Pregled učinkovitosti i nuspojava 0,1 %-tnog fluocinolon acetonida u liječenju bolesti oralne sluznice

A Review of the Effectiveness and Side-Effects of Fluocinolone Acetonide 0.1% in the Treatment of Oral Mucosal Diseases

Introduction

Over the past decade, various treatments have been used to treat chronic or severe oral lesions, however, a complete cure is difficult to achieve. Topical steroids are considered to be the first-line therapy for oral autoimmune diseases. These drugs have been widely used in the treatment of symptomatik oral lesions, such as recurrent aphthous ulceration (1), oral lichen planus (OLP) (2, 3), oral lichenoid drug reaction (OLDR) (4), pemphigus (5-7), mucous membrane pemphigoid (MMP) (8), and Herpes Associated Erythema Multiforme (HAEM) (9). Topical steroids can be used alone or combined with systemic steroids in the treatment of severe oral mucosal diseases. Since topical steroids directly contact and penetrate through the mucous membrane of erosive/ulcerative oral lesions, they can enhance lesion healing.

Fluocinolone acetonide (FA) was first synthesized in 1959 in the Research Department of Syntex Laboratories S.A. Mexico City. FA is a synthetic hydrocortisone derivative primarily used to treat skin inflammation and relieve itching. The fluorine substitution at position 9 in the steroid nucleus ring greatly enhances its activity (11) (Figure 1). FA in orabase (FAO) or FA in solution (FAS) 0.1% can
alternativna terapija za tvrdokorne oralne lezije poput OLP-a, OLR-L-a, pemfigusa i HAEM-a kako bi se smanjile bol i upala. U ovom preglednom radu raspravlja se o učinkovitosti i nuspojavama terapije simptomatskih oralnih lezija FAO-om ili FAS-om. Opisuje se korištenje FAO-a ili FAS-a 0,1 % u liječenju različitih oralnih lezija.

Oralne lezije koje se liječe 0,1 %-tnim fluocinolon acetonidom

Oralni lichen planus (OLP)

Godine 1985., predstojnik Zavoda za farmakologiju i oralnu medicinu Stomatološkog fakulteta Sveučilišta Chulalongkorn u Bangkoku na Tajlandu prvi put je pripremio 0,1 %-tnu otopinu topikalnog steroīda FA, a 1988. pripremljen je i u orabazi 0,1 % (12). FA u otopinama (FAO) bio je učinkovit u liječenju tvrdokornog ulcerativnog OLP-a kod 36-godišnje pacijentice (Slika 2. a). Lezije na bukalnoj sluznici gotovo su se potpuno povukle nakon dva tjedna primjene FAO-a 0,1 % (Slika 25.). Nadalje, 29-godišnja pacijentica došla je u Kliniku za oralnu medicinu sa atrofičnim OLP-om na bukalnoj sluznici obostrano pri čemu lezije nisu odgovarale na prethodnu terapiju. Nakon liječenja FAO-a 0,1 % lezije na bukalnoj sluznici postupno su se smanjivali do potpunog povlačenja nakon 22 mjeseca (Slike 3.a i b). Dodatno, i FAO i FAS pokazali su dobre rezultate u liječenju OLP-a tijekom dvogodišnjeg praćenja (13). Međutim, u ovom istraživanju FAO 0,1 % pokazao se učinkovitim u usporedbi s FAS-a 0,1 %.

U vezi s imunopatogenezom oralnog liena planusa otkrivena je ekspresija proinflamatornog citočina TNF-α u svakom slučaju oralnog liena planusa kod tajlandskih pacijenata, što upućuje na to da TNF-α igra važnu ulogu u imunopatogenezi OLP-a (14). Nakon liječenja lezija FAO-a 0,1 % ponovno je uzeta biopsija istih lezija kako bi se istražila ekspresija TNF-α. Otkriveno je da je FAO 0,1 % izazvao smanjenje ekspresije u svakom slučaju. Stoga, FAO 0,1 % smanjuje proinflamatorni citočin TNF-α.

