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PRIMENA KORTIKOSTEROIDA U STOMATOLOGIJI

APPLICATION OF CORTICOSTEROIDS IN DENTISTRY

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Sažetak

Uvod: *Kortikosteroidi(KS) su prirodni ili sintetički hormoni koji utiču na skoro svaki aspekt ljudske fiziologije. Smanjenjem simptoma zapaljenja i imunosupresijom, u kliničkom smislu, KS deluju simptomatski, olakšavajući tegobe osnovne bolesti ili trenutnog stanja kod pacijenata. Prema načinu uporebe, kortikosteroide u stomatologiji delimo na topikalno,lokalno i sistemski primenjene. Topikalna upotreba vazokonstrikcijom sprečava degranulaciju mastocita, smanjuje propustljivost kapilara delujući na smanjenje količine histamina koji se oslobađa iz bazofila i mastocita. Glavni cilj ove terapije kortikosteroidima je ukloniti ili barem smanjiti bol kod pacijenata, što ima uticaj na celokupno zdravlje, ishranu, govor. Neinfektivne upale mekog tkiva koje zahtevaju primenu KS su: rekurentni aftozni stomatitis, oralna submukozna fibroza, keloidi i hipertrofični ožiljci, mukokele. Kod bolnih sindroma sa manifestacijama u predelu glave i vrata: Bechet sindrom,bulozni pemfigoid, oralni lichen planus itd. U oralnoj hirurgiji već se dugo u postoperativnoj terapiji donjeg impaktiranog umnjaka i drugih težih intervencija, pored analgetika (NSAIL i narkotički analgetici) koriste KS u cilju smanjenja tizmusa, otoka i bola. Postoje brojne studije koje sugerišu na vreme i put administracije KS u hirurgiji donjeg impaktiranog umnjaka, kao i različite kombinacije KS sa drugim medikamentima u cilju smanjenja morbiditeta posle ovakvih intervencija. Lokalna primena KS indikovana je u lečenju gigantocelularnih lezija i može zameniti hiruške procedure.*
Zaključak: *Kortikosteroidi našli su široku primenu u stomatologiji u svojim indikacionim područjima.*

Ključne reči: *kortikosteroidi,stomatologija,inflamacija*

Abstract

Introduction**:** *Corticosteroids (CS) are natural or synthetic hormones that affect nearly every aspect of human physiology. In the clinical sense, by reducing the symptoms of inflammation and immunosuppression, CS act symptomatically, decreasing problems of the underlying disease or the current state of the patient. According to application, corticosteroids are divided into topical, local and systemic way of use. Topical use of CS makes vasoconstriction, lowers mast cells degranulation, and reduces the permeability of capillaries reducing the amounts of released histamine from basophils and mast cells. The main goal of this therapy is to relieve or at least reduce pain in patients, which has an impact on overall health, nutrition, speech. Soft tissue inflammations that require the application of CS are: recurrent aphthous stomatitis, oral submucosal fibrosis, keloids and hypertrophic scars, mucocele; painful syndrome with manifestations in the head and neck: Bechet syndrome, pemfigoid syndrome, bullous pemfigoid,Oral Lichen planus, etc.; that reduces the need for taking analgetics .In oral surgery they are used for the treatment of the impacted wisdom teeth and other serious interventions which apart from analgesics (NSAIDS and narcotic analgesics) require CS in order to reduce trizmus, swelling and pain. There are numerous studies that suggest the time and route of the administration CS in lower impacted wisdom teeth surgery, as well as different combinations of CS with other medications in order to reduce morbidity this such an intervention. Local application of CS is indicated in this treatment of gigantocellular lesions and can replace the surgical procedures.*
Conclusion*: Corticosteroids have wide application in dentistry in their indicational areas.*

Key words: *corticosteroids, dentistry, inflammation*

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Uvod

Kortikosteroidi (KS) su prirodni ili sintetički hormoni koji utiču na skoro svaki aspekt ljudske fiziologije. Još sredinom devetnaestog veka, Adisson i Brown-Sequard proučavali su ulogu nadbubrežnih žlezda u regulaciji fizioloških funkcija ljudskog organizma. Godine 1950. trojica naučnika Philip Hench, Edward Kendall i Tadeus Reichstein dobijaju Nobelovu nagradu za otkrića vezana za funkciju kore nadbubrežne žlezde[1].

Svakog dana nadbubrežna žlezda proizvodi oko 24-30 mg kortizola. Polovina količine ukupnog dnevnog kortizola izluči se u ranim jutarnjim satima. Najviši nivo kortizola je rano ujutru, između 8 i 9 sati, tokom dana opada i najniži nivo dostiže sat ili dva po početku spavanja[2]. Nadbubrežna žlezda može proizvesti i do 300 mg kortizola dnevno u uslovima povećanog stresa. Povećano lučenje kortizola može dovesti do supresije hipotalamo-hipofizno-nadbubrežne sprege, kojoj treba i do godinu dana za potpuni oporavak. Ipak, funkcionalni odgovor na stres može se oporaviti za dve nedelje do mesec dana[3].

Hipotalamus - hipofizno - nadbubrežni sistem ima važnu ulogu u regulisanju signala od strane glukokortikoidnih receptora, koji postoje na skoro svim ćelijama organizma. Neuronski, endokrini i citokini signali u vezi su sa periventrikularnim jedrima hipotalamusa kako bi se kontrolisala sekrecija hormona koji oslobađaju ACTH u hipofizi.90% izlučenog kortizola vezuje se za kortizol-vezujuće globuline krvi. Nevezani, slobodni kortizol biološki je aktivan oblik hormona i pretvara se u kortizon.

Kompleks kortizol-receptor koji nastaje u citoplazmi, dolazi do jedra, vezuje se kao homodimer na DNA sekvenci poznatoj kao glukokortikoid reagujući element. Nastali kompleks aktivira transkripcione faktore u jedru koji menjaju strukturu hromatina (proces poznat kao transaktivacija), čime se olakšava ili inhibira sastavljanje bazalnog transkripcijskog mehaniznma za inicijaciju transkripcije RNK polimerazom II , (slika 1). Na taj način dolazi do promene u regulaciji ekspresije gena-transrepresija[4].

