Because the mandibular endochondral growth zone is located at the head of condyle (at the site of corticosteroid injection), the concern is whether intra-articular corticosteroid injection per se may cause growth retardation. Stoustrup et al., in an animal study demonstrated that intra-articular glucocorticoid injection may result in even more pronounced mandibular growth reduction than that caused by the arthritis alone. [19] Schindler et al. reported a case of severe temporomandibular dysfunction and joint destruction after intra-articular injection of triamcinolone, and El-Hakim et al. showed TMJ resorption with active osteoclastic activity after intra-articular injection of a single dose of dexamethasone in rats. [20,21]

intra-articular corticosteroid injection has been used to improve mouth opening in patients with anterior disk displacement without reduction (ADDWOR), i.e., closed lock. [22]

2.2. Oral ulcerative and vesiculobullous lesions

Corticosteroids are successfully used for the treatment of several ulcerative and vesiculobullous lesions involving the oral cavity and perioral areas including recurrent aphthous stomatitis (RAS), Behcet's syndrome, pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, erythema multiforme and Stevens-Johnson syndrome (Tables 3-5). [23]

Recurrent aphthous stomatitis: These superficial painful ulcers occur commonly in the oral cavity. Minor form of the disease has 1 to 5 ulcers at one episode. The ulcers which are under 1 cm in diameter persist 8 to 14 days, and heal spontaneously without sequelae. The

major aphthous ulcers are larger than 1 cm, and persist for weeks to months. Corticosteroids either alone or in combination with other drugs have been used for treatment of these lesions. [24-28] Topical steroids, such as triamcinolone acetonide and prednisolone (2 times/day), are formulated as oral pastes. Therapeutic benefit can be derived from a mouthwash containing betamethasone. It should be noted that the long-term use of topical steroids may predispose patient to developing oral candidiasis. [28]

Topical and injectable (intralesional) corticosteroids are useful for large and painful lesions. Systemic administration of corticosteroids is reserved for severe cases to prevent lesion formation or to reduce the number of lesions. Systemic corticosteroids should be prescribed in short courses, and only for severe outbreaks or cases that don't respond to topical or injectable corticosteroids. [23]

Behcet's syndrome: The treatment of oral lesions of Behcet's syndrome is similar to the treatment of severe or major RAS. [23]

Pemphigus vulgaris: Pemphigus vulgaris is a severe, potentially life-threatening vesiculobullous disease that may affect skin and mucous membranes. Oral cavity is involved in nearly 80% of patients. In the past, corticosteroid therapy was the treatment of choice but later, combination therapy involving the use of systemic corticosteroids with immunosuppressive agents was introduced, in an attempt to achieve disease control with lower doses of steroids. [29-31]

The principal treatment of pemphigus vulgaris is systemic administration of corticosteroids at doses of 1 to 2 mg/kg/day. Maintenance of remission may be achieved with topical corticosteroids, allowing reduction of systemic drugs. Isolated lesions can be treated with injectable corticosteroids. [23]

Bullous and mucous membrane pemphigoid: The choice of drugs used for the treatment of pemphigoid is based upon the sites of involvement, clinical severity, and disease progression. For more severe disease, or with rapid progression, systemic corticosteroids are the agents of choice for initial treatment, combined with steroid-sparing agents for long-term maintenance. [32] Topical and injectable corticosteroids are useful for treatment of mild or localized oral lesions. [23]

Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS): It has been shown that corticosteroids have a favorable influence on the outcome of EM and SJS, if administered in high doses, over a short period of time, early in the course of the disease, and with proper tapering of medication. [33-37] However, the dosing and route of administration that provides the most benefit for EMM and SJS patients is in question. Treatment protocols such as early therapy with systemic prednisone (0.5 to 1.0mg/kg/day) or pulse methylprednisolone (1mg/kg/day for 3 days), intravenous pulsed dose methylprednisolone (3 consecutive daily infusions of 20–30mg/kg to a maximum of 500mg given over 2 to 3 hours), and dexamethasone pulse therapy (1.5mg/kg IV over 30 to 60 minutes on 3 consecutive days), all have been shown to be effective. [33-35,37-39]