Oralna lichenoidna reakcija na lijekovke (OLR)

OLR je uobičajena lezija u tajlandskoj populaciji. Oralne manifestacije i patohistološke značajke ove lezije slične su onima OLP-a (15). Oralne lezije kod OLR-L-a pojavljuju se nakon uzimanja određenih lijekovki i nastaju nakon prestanka uzimanja sumnjivog lijeka. Nije teško dijagnosticirati i liječiti OLR ako pacijent uzima samo jedan lijek (16). No, većina pacijenata uzima više lijekovke i može biti teško odrediti koji je lijek izazvao reakciju (17). Potentni lokalni steroīdi mogu se koristiti u liječenju OLR-a. Pacijentica u dobi od 72 godine, s anamnezom kardiomegalije, hipertenzije i dijabetesa melitusa, razvila je ozbiljnu OLR uljena poslije upotrebe insulinina s velikim lezijama koje su se pojavile obostrano na bukalnoj sluznici. Na desnoj strani pojavile su se bijele strije i krvarenje na bukalnoj melitusa, razvila je ozbiljnu OLR-a nakon injekcije insulina u bukalnoj sluznici u roku od 6 mjeseci terapije FAO-om 0,1 % vratila se u normalno stanje (Slika 4.b). Utvrđeno je da je FAO 0,1 % učinkovit u smanjenju boli i ubrzavanju cijelje-

be used as an alternative treatment for recalcitrant oral lesions such as OLP, OLR, pemphigus, and HAEM to reduce pain and inflammation. The present review discusses the effectiveness and side-effects of FAO/FAS in the treatment of symptomatic oral lesions. The use of FA as orabase (FAO) or solution (FAS) 0.1% in the treatment of various oral lesions is described.

Oral lesions that were treated using FA 0.1%

Oral lichen planus (OLP)

In 1985, topical steroid–FAS 0.1% was first prepared by the head of the Pharmacology and Oral Medicine Departments, Faculty of Dentistry, Chulalongkorn University, Bangkok, Thailand, and later developed as FAO 0.1% in 1988 (12). FAO 0.1% was effective in the treatment of recalcitrant ulcerative OLP in a 36-year-old female (Figure 2a). Notably, the OLP lesions on her buccal mucosa showed nearly complete remission after 2 weeks of FAO 0.1% treatment (Figure 2b). Moreover, a 29-year-old female presented to the Oral Medicine Clinic with atrophic OLP on both buccal mucosae and these lesions were unresponsive to previous medications. After treatment with FAO 0.1%, the lesions on her buccal mucosa showed a gradual improvement until complete remission was seen at 22 months (Figure 3a, 3b). In addition, both FAO and FAS use resulted in improved results in the treatment of OLP during a 2 year-follow-up (13). However, in this study, FAO 0.1% was shown to be more effective compared with FAS 0.1%.

Regarding the immunopathogenesis of OLP, we found that the proinflammatory cytokine TNF-α was expressed in every case of OLP in Thai patients, indicating that TNF-α plays an important role in the immunopathogenesis of OLP in Thai patients (14). After treating their OLP lesions with FAO 0.1%, the same lesions were re-biopsied to investigate their TNF-α expression. We found that FAO 0.1% inhibited TNF-α expression in every case. Therefore, FAO 0.1% reduced the OLP inflammatory process by inhibiting the expression of the proinflammatory cytokine TNF-α.

Oral lichenoid drug reaction (OLDR)

OLDR is a common lesion in Thai patients. The oral manifestations and histopathological features of this lesion are similar to those of OLP (15). The oral lesions in OLDR erupt after taking a specific drug and resolve after withdrawing the suspected drug. It is not difficult to diagnose and treat OLDR if a patient is taking only one drug (16). However, most patients take multiple drugs and it can be difficult to withdraw the suspected drug (17). Potent topical steroids can be used in the treatment of OLDR. A 72-year-old female patient with a history of cardiomegalia, hypertension, and diabetes mellitus developed severe OLDR after an insulin injection, with severe lesions erupting on her bilateral buccal mucosae. White striae and excessive bleeding were seen on her right buccal mucosa (Figure 4a). After withdrawing the type of insulin injected and replacing it with another type of insulin, her buccal mucosa returned to normal state within 6 months of FAO 0.1% treatment (Figure 4b).
Učinkovitost 0,1 %-tnog fluocinolon acetonida u liječenju bolesti oralne sluznice

Oralni pemfigus

Pemfigus je autoimuna bolest čije oralne manifestacije obično prethode lezijama na koži. Gingiva je prvo i najčešće mjesto oralnih manifestacija pemfigusa (18). U liječenju oralnog pemfigusa koriste se sustavni steroidi. Međutim, kada se koriste u kombinaciji s lokalnim steroidima, sistemske doze mogu se smanjiti. Pacijentica u dobi od 35 godina došla je u Kliniku za oralnu medicinu s jakom boli i generaliziranim deskvamativom epitela gingive koji se pojavio mjesec dana prije (Slika 5.a). Mjesec dana nakon kombiniranog lije-

found to be effective in rapidly reducing pain and enhancing lesion healing. This topical steroid formulation is also safe to use in treating patients with multiple systemic diseases (4).