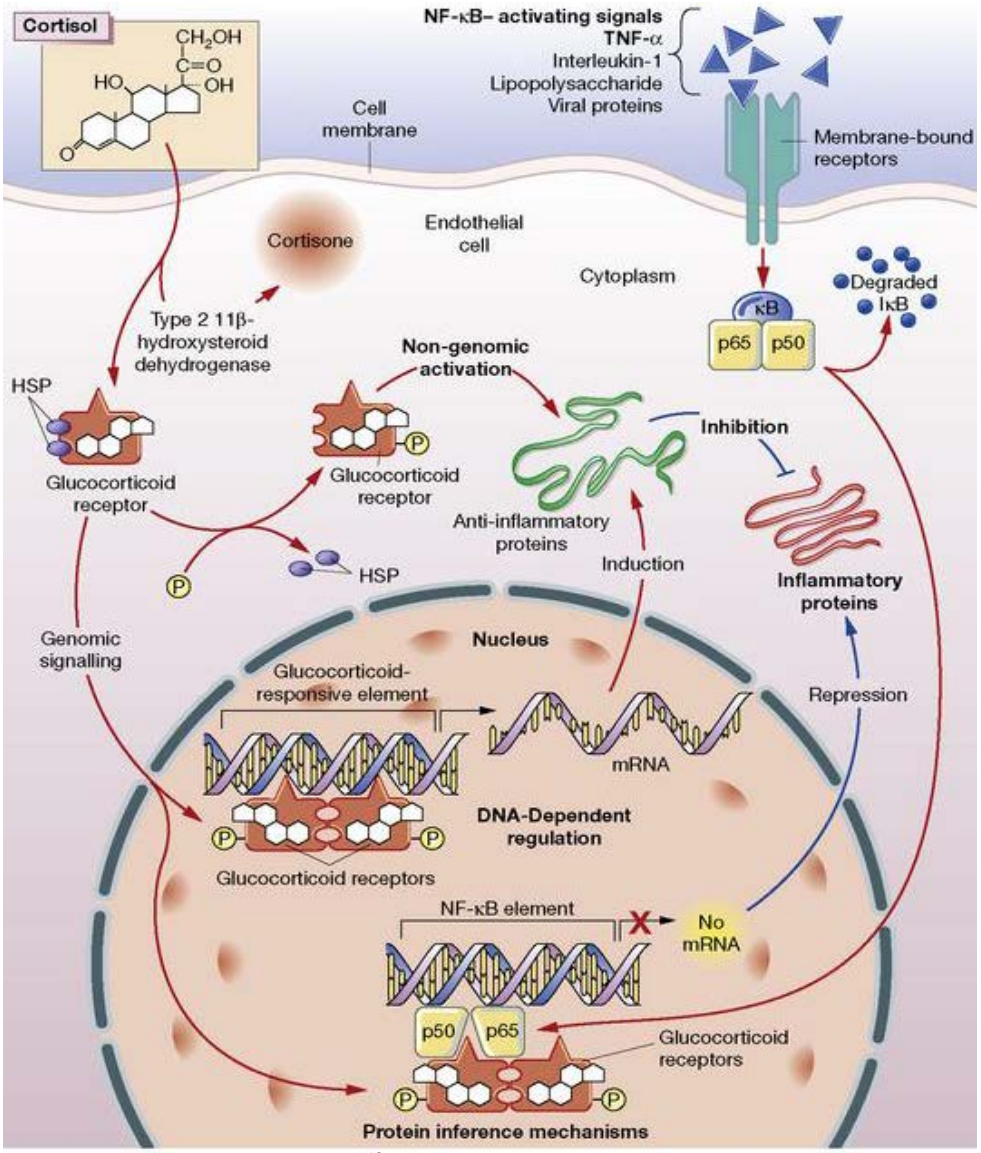
Introduction

Corticosteroids (CS) are natural or synthetic hormones that affect nearly every aspect of human physiology. In the mid nineteenth century, Addison and Brown-Sequard studied the role of the adrenal glands in the regulation of the physiological functions of the human body. In 1950 three scientists, Philip Hench, Edward Kendall and Thaddeus Reichstein won The Nobel Prize for discoveries related to the function of adrenal gland cortex[1].

Every day, adrenal glands produce about 24-30 mg of cortisol. Half of the amount of the total daily cortisol is secreted in the early morning hours. Cortisol levels are the highest early in the morning, between 8 and 9 a.m., decline throughout the day and reach their lowest 1-2 hours after falling asleep[2]. The adrenal glands can produce up to 300 mg of cortisol daily in periods of increased stress. Increased secretion of cortisol can lead to suppression of the hypothalamus-pituitary-adrenal axis, which takes up to a year for a full recovery. However, the functional response to stress may recover in 2-4 weeks[3].

Hypothalamus-pituitary-adrenal system plays an important role in regulating signals of glucocorticoid receptor, which exist in almost all cells of the organism. Neural, endocrine and cytokine signals are connected to periventricular nuclei of the hypothalamus to control the secretion of the hormones that release ACTH in the pituitary gland. Ninety per cent of secreted cortisol is bound to cortisol-binding blood globulins. Free cortisol is the biologically active form of the hormone and is converted to cortisone.

Cortisol-receptor complex, formed in the cytoplasm, reaches the nucleus and is bound as a homodimer to the DNA sequence known as glucocorticoid response element. Thus formed complex activates transcription factors in the nucleus, which change the structure of chromatin (a process known as transactivation) and facilitate or inhibit the basal transcription mechanism for RNA PCR II transcription initiation (figure 1). That leads to the change in the gene expression regulation- transrepression[4].



Slika1. Metabolički efekat KS[40] ***Fig. 1.*** Metabolic effect of CS[40]

Kortikosteroidi inhibiraju enzim fosfolipazu A2, koja je prvi enzim uključen u konverziju fosfolipida u arahidonsku kiselinu. Od arahidonske kiseline nastaju upalni produkti kao što su prostaglandini, leukotrieni, tromboksan A2 i druge supstance povezane sa ovim osnovnim medijatorima zapaljenja(slika 2).

Sintetički analozi kortizolu proizvode se od polovine prošlog veka. Kod njih su farmaceutskom tehnologijom suprimirani metabolički, a potencirani antiinflamatorni i imunosupresivni efekti.

Corticosteroids inhibit enzyme phospholipase A2, that is the first enzyme included in conversion of phospholypides to arachidonic acid. Arachidonic acid produces inflammation products such as prostaglandins, leukotrienes and tromboxane A2, and other substances that are in relation with mediator of inflammation (figure 2).