Drug	Triamcinolone (10 mg/ml)	Dexamethasone (4 mg/ml)
Indications	Severe recurrent aphthous stomatitis, major aphthous stomatitis, erosive lichen planus	
Usual dosage	Inject 0.1 cc/cm lesion	
Contraindications	Hypersensitivity to corticosteroids, systemic fungal infection, live vaccines, active tuberculosis	
Common side effects	Candidiasis, hyperglycemia	
Unusual side effects	Peptic ulceration with perforation, osteoporosis, impaired wound healing, mucosal atrophy	

Adapted and modified from [23].

Table 3. Injectable (intralesional) corticosteroids used for treatment of oral lesions

Drug	Beclomethasone	Betamethasone	Clobetasol	Halobetasol	Fluocinonide
Indications	Severe recurrent aphthous stomatitis, Behcet's syndrome, pemphigus vulgaris, pemphigoid				
Administration	Inhaler spray topically to mucosal lesions	Topical intraoral cream or gel, soluble tablets as mouth wash	Topical intraoral cream or gel	Topical intraoral cream or ointment	Topical intraoral cream
Usual dosage	50-100 µg sprayed onto oral lesion	0.1% cream or 0.05% gel applied thinly bid; 0.5 mg 2-4 times daily as mouth wash	0.05% cream or gel applied thinly bid	0.05% cream or ointment applied thinly bid	0.05% cream applied thinly bid
Contraindications	Untreated infections				
Common side effects	Oral candidiasis				
Unusual side effects	Adrenal suppression if doses exceeded				

Adapted and modified from [23].

Table 4. Topical corticosteroids used for treatment of oral lesions

Drug	Prednisone (tablets)
Indications	Severe recurrent aphthous stomatitis, Behcet's syndrome, pemphigus vulgaris, pemphigoid, erythema multiforme
Usual dosage	1. 30-40 mg daily after breakfast for 4-5 days 2. 1-2 mg/kg/day after breakfast until disease controlled 3. 1-2 mg/kg/day, then maintenance of 2.5-15 mg daily 4. 20-40 mg daily for 7-10 days at onset of lesions or until lesions resolve 5. 60 mg daily for 2 days, 50 mg daily for 2 days, 40 mg daily for 2 days, 30 mg daily for 2 days, 20 mg daily for 2 days, 10 mg daily for 2 days
Contraindications	Hypersensitivity to corticosteroids, systemic infection (unless specific antimicrobial therapy given), peptic disease (unless proton pump inhibitor given), live vaccines
Common side effects	Dyspepsia, candidiasis, myopathy, osteoporosis, adrenal suppression, Cushing's syndrome, euphoria, depression
Unusual side effects	Peptic ulceration with perforation, Cushingoid side effects increasingly likely with doses above 7.5 mg daily

Adapted and modified from [23].

Table 5. Systemic corticosteroids used for treatment of oral lesions

2.3. Keloid and hypertrophic scars

Keloid and hypertrophic scar (HS) represent pathologic overhealing conditions which are caused by excessive production of fibrous tissue following healing of skin injuries. Keloid produces significantly more collagen than HS. Their exact cause is unknown but inflammation, tension, and genetic background are mentioned as contributing factors. Keloid and HS have different clinical features. Keloids extend beyond the confines of the original wound, develop months after injury, and rarely regress. HS is a raised scar that remains confined to the area of the injury, usually form within weeks, and may regress without intervention.

Various treatment modalities have been used for prevention and treatment of keloid and HSs such as pressure therapy, silicone gel sheeting, topical flavonoids, corticosteroid therapy, radiotherapy, and surgery.