Oral Pemphigus

Pemphigus is a fatal autoimmune disease the oral manifestations of which typically precede its skin lesions. The gingiva is the first and most common site of the oral manifestation of pemphigus (18). Systemic steroids have been used in the treatment of oral pemphigus. However, when used in combination with topical steroids, systemic steroid doses can be reduced. A 35-year-old female patient presented to the Oral Medicine Clinic with severe pain and generalized desquamative gingival epithelium for one month (Figure 5a).
čenja s 40–60 mg/dan prednizolona i topikalni primijenjenog FAS-a 0,1 % tri puta na dan na gingivu, lezije su pokazale gotovo potpunu remisiju (Slika 5.b). Nažalost, pacijentica je poslije razvila Cushinog sindrom: mjesečevi lice, steroidne akne i hirzutizam (Slika 6.). Njezin je liječnik postupno smanjio sistemsku dozu steroida i stanje joj se poboljšalo. Zanimljivo je da su se nakon dugotrajnog liječenja 43-godišnjeg pacijenta s pemfigusom FAS-om 0,1 %, u kombinaciji sa 60 mg prednizolona na dan, oralne lezije potpuno povukle nakon godinu dana (6). Stoviše, oralne lezije pemfigusa ostale su u potpunoj remisiji tijekom 12 godina praćenja bez po-
novnog pojavljanja ili bilo kakvih nuspojava.

One month after combined treatment with 40–60 mg/day prednisolone and topical FAS 0.1% three times/day on the gingiva, the lesions showed nearly complete remission (Figure 5b). Unfortunately, the patient subsequently developed Cushing syndrome: moon face, steroid acne, and hirsutism (Figure 6). Her physician gradually reduced the systemic steroid dose and her condition showed improvement. Interestingly, following long-term treatment of a 43-year-old male pemphigus patient with FAS 0.1% combined with 60 mg/ day prednisolone, the oral lesions showed complete remis-

sion after 1 year (6). Moreover, his oral pemphigus lesions re-

mained in complete remission during 12 years of follow-up without recurrence or any side-effects.
Erythema Multiforme povezana s herpesom (HAEM)

Multiformni eritem povezan s herpesom (engl. herpes associated erythema multiforme – HAEM) je atipična lezi-ja uzrokovana infekcijom herpes simplex virusom i rijetko se pojavljuje u trudnica (9). FAO i FAS u koncentraciji od 0,1 % pokazali su se učinkovitima u liječenju bolnih oralnih ul-kusa kod 28-godišnje trudnice s HAEM-om (9). Kratkotraj- na terapija (2 tjedna) tim potenitim topikalnim steroidom brzo je smanjila bol s gotovo potpunim cijeljenjem lezije. FAO i FAS bili su učinkoviti i sigurni u terapiji HAEM-a kod ove trudnice koja je rodila zdravog dječaka. Nadalje, FAO i FAS su jeftini i u ovom slučaju bez popratnih pojave.

Rasprava

FA 0,1 %, u otopini ili u orabazi, koristi se u liječenju različitih bolesti oralne sluznice. Štoviše, u sklopu dugoročnog praćenja pronađene su samo manje nuspojave, kao što su pseudomembranozna kandidijaza ili postupalna hiperpigmentacija. FA se može koristiti samostalno ili u kombinaciji sa sistemskim steroidima u liječenju teških oralnih lezija u pacijenata s multiplim sustavnim bolestima. Carrozzo i sur. nađu da FAS su učinkoviti i sigurni u terapiji HAEM-a kod 28-godišnje trudnice s HAEM-om (9). FA, ali i FAS bili su učinkoviti i sigurni u liječenju teških oralnih lezija kod trudnice s HAEM-om (9). FA, ali i FAS bili su učinkoviti i sigurni u terapiji HAEM-a kod ove trudnice koja je rodila zdravog dječaka. Nadalje, FAO i FAS su jeftini i u ovom slučaju bez popratnih pojave.