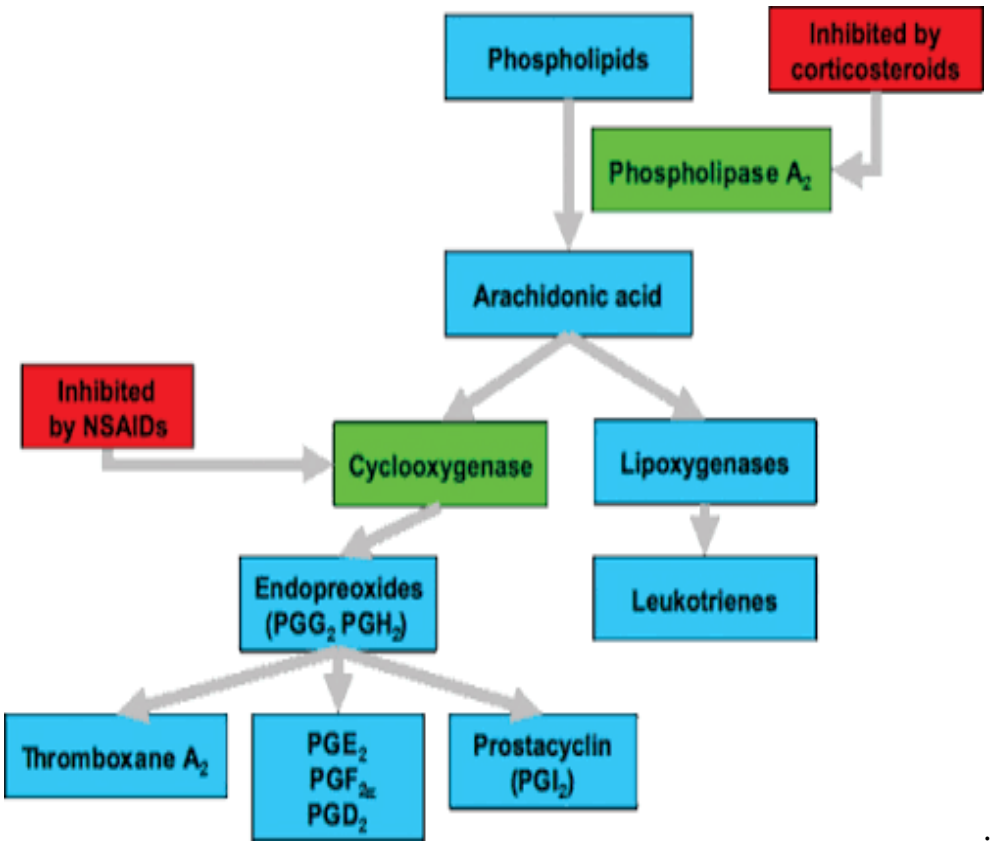
Synthetic analogues of cortisol have been produced since the end of last century. By using pharmaceutical technology, metabolic effects are suppressed, and anti-inflammatory effects are potentiated in them.

U kliničkom smislu glukokortikoidi, smanjenjem simptoma zapaljenja i imunosupresijom, deluju simptomatski, olakšavajći tegobe osnovne bolesti ili trenutnog stanja kod pacijenata.

Upale su, bez obzira na uzrok, praćene pojavom ekstravazacije i infiltracije leukocita u zahvaćenom tkivu. U njima dolazi do niza interakcija adhezijskih molekula na leukocitima i na endotelnim ćelijama. Protivupalno dejstvo kortikosteroida ogleda se njihovim delovanjem na broj, rasprostranjenost i funkciju perifernih leukocita kao i supresivnim delovanjem na upalne citokine, hemokine i ostale posrednike upale.

In the clinical sense, glucocorticoids, by reducing the symptoms of inflammation and by immunosuppression, relieve symptoms of the underlying disease or the current patient condition.

Inflammation is, regardless of cause, always followed by the extravasation and infiltration of leukocytes in the affected tissue, leading to a series of adhesion molecule interaction on leukocytes and endothelial cells. The anti-inflammatory property of corticosteroids is their effect on the number, distribution and function of peripheral leukocytes, as well as their suppression of cytokines, chemokines and other inflammatory agents.



Slika 2. Farmakološki efekat KS[40]
Fig. 2. Pharmacological effect of CS[40]

Glukokortikoidi inhibiraju oslobađanje mediiatora zapaljenia iz mnogih tipova ćelija uključenih u inflamatorne procese kao što su makrofagi. T-limfociti. mastociti, dendritične ćelije i neutrofilni leukociti[5].

KS takođe imaju sposobnost stabilizovania lizozimskih membrana. smaniuju propustliivost kapilara i redukuju diiapedezu redukuju sintezu bradikinina, snažne vazodilatatorne supstance[6].

Posle jednokratne doze glukokortikoida, broj neutrofila u cirkulaciji raste zbog njihovog povećanog pristizanja iz koštane srži u krv i zbog njhove smanjene migracije iz krvnih sudova. Broj limfocita, monocita, eozinofila i bazofila smanjuje se zbog kretanja iz mreže krvnih sudova u limfatično tkivo. To će za posledicu imati smanjeni broj ćelija na samom mestu upale. Delujući na makrofage, glukokortikoidi ograničavaju njihovu sposobnost fagocitoze i uništavanja mikroorganizama, stvaranja faktora nekroze tumora-α, interleukina-1, metaloproteinaza i aktivatora plazminogena[7]. Najizraženiie dejstvo KS je 6 sati posle primene, a farmakološko dejstvo traje do 24 sata posle primene.

Upotreba glukokortikoida u terapijske svrhe raste iz godine u godinu. Oni se mogu upotrebljavati samostalno ili u kombinaciji sa drugim medikamentima. U medicini se koriste u skoro svim granama.

Glukokortikoidi upotrebljavaju se još od prenatalnog perioda kod majki kod kojih je moguć prevremeni porođaj, kao i kod prevremeno rođene dece, u cilju stimulacije formiranja surfaktanata u plućima. Oni pospešuju sintezu fosfolipida i produkciju proteina koji su važni za sintezu surfaktanta[8]. Glukokortikoidi se koriste u tretmanu kaheksije kod pacijenata koji boluju od tumora bronha i ostalih vrta malignih tumora[9]. Njihov efekat na apetit uključuje inhibiciju sinteze i / ili otpuštanja pro-inflamatornih citokina kao što je TNF- α; IL-1 koji direktno smnjuje potrebu za hranom. Slično tome, oni utiču na druge medijatore, kao što su leptin, kortikotropin otpuštajući faktor (CRF) i serotonin[10]. Kortikosteroidi mogu povećati nivo neuropeptida Y (NPY) u hipotalamusu koji mogu donekle povećati apetit i poboljšati ishranu[11].

Glucocorticoides inhibit the releasing of inflammation products from many cell types involved in inflammation such as macrophages, T lymphocytes, mast cells, dendritic cells and neutrophil leukocytes[5].

Corticosteroides also have the ability to stabilize membrane of lysosomes that can cause inflammation, reduce vascular permeability, and reduces diapedesis. They reduce the synthesis of bradykinins, powerful vasodilator substance[6].

After a single dose of corticosteroids, the number of neutrophils in circulation rises due to their increased inflow from the bone marrow into the blood, and because of their reduced migration from the blood vessels. The number of lymphocytes, monocytes, eosinophils and basophils decreases due to their movement from the blood vessel network into the lymphatic tissue. This in turn reduces the number of cells at the site of inflammation. When it comes to macrophages, glucocorticoids limit their capability of phagocytosis and destruction of microorganisms, as well as creation of tumor necrosis factors, interleukins-1, metalloproteinase and plasminogen activators[7]. The effect of CS is the most pronounced 6 hours after administration, while their pharmacological effect lasts up to 24 hours.
The use of glucocorticoids for therapeutic purposes is increasing every year. They can be used alone or in combination with other medications. They are used in almost all fields of medicine.