Topical and intralesional glucocorticoids are frequently used to treat existing keloid and HS or, prophylactically, to prevent their formation or recurrence after surgical removal. Topical administration of steroids doesn't appear to be as efficacious as intralesional injection of the drug. Intralesional steroid injection, either on its own or in combination with other treatment modalities is the most common treatment used for keloid and HSs. Glucocorticoids have a multiplicity of effects on scars including suppressive effects on the inflammatory process in the wound, diminishing collagen and glycosaminoglycan synthesis, inhibition of fibroblast growth, and enhancing collagen and fibroblast degeneration. [40,41] Triamcinolone acetonide is the most commonly used steroid for the treatment of HS and keloid. It is used in a concentration of 10-20 mg/ml, though it can be given at a dose of 40 mg/ml for a tough bulky lesion; the concentration depends upon the size and site of the lesion and age of the individual. [42] Side effects of steroid injection include hypopigmentation, dermal atrophy, telangiectasia, and cushingoid effects from systemic absorption. [41] Cushing's syndrome secondary to injection of triamcinolone acetonide for the treatment of keloids have been reported by several investigators. [43,44]

2.4. Central giant cell granuloma

Central giant cell granuloma of the jaws is a benign tumor which occurs most often in children and young adults. This tumor is made up of loose fibrous connective tissue stroma with many interspersed proliferating fibroblasts, aggregations of multinucleated giant cells, and foci of hemorrhage.

Various surgical and nonsurgical treatments have been advocated for this lesion. One of the nonsurgical treatments proposed is intralesional corticosteroid injections. Intralesional injection of triamcinolone acetonide has been shown to induce partial and in some cases complete resolution of central giant cell granuloma. However, there is no reasonably strong consensus in the literature regarding optimal dosage and duration of treatment that provides the most benefit. The mechanism of action of corticosteroids in the treatment of central giant cell granuloma is unknown. A rationale for its use has been the histologic

resemblance of central giant cell granuloma to sarcoid. Because corticosteroids have been effective in the treatment of sarcoid, it was thought that they may have a similar therapeutic effect on central giant cell granuloma. In addition, corticosteroids may act by suppressing any angiogenic component of the lesion. [45]

2.5. Bell's palsy

Bell's palsy is an idiopathic inflammation of the facial nerve (the seventh of twelve paired cranial nerves) which occurs almost always on one side only. It is characterized by facial muscle weakness, hyperacusis, decreased tearing, and loss of taste on the anterior two thirds of the tongue. Because Bell's palsy results from inflammation and edema of the facial nerve, corticosteroids constitute the standard medicine in the treatment of this condition. [46-48] For adults, prednisolone at doses of 1 mg/kg/day for 7 to 10 days, taken in divided doses in the morning and evening, is suggested.

2.6. Management of post-operative morbidities associated with maxillofacial surgeries

Facial pain, edema, ecchymosis and limitation of mouth opening are the expected sequelae of oral and maxillofacial surgeries. These post-operative complications affect the ability of patient to interrelate and to return to the daily life and activities, and deteriorate the quality of life of patient. [49,50]

Many modalities are used to abate sequelae in the oral and maxillofacial surgery including use of ice pack, pressure dressing, surgical drain, and drugs.

Corticosteroids are commonly used to control post-operative morbidities and to provide comfort for patients. However, there are no definite protocols relative to molecules, doses, schedules, and routes of administration. [51] The most commonly administered types of corticosteroids are betamethasone, dexamethasone, and methylprednisolone, administered intravenously, orally or by injection into the masseter muscle. The morbidity-management protocol also varies depending upon the type of surgery being performed.

To decrease post-rhinoplasty edema, the administration of corticosteroids has been advocated for many years. In a study by Gurlek et al., it was shown that high dose methylprednisolone was effective in preventing and reducing both the periorbital ecchymosis and edema in open rhinoplasty. [52] In the same line, Kargi et al., and Kara and Gokalan showed that the perioperative use of corticosteroids reduced edema and ecchymosis associated with rhinoplasty surgery. [53,54] In contrast, Hoffmann et al. did not observe any increase either in the edema or the ecchymosis after rhinoplasty surgery. [55]

Regarding orthognathic surgery, several investigations demonstrated that perioperative corticosteroid administration significantly reduced post-operative inflammation and edema. [56-59] In contrast, Munro et al. did not observe any significant decrease in postoperative edema even with the highest doses and the longest durations of corticosteroid treatment. ⁽⁵⁶⁾