Glucocorticioids are even used in the prenatal period in mothers at risk of premature delivery, as well as in prematurely born children to stimulate the formation of surfactants in the lungs. They enhance the synthesis of phospholipids and production of proteins important for the synthesis of surfactants[8]. Glucocorticioids are further used in the treatment of cachexia in patients suffering from bronchogenic carcinoma and other types of malignant tumors[9]. Their effect on appetite includes the inhibition of synthesis and/or release of pro-inflammatory cytokines such as TNF-α; or IL-l which directly reduce nutrition. Similarly, they affect other mediators, such as leptin, central corticotropin release factor (CRF) and serotonin[10]. Corticosteroids can increase the level of neuropeptides Y (NPY) in hypothalamus which can, to an extent, increase appetite and improve nutrition[11].

Upotreba KS u stomatologiji

Prema načinu upotrebe kortikosteroide u stomatologiji delimo na topikalno,lokalno i sistemski primenjene.

Topikalna upotreba KS vazokonstrikcijom sprečava degranulaciju mastocita, smanjuje propustljivost kapilara, delujući na smanjenje količine histamina koji se oslobađa iz bazofila i mastocita. Na ovaj način KS koriste se za prekrivanje pulpe i preosetljivosti dentina, kao i za sprečavanje i ublažavanje upalnih reakcija, crvenila i edema kod vezikulobuloznih i ulcerativnih bolesti poput afti, pemfigusa, pemfigoida i lichen planusa. Glavni cilj ove terapije kortikosteroidima je ukloniti ili barem smanjiti bol kod pacijenata, što ima uticaj na celokupno zdravlje, ishranu, govor.

Neinfektivne upale mekog tkiva koje zahtevaju primenu KS su:1. Rekurentni aftozni stomatitis; 2. Oralna submukozna fibroza; 3. Keloidi i hipertrofični ožiljci; 4. Mukokele. Kod bolnih sindroma sa manifestacijama u predelu glave i vrata: 5. Behcet (Behčet) sindrom; 6. Bulozni pemfigoid; 7. Oralni lichen planus; 8. Pemphigus vulgaris; 9. Erythema multiforme, 10. Stevens-Johnson sindrom, 11. Belova paraliza; 12. Ramsay Hunt syndrom (Remzi Hant sindrom); 13. Postherpetična neuralgija. Poremećaji lokomotornog sistema ove regije: 14. Disfunkcije temporomandibularnog kompleksa. Neinfektivne bolesti tvrdih oralnih tkiva: 15. Sprečavanje resorpcije korena; 16. Centralni gigantocelularni granulom; 17. Rekurentni pulpit.

1. Rekurentni aftozni stomatitis: Afte minor se karakterišu manjim brojem ulcerativnih promena (od 1 do 5), promera do 1 cm. Bolest obično prolazi za 8 do 14 dana, spontano i bez posledica. Afte major su promera preko 1 cm, perzistiraju nedeljama čak i mesecima. KS se kod ovog oboljenja primenjuju topikalno i intralezijski, ređe, u najtežim slučajevima parenteralno[3,12].

2. Oralna submukozna fibroza je podmukla, hronična, rezistentna bolest koja se javlja na mukozama, submukozi usne duplje uključujući ždrelo i jednjak. Bolest je praćena jakom salivacijom, peckanjem, otežanim, gutanjem i ograničenim otvaranjem usta. Topikalna primena orobaza sa KS ubrzava zarastanje ulceracija i smanjuje bol, jer dovodi do supresije T limfocita, redukuje broj fibroblasta i smanjuje formiranje kolagena. U poslednje vreme intralezijska primena KS daje najbolje rezultate u lečenju manifestacija ove bolesti[13].

The application of corticosteroids in dentistry

According to the route of administration, corticosteroid application in dentistry is divided into topical, local and systemic.

Topical application acts vasoconstrictory preventing degranulation of mast cells, reducing the permeability of capillaries and thus lowering the levels of histamine released from basophils and mast cells. Consequently, corticosteroids are used to protect the pulp, reduce dentin sensitivity and prevent or relieve inflammatory reactions, redness and edema in vesicobullous and ulcerative diseases such as aphthae, pemphigus, pemphigoid and lichen planus. The main goal of this treatment is to eliminate or at least reduce pain in patients, which has an impact on overall health, nutrition, speech. Noninfectious inflammations of soft tissue that require the application of corticosteroids are1. Recurrent aphthous stomatitis; 2.Oral submucous fibrosis;3. Keloids and hypertrophic scars 4. Mucocele; 5.Bechet syndrome; 6. Bullous pemphigoid;7. Oral lichen planus;8. Pemphigus vulgaris ;9. Erythema multiforme ;10. Stevens-Johnson syndrome;11. Bell's paralysis;12. Ramsay Hunt syndrome;13. Postherpetic neuralgia. Furthermore, corticosteroids are used to treat locomotory system disorders, such as. Temporomandibular complex dysfunction; 14. Noninfectious diseases of the hard oral tissue 15. Prevention of root resorption; 16. Central gigantocellular granuloma 17. Recurrent pulpitis.

1. Recurrent aphthous stomatitis: Aphthae Minor are characterized by a small number of ulcerative changes (1-5) diameters up to 1 cm. Disease usually disappears in 8-14 days, spontaneously and without consequences. Aphthae Major are in diameter over 1 cm, persist for weeks and even months. Corticosteroids are here used topically and intralesionally, and rarely, in the most severe cases parenterally[3,12].

2. Oral submucous fibrosis is an insidious, chronic, resistant disease that occurs in the mucosa and submucosa of the oral cavity including pharynx and esophagus. The disease is accompanied by strong salivation, tingling sensation, difficulty swallowing and limited opening of mouth. Topical application of orobase with corticosteroids accelerates the healing of ulceration and reduces pain, because it suppresses T-lymphocytes and reduces fibroblast numbers and the formation of collagen. Lately, intralesional application of corticosteroids produces the best results in the treatment of the disease manifestation[13].

3. Keloidni i hipertrofični ožiljci (HO) predstavljaju patološko zarastanje tkiva zbog prekomerne produkcije kolagena usled povrede kože. Keloid zarasta sa znatno većom produkcijom kolagena nego hipertrofični ožiljak. Uzrok nije potpuno razjašnjen, ali infekcija, tenzija rane i genetski faktori imaju presudni značaj u pojavi ovakvog stanja tkiva. Keloidi se protežu dalje od granica rane, razvijaju se i više meseci posle povrede i retko regresiraju. HO je prominirajući ožiljak koji ostaje ograničen na područje rane, obično se javlja za nekoliko nedelja i može regresirati bez intervencije i zahteva hirurško uklanjanje. Glukokortikoidi redukuju upalne procese u rani, smanjuju sintezu kolagena i glikozaminoglikana, pospešuju degeneraciju kolagena i fibroblasta.Najbolji efekat se postiže intralezijskom primenom KS u cilju smanjenja i regresije promene, kao i za prevenciju recidiva.

4. Mukokela je cista ispunjena mukusom koja se javlja u usnoj šupljini i paranazalnim sinusima, veličine 1 ili 2 mm do nekoliko centimetara. Karakteristično je da fluktuira, ali su neke mukokele čvrste na palpaciju. Najčešće se javljaju na donjoj usni, podu usta, ventralnoj strani jezika, nepcu, bukalnoj sluznicu i retromolarnom predelu. Uzrok nastanka je trauma ili opstrukcija izvodnog kanala pljuvačne žlezde. Intralezijska aplikacija KS može dovesti do privremene regresije promene, ali definitivno lečenje podrazumeva hirurški tretman[14].

5. Behcetova bolest je multisistemska, hronična, inflamatorna bolest nepoznatog uzroka, koja se karakteriše recidivantnim oralnim aftaznim ulceracijama, genitalnim ulkusima, uveitisom i kožnim lezijama. Postoji i niz sporednih manifestacija, kao što su promene na zglobovima, centralnom nervnom sistemu, vaskularne i intestinalne lezije različite težine. Imunosupresivna terapija ima za cilj modifikaciju aktivnosti neutrofila. U akutnoj fazi daje se pulsna terapija KS u kombinaciji sa drugim imunosupresivnim sredstvima. Lokalna primena KS može biti od koristi samo kod vrlo blagih oblika, gde se promene javljaju samo na sluzokoži[3,12].

6. Bulozni pemfigoid je autoimuno oboljenje koje češće zahvata stariju populaciju. Ovaj tip autoimune reakcije dovodi do stvaranja antitela na dermoepidermalnim vezama, pogađa hemidezmozome, stvarajući subepidermalne bule.

3. Keloid and hypertrophic scars are a pathological remodeling of tissue due to excessive production of collagen caused by skin injuries. Keloid scars heal with significantly higher production of collagen than hypertrophic scars. The cause is not fully understood, but infection, wound tension and genetic factors have crucial significance in the appearance of this condition. Keloids extend beyond the borders of wounds, develop even several months after injury and rarely regress. Hypertrophic scar is a prominent scar that remains limited to the area of the wound, usually occurs within a few weeks, can regress without intervention and requires surgical removal. Glucocorticoids reduce inflammatory processes in the wound, decrease the synthesis of collagen and glycosaminoglycan and enhance the degeneration of collagen and fibroblasts. The best effect is achieved by intralesial application of corticosteroids used to reduce and regress the changes, as well as for the prevention of recurrence.

4. Mucocele is a cyst filled with mucus that occurs in the oral cavity and paranasal sinuses, 1 or 2 mm to several centimeters in size. It typically fluctuates, but there are some mucoceles that present hard to palpation. They most commonly occur on the lower lip, floor of the mouth, ventral side of the tongue, palate, buccal mucosa and retromolar area. The cause is trauma or salivary gland. Although the intralesional application of corticosteroids can lead to a temporary change regression, complete remission requires surgical removal[14].

5. Behcet's disease is a chronic inflammatory multisystemic disease with an unknown cause which is characterized by recurrent oral aphthous ulcerations, genital ulcers, uveitis and skin lesions. There is a number of secondary symptoms, such as changes in the joints, central nervous system, vascular and intestinal lesions of different severity. Immunosuppressive therapy is aimed at modifying the activity of neutrophils. In the acute stage, a pulse corticosteroid treatment is administered in combination with other immunosuppressive agents. Local application of corticosteroids is only useful with very mild forms, where the changes occur only on mucosa[3,12].

Razlikuje se od pemfigusa po izgledu bula, zatim po negativnom testu Nikolsky i manjem mortalitetu. Kod pemfigoida je prisutan svrab u predelu promena i oralne lezije javljaju se kod jedne trećine pacijenata, za razliku od pemfigusa gde nema svraba, a manifestacije bolesti su većinom prisutne u ustima[15]. Lečenje podrazumeva primenu KS per os do remisije bolesti, pri čemu se doza obično smanjuje na polovinu početne radi održavanja postignutog stanja.

7. Pemphigus obuhvata grupu retkih hroničnih mukokutanih bolesti koje se karakterišu bolnim lezijama uzrokovanim intraepidermalnim dezintegrisnanim strukturama u koži i sluznici. Oralne mukozne lezije javljaju se u 50% do 70% slučajeva i pretežno se javljaju kao bukalne erozije u okluzalnoj liniji koja je najizloženija trauma, kao i na nepcu, gingivi i jeziku[13]. Pemfigus je praćen intraepitelnim buloznim formacijama zbog autoantitela koja reaguju sa proteinima dezmozomsko-tonofilamentnog kompleksa između keratinocita[16]. Pemphigus vulgaris (PV) ima visoku stopu morbiditeta bez lečenja. Cilj lečenja je smanjiti pojavu bula i bolove pacijentu. Lečenje podrazumeva upotrebu KS i drugih imunosupresiva uz pomoć kojih je morbiditet smanjen sa 60% do 90% na 30%. Topikalna primena KS nema značajnog efekta, osim na oralnu sluzokožu[17]. Akutna faza pemfigusa povezana je sa promenama na mukozi želuca, pa ovakvo stanje može još otežati resorpciju KS.

8. Lichen Planus (LP) je jedinstveni inflamatorni poremećaj koji se ispoljava promenama na koži, sluzokožama, noktima i kosi. Prvi put je opisan i imenovan od strane Erasmus Wilsona (Erasmus Vilsona) 1869[18]. Patogeneza LP nije potpuno razjašnjena. Radi se o poremećaju celularnog imuniteta koji je izazvan egzogenim antigenima, čije se manifestacije registruju na epidermisu. LP može biti praćen erozijama, bulama i ulceracijama. Prednost steroida može se u određenoj meri objasniti antiimunološkim svojstvima sa potisnutim funkcijama T limfocita i smanjenom sintezom IgG.

6. Bullous pemphigoid is an autoimmune disease that occurs more often in the older population. This type of autoimmune reaction leads to the formation of antibodies on the dermoepidermal junctions, affects hemidesmosomes, creating subepidermal bullae. It differs from Pemphigus in appearance the negative Nikosky test and lower per cent of mortality. Pemphigoid presents with itching in the affected area and with oral lesions occurring in one-third of patients, whereas pemphigus doesn't cause itching and the symptoms of the disease are almost always present in the mouth[15]. Treatment involves application of corticosteroids per os until remission, when the dosage is typically reduced to half of the initial one in order to maintain the status achieved.

7. Pemphigus includes a group of rare chronic mucocutaneous diseases characterized by painful lesions caused by intraepidermal desintegrated structures in the skin and mucosa. Oral mucous lesions occur in 50%-70% of cases, mainly as buccal erosion in the occlusal line, which is the most exposed to trauma, and on the palate, gingiva and tongue. Pemphigus is accompanied by intraepithelial bullous formations, due to autoantibodies reacting with desmosome-tonofilament complex proteins between keratinocytes[16]. Pemphigus vulgaris (PV) has a high morbidity rate without treatment. The goal of treatment is to reduce the occurrence of bullae and to relieve the pain. Treatment consists of corticosteroids and other forms immuno-suppressive therapy, which reduce morbidity from 60%-90% to 30%. Topical application of KS has no significant effect, except on oral mucosa[17]. The acute phase of pemphigus is associated with changes in gastric mucosa, and this condition can make it more difficult to absorb KS.