The effects of corticosteroids on post-operative edema after oral surgery have been widely investigated in the literature. Many prior studies demonstrated a significant decrease in post-operative edema after administration of corticosteroids. [60-63] In a study by Zandi, it was shown that steroids not only reduced the facial swelling, but also the severity of pain after surgery. [60] Similarly, several studies reported that corticosteroids significantly decreased post-operative edema and pain, indicating a strong correlation between edema and pain decreases. [62-64]

Even though the effects of corticosteroids on post-operative morbidities after various oral and maxillofacial surgeries have been widely investigated in the literature, methodological differences, variation in agents, doses, and routes of administration of the drugs have compromised the scientific conclusions.

2.7. Other uses of corticosteroids in oral and maxillofacial surgery

In addition to the aforementioned indications, corticosteroids are successfully used in the management of acute trigeminal nerve injuries, traumatic facial nerve paralysis, chronic facial pain, and allergic diseases involving maxillofacial area.

3. Corticosteroids contraindications

In prescribing corticosteroids, physicians must be aware that some patients are poor candidates for systemic, locally injected, or topical corticosteroid therapy.

Systemic corticosteroids must be used with the greatest of caution in patients with uncontrolled hypertension, diabetes, active peptic ulcer, heart diseases, infections, psychiatric disorders, osteoporosis, cataract, glaucoma, tuberculosis, mycobacterial diseases, herpes simplex infection, pregnancy, varicella zoster infection, immune deficiency, underactive thyroid, and mental disorders.

Injectable corticosteroid use is contraindicated in patients with hypersensitivity to corticosteroids, infections, and active tuberculosis.

Use of topical corticosteroids is absolutely contraindicated in the treatment of primary bacterial infections such as impetigo, furuncles, carbuncles, erysipelas, cellulitis, lymphangitis, and erythrasma. Topical corticosteroids are also contraindicated in patients with a history of hypersensitivity to any of the components of the preparation. Currently, little is known about the safety of topical corticosteroids in pregnancy. Although it has been reported that there is an association between very potent topical corticosteroids and congenital abnormalities including low birth weight and orofacial clefts, use of these drugs in pregnancy is not recommended unless the potential benefit justifies the potential risks to fetus. [65]

Ophthalmic use of topical corticosteroids is contraindicated in most viral, bacterial, and fungal diseases of ocular structures.

4. Corticosteroids side effects

Although corticosteroids have great potential in the treatment of various diseases and conditions affecting oral and maxillofacial region, they also carry the risk of many side effects. Therefore, benefits from corticosteroids should always be weighed against their potential risks. Side effects of corticosteroids vary depending on the type and dose of the medication, route of administration, and length of treatment. Significant adverse effects are most likely to occur in patients using oral corticosteroids for a long period of time. These may include weight gain, impaired growth, adrenal insufficiency, electrolyte abnormalities, increased susceptibility to infection, myopathy, osteoporosis, osteonecrosis, cataract, glaucoma, psychological problems, fractures, hypertension, insomnia, moon face, diabetes, and peptic ulcer. [1,66]

Topical glucocorticoids may cause adverse effects such as skin atrophy, hypopigmentation, subcutaneous fat wasting, telangiectasia, contact dermatitis, oral thrush, and cushingoid effects from systemic absorption. [28,41] Application of topical corticosteroids on eyelids has been reported to cause glaucoma. Adrenal suppression, growth retardation in children, and cushing's syndrome are rare adverse effects of long term topical corticosteroid use.

Intralesional glucocorticoids may cause sterile abscess, skin atrophy, hypopigmentation, panniculitis, and skin necrosis.