8. Lichen Planus (LP) is a unique inflammatory disorder which presents with changes on the skin, mucosa, nails and hair first described and named by Erasmus Wilson in 1869[18]. Pathogenesis of LP is not completely clarified. It is a cellular immunity disorder caused by exogenous antigens causing pathological changes on the epidermis.

Ublažavanjem upale smanjena je destrukcija tkiva i tako se oslobađanje antigena svodi na minimum. Na ovaj način (KS) prekidaju začarani krug[19]. Kod ovog oboljenja KS koriste se topikalno, u vidu orobaze ili gela, dok se u težim slučajevima mogu davati i intraleziiski od 2 do 3 dana. U teškim formama sistemska primena KS je neophodna.

9. Erythema Multiforme je kožna bolest koja je klinički poznata još od prve polovine XIX veka. Nastaje zbog preosetljivosti na infekciju i medikamente. Sastoji se od polimorfnih eruptivnih makula, papula i karakterističnih "cilinih" lezija koje su simetrično raspoređene na distalnim ekstremitetima. Sluzokoža je minimalno zahvaćena. Herpes simplex virus (HSV) je u etiologiji ove reakcije preotljivosti u više od 50 posto slučajeva identifikovan kao uzrok. Erythema multiforme (EM) je nekada bila smatrana kao manifestacija Stevens-Johnsonovog sindroma (SJS), povezanog sa toksičnom epidermalnom nekrozom (TEN). Danas je prihvaćeno da postoji razlika između EM i SJS. Trenutno postoje dve različite klasifikacije: Prva – eritema multiforme spektar (major i minor) i druga – SJS i TEN spektar.

10. SJS i TEN, su retke mukokutane bolesti koje mogu biti opasne po život i gotovo uvek uzrokovane lekovima. SJS je prvi put opisan 1922. godine od strane dva lekara Stevensa i Johnsona, koji su uočili da se u sklopu promena koje prate eritemu multiforme pojavljuju još i gnojni konjuktivitis, stomatitis i groznica[20]. Terapija eriteme multiforme uključuje određivanje etiologije kada je to moguće i prestanak konzumacije leka.

Protokol upotrebe KS kod pacijenata obolelih od EM je različit, zavisno od težine kliničke slike. Mogu se upotrebiti topikalni, u vidu orobaze ili gela, ili vodica za ispiranje usta. U težim slučajevima koristi se inhalacioni rastvor. Kod Stevens Johnsonog sindroma i težim oblicima eriteme multiforme može se upotrebiti pulsna terapija do 500 mg Pronizona koji se daje i u trajanju tročasovne infuzije, tri dana. Na ovaj način izbegava se dugotrajna upotreba KS, koji smanjuju otpornost organizma na herpes simplex virusne infekcije, a koje dovode do rekurentne eriteme multiforme. Autori su opisali pleomorfni učinak deksametazona na imunološki sistem, uključujući inhibiciju epidermalne apoptoze pomoću nekoliko mehanizama. Ti mehanizmi uključuju supresiju različitih citokina, kao što je TNF-alfa, inhibiciju interferon-gama-inducirane apoptoze i inhibiciju FAS posredovane keratocitne apoptoze[21].

LP can be accompanied by bullae, erosions and ulcerations. The advantage of steroids can to some extent be explained by their anti-immune properties, demonstrated in suppressed T lymohocyte functions and reduced synthesis of IgG. By reducing inflammation, the destruction of tissue is decreased and the release of antigens is minimized. That way, corticosteroids disrupt the vicious cycle[19]. With this disease, corticosteroids are usually applied topically, in the form of orobase or gel, while in more severe cases they can also be administered intralesionally for 2 to 3 days. In the most severe case, systemic application of corticosteroids is necessary.

9. Erythema Multiforme is a skin disease caused by hyper-sensitivity to infection and medication that has clinically been known since the first half of the 19 th century. It presents with polymorphous eruptive maculae, papules and characteristic "target" lesions that are symmetrically distributed on the distal extremities. Mucosa is minimally affected. Herpes simplex virus (HSV) is identified as the cause of this hyper-sensitivity reaction in more than 50 percent of the cases. Erythema multiforme (EM) used to be considered a clinical presentation of Stevens-Johnson Syndrome (SJS) associated with toxic epidermal necrosis.

Nowadays it is widely accepted that there is a difference between EM and SJS. Currently there are two different classifications: first, erythema multiforme spectrum (major and minor) and second, SJS and TEN spectrum.

10. SJS and TEN are rare mucocutaneous diseases that can be life-threatening and are almost always caused by medication. SJS was first described in 1922 by two doctors, Stevens and Johnson, who observed that changes accompanying erithema multiforme also include purulent conjunctivitis, stomatitis and fever[20]. The treatment of erithema multiforme consists of determining the etiology where possible, and discontinuing the medication. Protocol of corticosteroid application in patients with EM varies, depending on the severity of the clinical presentation. They can be applied topically in the form of orobase, gel, or mouthwash solution. In severe cases inhalation solution is used. With Stevens-Johnson syndrome and with severe cases of erithema multiforme, pulse therapy of up to 500 mg of Pronison can be used intravenously in three-hour infusion for three days. This way, long-term use of corticosteroids which decrease human body's resistance to Herpes Simplex Virus infections leading to erythema

11. Belova paraliza je idiopatska paraliza lica. Najverovatnije se radi o inflamaciji n. facialisa i njegovog koštanog kanala. Ovaj akutni poremećaj nervusa facialisa može početi sa simptomima bola u mastoidnom predelu i dovesti do pune ili delimične paralize jedne strane lica. Paraliza n.facialisa može biti kongenitalna ili neoplastična ili može nastati zbog infekcije, ishemije, autoimunih mehanizama, traume, delovanja toksina ili jatrogenih uzroka. Ima dokaza da je glavni uzrok Belove paralize reaktiviranje latentnog herpes simplex virusa tipa 1 iz kranijalnih nervnih ganglija. Kako virus oštećuje n.facialis nije razjašnjeno. Bolest počinje naglo, maksimalna paraliza jedne strane lica razvija se u toku prvih od 2 do 5 dana. Većina pacijenata posle terapije KS bude u potpunosti izlečena. KS daju se u visokim dozama, prva od 3 do 4 dana, a onda se doza u narednom periodu od 7 do 10 dana smanjuje[22].