Although the frequency of side effects of inhaled corticosteroids is lower than systemic corticosteroids, high doses of inhaled corticosteroids have the potential to produce various local and systemic side effects. Systemic side effects associated with inhaled corticosteroids include osteoporosis, retarded growth in children, cataracts, glaucoma, and skin thinning. Inhaled corticosteroids may cause local side effects including oropharyngeal candidiasis, dysphonia, reflex cough, bronchospasm, and pharyngitis. [67]

5. Perioperative management of patients with adrenal insufficiency

Insufficient adrenocortical function is a rare disorder resulting from endogenous deficiency (primary) or from the administration of exogenous corticosteroids (secondary). Adrenal suppression should be suspected in those patients receiving the equivalent of 20 mg of prednisone daily for one week or the equivalent of 7.5 mg of prednisone daily for one month within the past year. [2] In adrenal suppression the body is not able to appropriately manage the challenge of stresses such as medical illness, surgery, and trauma. This may precipitate an adrenal crisis, signaled by the onset of fever, restlessness, flank and abdominal pain, vomiting, lethargy, hypotension, or coma.

Any patient suspected of having adrenal insufficiency should be evaluated with an ACTH (cortrosyn) stimulation test or be given supplemental corticosteroids empirically perioperatively. Cortrosyn stimulation test measures how well the adrenal glands respond to a synthetic ACTH administered to the patient.

The currently recommended corticosteroid coverage for various surgical procedures is based on the magnitude of stress and the known glucocorticoid production rate associated with it, and includes the following: [2,68]

- Minor surgical stress such as tooth extraction, biopsy, periodontal surgery, genioplasty, etc: 25 mg of hydrocortisone equivalent, the day of surgery
- Moderate surgical stress such as panfacial fractures, two jaw surgery, etc: 50-75 mg of hydrocortisone equivalent for 1 to 2 days.
- Major surgical stress such as extensive head and neck resection and reconstruction, etc: 100-150 mg of hydrocortisone equivalent for 2 to 3 days.

In the case of postoperative complications such as fever and pain, it is recommended that the corticosteroid administration be continued consistent with the post-operative stress response. [68]

6. Maternal corticosteroid use and the risk of orofacial clefts in infants

Orofacial clefts are the most common congenital deformity affecting maxillofacial area. The etiology of facial clefting is complex and has been extensively investigated. There are both major and minor genetic influences involved, with variable interactions from environmental factors. [69] Several environmental factors such as maternal drug intake, trauma, smoking, and exposure to x-rays during the pregnancy period have been suggested to increase the chance of cleft development in infants. [70]

Pregnant women often use topical, inhaled, or systemic corticosteroid drugs for a variety of inflammatory and allergic conditions. Several investigations have reported that the use of corticosteroids during early pregnancy is associated with a 3- to 6-fold increased risk of orofacial clefts. [71-75] Although systemic corticosteroids are associated with a higher risk of orofacial clefts than topical corticosteroids, the latter is not without risk. It has been shown that application of hydrocortisone cream on eczematous skin is associated with significant increase in the level of plasma cortisol. [76] In a study by Edwards et al., a significant association between topical corticosteroids and orofacial cleft was observed. [77] Epidemiologic data have shown that low-to-moderate doses of inhaled corticosteroids taken during the first trimester of pregnancy are safe but raise concerns about high doses. [78]

The mechanism of cleft palate production by corticosteroids is uncertain; it is a complicated interference in a complex developmental program involving many genetic and biochemical processes. Glucocorticoids may cause cleft palate deformity by delaying palatal shelf elevation. [79] Corticosteroids can reduce the collagen content of connective tissue by inhibiting collagen synthesis, which could disrupt cell-cell interaction and tissue-tissue interactions. [71]

7. Conclusion

Glucocorticoids are used, either singly or in combination with other drugs, for the treatment of various diseases affecting oral and maxillofacial area. They are also frequently used to

minimize expected post-operative morbidities such as pain and edema after oral and maxillofacial surgeries. Because of anti-inflammatory and anti-allergic actions of glucocorticoids, they have their widest application in the management of acute and chronic conditions which have allergic, immunologic, or inflammatory basis. However, corticosteroids carry the risk of potential side effects which are sometimes severe and life threatening. Therefore, benefits from corticosteroids should always be weighed against their potential risks in each patient.

Prescribing the minimal dose and the least potent type of corticosteroids necessary to produce a given therapeutic effect, simultaneous use of non-steroidal agents to reduce the dose of corticosteroids, and prescribing corticosteroids for a short period of time or sporadically are some strategies to minimize corticosteroids adverse effects.

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