12. Ramsay Hunt sindrom (RHS) uzrokovan je reaktiviranjem prethodne infekcije virusom *Varicella zoster* (VZV). RHS je potencijalno ozbiljna virusna infekcija koja u 12% slučajeva može pratiti nerve orofacijalnog predela[23]. VZV se širi duž određenog nerva i zahvata određeno područje kože ili sluzokože, tzv. "dermatom", na kome se pojavljuju sitne vezikule i kasnije kruste. Uz alarmantnu paralizu lica, RHS može biti praćen ozbiljnom otalgijom, delimičnim gubitkom sluha, vrtoglavicom, bolnim vezikulama kože i ageuzijom usled širenja duž *n. maxillarisa ili n. mandibularisa*. Definitivni tretman sastoji se od antivirusne terapije i ponekad uključuje steroide kod paralize lica. Međutim, postoji oprez sa primenom steroidne terapije, naročito kod periookularnih lezija, zbog mogućnosti prenošenja VZV infekcije[24].

13. Postherpetična neuralgija (PHN) i dalje predstavlja značajan klinički problem, jer se 25% pacijenata žali na neuropatiju zahvaćenog nerva i posle povlačenja promena na koži i ostalih kliničkih simptoma, kao i nakon akutnih simptoma *herpes zoster* virusa[25]**.** Obično, pacijenti mogu osetiti oštar ili dubok bol u tom području gde su se prvi put pojavile vezikule. Smatra se da ponovljeni bolni nadražaji koji su stizali do CNS-a mogu dovesti do centralne senzibilizacije nociceptivnog sistema, najvažnijeg mehanizma koji leži u osnovi dugotrajnog hroničnog bola.

multiforme is avoided. Authors explained pleomorphic effect of dexamethasone on the immune system, including the inhibition of epidermal apoptosis, with several mechanisms of action.These mechanisms include suppression of various cytokines, such as TNF-alfa, the inhibition of interferon gamma induced apoptosis and inhibition of FAS mediated keratocyte apoptosis[21].

11. Bell's palsy is an idiopathic facial paralysis. It most probably occurs due to the inflammation of the facial nerv and its bone canal. This acute disorder of the facial nerv can begin with pain in the mastoid region and lead to a full or partial paralysis of one side of the face. It can be congenital or neoplastic, or it can be a result of infection, ischemia, autoimmune mechanisms, trauma, toxins or iatrogenic causes. There is evidence that the major cause of Bell's palsy is the reactivation of latent herpes simplex virus type 1 from the cranial nerve ganglia. How the virus damages the facial nerve is not clarified. The disease starts suddenly and the maximal paralysis of one side of the face develops within the first 2-5 days. The majority of patients treated with corticosteroids recover completely. High doses of corticosteroids are administered in the first 3-4 days, after which they are reduced in the following 7 to 10-day period[22].

12. Ramsay Hunt syndrome (RHS) is caused by a reactivation of the previous infection with varicella zoster virus (VZV). It is a potentially serious viral infection that can, in 12% of cases, affect orofacial area nerves[23]. VZV spreads along a certain nerve and affects a specific area of skin or mucosa, a so-called "dermatome", on which tiny vesicles and later crusts appear. Together with alarming paralysis, RHS may be accompanied by severe otalgia, partial hearing loss, dizziness, painful skin vesicles and ageusia due to its spreading along the maxillary nerve or mandibular nerve. Definitive treatment consists of antiviral therapy and sometimes includes steroids for facial paralysis. However, steroids should be used with caution, especially with periocular lesions, due to the possibility of transmitting the VZV infection[24].

13. Postherpetic neuralgia (PHN) still remains a significant clinical problem because 25% of patients complain of affected nerve neuropathy even after the regression of skin changes and other clinical symptoms of acute herpes zoster infection[25]. Usually, patients may feel sharp or deep pain in the area where vesicles first appeared. It is considered that

14. Temporomandibularne disfunkcije podrazumevaju kliničke poremećaje temporomandibularnog zgloba ili mastikatornih mišića ili udružene promene koštano-mišićnog sistema. Trauma, naročito hronična mikrotrauma najčešći je uzrok ovih poremećaja. Od ostalih uzroka u etiologiji ovog poremećaja najčešće se javljaju benigne i maligne neoplazme, razvojne anomalije i sistemske bolesti. Zavisno od uzroka, pored ostale farmako i fizikalne terapije, KS imaju važnu ulogu u lečenju ovakvih stanja, jer smanjuju bolove, hipomobilnost TMZ i inflamaciju. Intrakapsularna injekcija KS može u velikoj meri olakšati simptome bolesti[26].

15. Centralni gigantocelularni granulom je benigni tumor koštanog tkiva koji se javlja kod dece i omladine, sa dvostruko većom incidencom kod ženskog pola. Sastoji se od slabe vezivnotkivne strome sa velikim brojem proliferišućih fibroblasta, multijedarnim džinovskim ćelijama i hemoragičnim žarištima. Smatra se da su ćelije tumora poreklom od odontoklasta, koji resorbuju koren mlečnih zuba za vreme fiziološke smene zuba[27]. KS se mogu upotrebiti za intralezijsko davanje u cilju smanjenja promene delujući na redukciju broja fibroblasta i angiogenezu[28,29].

16. Kortikosteroidi se upotrebljavaju u endodonciji u sastavu lekova za prekrivanje pulpe, jer smanjenjem inflamacije smanjuju mogućnost njene nekroze. Isto tako već se dugo koriste u medikaciji kanala korena kombinovani sa antibioticima. Forsiranje kanala korena i delovanje KS na periapikalno tkivo povećava uspeh endodontske terapije .

17. U cilju smanjenja bola posle endodontskih zahvata, naročito rekurentnog pulpita, mogu se primeniti *per os*, intramuskularno, intraligamentarno i subperiostalno u predelu problematičnog zuba[30,31]. Ovakva primena pre endodontskog tretmana može smanjiti bol kod pacijenata sa akutnim pulpitom efikasnije nego primena morfina[32].

18. U oralnoj hirurgiji već se dugo, u postoperativnoj terapiji donjeg impaktiranog umnjaka i drugih težih intervencija, pored analgetika (NSAIL i narkotički analgetici) koriste KS u cilju smanjenja tizmusa, otoka i bola. Na pojavu i intenzitet bola utiču dve klase enzima: fosfolipaza i ciklooksigenaza. Fosfolipaza sintetiše arahidonsku kiselinu iz fosfolipida, dok ciklooksigenaza sintetiše prostaglandine. Steroidni antiinflamatori deluju inhibicijom fosfolipaze A2, što smanjuje proizvodnju i koncentraciju prostaglandina i leukotriena.

repeated painful stimuli which reached the CNS may lead to a central sensitization of the nociceptive system, the most important mechanism in long-term chronic pain.

14. Temporomandibular dysfunction includes clinical disorders of the temporomandibular joint or masticatory muscles, or combined musculoskeletal system changes. Trauma, especially chronic microtrauma, is the most common cause of these disorders. Among the other causes in the etiology of this disorder, benign and malignant neoplasms, developmental anomalies and systemic diseases are the most common ones. Depending on the cause, in addition to other pharmaco-physical treatment, corticosteroids play an important role in the treatment of such conditions because they reduce pain, temporomandibular joint hypomobility and inflammation. Intracapsular corticosteroid injection can ease the symptoms of the disease to a significant extent[26].

15. Central gigantocellular granuloma is a benign bone tissue tumor that occurs in children and young people, twice as frequently in females than in males. It consists of low connective tissue stroma with a large number of polyphyletic fibroblasts, multinuclear giant cells and hemorrhagic hot spots. It is believed that the tumor cells originate from odontoclasts, which absorb the root of primary teeth in the physiological teeth change[27]. Corticosteroids can be applied intralesionally to decrease the extent of changes by reducing the number of fibroblasts and angiogenesis[28.29].

16. Corticosteroids are applied in endodontics as part of the pulp capping medications because they lower the possibility of pulp necrosis by reducing inflammation. They have also been long used in root canal treatment in combination with antibiotics. Forcing of the root canal and corticosteroid application to periapical tissue increases the success of endodontic treatment.

17. In order to reduce the pain after endodontic surgery, especially that of recurrent pulpitis, corticosteroids can be applied per os, intramuscularly, intraligamentary and subperiosteally in the affected tooth area[30,31]. Their application before the endodontic treatment can reduce pain in patients with acute pulpitis more effectively than morphine[32].

18. In oral surgery, corticosteroids have long been used (together with NSAIDs and narcotic analgesics) postoperatively after lower impacted wisdom teeth removal and other major procedures in order to reduce trismus, swelling and pain.

Nesteroidni antiinflamatorni lekovi deluju inhibicijom ciklooksigenaznih enzima, što smanjuje prostaglandine, ali ne utiču na proizvodnju leukotriena.

Najčešći put administracije KS je *per os*, intramuskularno ili intravenski. Najizraženiji efekat KS imaju u prva 24h posle operacije, ali se ordiniraju do 3 dana posle operacije, iako sa nešto manjim dejstvom. Postoje brojne studije koje sugerišu na vreme i put administracije KS u hirurgiji donjeg impaktiranog umnjaka, kao i različite kombinacije KS sa drugim medikamentima u cilju smanjenja morbiditeta posle ovakvih intervencija[33-37].

Međutim, neki autori sugerišu da je submukozna injekcija deksametazona ubrizgana u pterigomandibularni prostor, posle intervencije, pokazala jednako dobar efekat na bol, otok i trizmus posle hirurškog vađenja donjeg impaktiranog umnjaka, kao parenetralno data u istoj dozi.

Isto tako, postoje podaci da povećanje doze KS (deksametazona), preko 4 mg, nema veći efekat na bol, otok i trizmus posle operacije trećeg molara.

U maksilofacijalnoj hirurgiji, KS su nezaobilazni u postoperativnom periodu kod većine hirurških intrevencija, kao i težih infekcija, jer olakšavaju postoperativni period pacijentu, a sa njihovom primenom smanjuje se i broj dana provedenih u bolnici[38].

Kontraindikacije i neželjeni efekti primene KS

Topikalna primena kortikosteroida kontraindikovana je u lečenju primarnih bakterijskih infekcija dok se sistemski KS ne primenjuju kod peptičkog ulkusa, dijabetes melitusa, hipertenzije, trudnoće, tuberkuloze i drugih infekcija, osteoporoze, *herpesa simplex* virusa, psihoza, epilepsije, kongestivnog srčanog zastoja i zastoja bubrega.

Nuspojave zavise od vrste i doze leka kao i dužine lečenja. Mogu se javiti povećanje težine, poremećaj rasta, insuficijencija nadbubrežne žlezde, smanjena otpornost na infekciju, miopatija, osteoporoza, osteonekroza, katarakta, glaukom, frakture, hipertenzija, nesanica, šećerna bolest i peptički ulkus[39].

The occurrence and intensity of pain depends on two classes of enzymes: phospholipase and cyclooxy-genase. Phospholipase synthesizes arachi-donic acid from phospholipids, while cyclooxygenase synthesizes prostaglandins. Steroid antiinflammatory drugs act by inhibiting phospholipase A2, which reduces the production and concentration of prostaglandins and leukotrienes. Nonsteroid anti-inflammatory drugs inhibit the cyclooxygenase enzymes, which reduces the production of prostaglandins, but does not affect leukotrienes.

The most common route of administration of corticosteroids is per os, intramuscular or intravenous. The effect of corticosteroids is the strongest in the first 24 hours after surgery, but they are prescribed for up to 3 days after surgery, although with somewhat less of an effect. There are numerous studies that suggest the time and route of corticosteroid administration in lower impacted wisdom teeth surgery, as well as different combinations of corticosteroids with other medications in order to reduce morbidity after such interventions[33-37]. However, some authors suggest that a submucous injection of dexasone to pterygo-mandibular area after a surgical removal of the lower impacted wisdom tooth has the same effect on pain, swelling and trizmus as parenteral application. Similarly, some data suggest that increasing the dose of corticosteroids (dexamethasone) to over 4 mg doesn't improve its effect on pain, swelling and trismus following third molar surgery.

In maxillofacial surgery, corticosteroids are indispensable in the postoperative period for most surgical interventions, as well as more severe infections, because they make the postoperative period easier for the patient and reduce the time spent in hospital[38].

Contraindications and side-effects of corticosteroids

Topical application of corticosteroids is contraindicated in the primary treatment of bacterial infections, as well as their systemic application with peptic ulcer, diabetes mellitus, hypertension, pregnancy, tuberculosis and other infections, osteoporosis, *herpes simplex* virus, psychosis, epilepsy, congestive heart failure and kidney failure.

Topikalno lečenje može dovesti do atrofije kože, hipopigmentacijskog kontaktnog dermatitisa, oralne kandidijaze, gubitka potkožnog masnog tkiva, i Cushingoidnog efekta posle sistemske apsorcije. Nuspojave izazvane inhalacijom kortikosteroida su orofaringealna kandidijaza, disfonija, refleksni kašalj, bronhospazam, faringitis[40].

Zaključak

Kortikosteroidi su našli široku primenu u stomatologiji, oralnoj i maksilofacijalnoj hirurgiji.

Side effects depend on the type of medication, its dosage and the length of treatment. Weight gain, growth disorder, adrenal gland insufficiency, reduced resistance to infection, myopathy, osteoporosis, osteonecrosis, cataract, glaucoma, fractures, hypertension, insomnia, diabetes and peptic ulcer may occur[39].

Topical application may lead to skin atrophy, contact dermatitis hypopigmentation, oral candidiasis, loss of subcutaneous fat and Cushingoid effect after systemic absorption. Side effects caused by corticosteroid inhalation are oropharyngeal candidiasis, dysphonia, reflex cough, bronchospasm and pharyngitis[40].

Conclusion

Corticosteroides has faund wide application in dentistry, oral and maxillofacial surgery.

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