Nuspojave korištenja FAO-a/FAS-a

Tijekom liječenja oralnih lezija, kao što je OLP, FAO-om/FAS-a 0,1 %, uobičajena je pojava pseudomembranozna kandidijaza. Bijeli plakovi koji se mogu skinuti, mogu se ra-zviti na bukalnoj sluznici nakon primjene FAS-a 0,1 % (Sli-ka 7.a). Međutim, pseudomembranozna kandidijaza učinko-vito se lijeće lokalnim antimikroticima (Slika 7.b) (13, 19). U nekim slučajevima OLP-a, dugotrajno liječenje površin- skim steroidom FAO 0,1 % izazvalo je hiperpigmentaciju na područjima prijašnjih oralnih lezija (Slika 8.a). Tijekom pra-ćenja, mukoza hiperpigmentacija postepno je nestajala ti-jekom 3 godine nakon prestanka primjene toga lokalnog ste-roida (Slika 8.b).

Discussion

FA 0,1 %, both in solution or orabase forms, has been used in the treatment of various recalcitrant oral mucosal dis-eases. Moreover, only minor side-effects such as pseudomembranous candidiasis or post-inflammatory hyperpigmentation were found with FA use in our long-term observation. Thus, careful monitoring of patients receiving corticosteroid therapy is recommended to avoid adverse local or systemic effects. However, some side-effects of potent topical steroids, including clobetasol propionate 0,05 % and betamethasone, as such as Cushing's syndrome, have been reported (21).

In this review, FAS 0,1 % in combination with 40-60 mg/day prednisolone for one month in the treatment of severe oral pemphigus resulted in Cushing's syndrome. Therefore, the treatment of severe oral lesions with a systemic steroid should be carefully monitored and these lesions should be treated by an expert.

A report of an HIV patient with OLR who had very painful erosive lesions involving the lip and buccal mucosa showed that this patient responded to topical FA 0,1 % treat-
pacijentovu bol. Zanimljivo je da se pokazalo kako su lokalni steroidi, kao što je FA 0,1 %, klobetazon propionat 0,05 % i deksametazon 0,05 %, učinkoviti u liječenju težih lichenoidnih reakcija na lijekove bez ozbiljnih nuspojava u pacijenata s multiplim sustavnim bolestima tijekom 7-godišnjeg praćenja (4). Međutim, uloga određenog lijeka u patogenezi OLR-e može biti važna jer lijek djeluje kao antigen, potičući T-stanice. Antigen-specificne CD8+ citotoksične T-stanice zatim lubite citokine, poput TNF-α ili interferona-α. Ti citokini zatim aktiviraju T-stanice i dendritičke stanice te aktiviraju apoptozu keratinoocita bazalnih stanica, uzrokujući upalni imunosni odgovor (23, 24).

Što se tiče hiperpigmentacije oralne sluznice, jedini rad o toj temi upućuje na to da hiperpigmentacija sluznice može biti sekundarni učinak lokalnog liječenja takrolimisom zbog povećanja broja melanocita i povećane proizvodnje melanina (25). Histopatološka slika hiperpigmentacije sluznice pokazala je porast broja melanocita i melanogeneze. Međutim, hiperpigmentacija je nestala kada je terapija završena, što je slično slučaju OLP-a liječenog FA-om u ovom radu.

Uz primjenu na oralnim lezijama, FA može imati i druge primjene. Istraživanje je pokazalo da FA potiče hondrogenzu mezenhalnih matičnih/progenitora stanica u koštanoj srži povezanu s TGF-β, povećavajući razinu kolagenog faza II više od 100 puta u usporedbi sa široko rasprostranjenim lijekom, deksametazonom (26). Prema tome, FA/TGF-β3 može se klinički primijeniti za povećanje učinkovitosti regenerativnih postupaka temeljenih na hondrogenoj diferencijaciji matičnih stanica. Također su zabilježeni učinci FA na formaciju terciarnog dentina i oporavak ozlijedene dentalne pulpe (27). Rezultati su pokazali da FA potiče proljećenu stanica stanice proizvodnje koline (DPCi), posebno subpopulacije CD146+. Pokazalo se da su stanice CD146+, stanice mezenhalne strome, sposobne za višenajesek diferencijaciju (28–30). Tako u oštećenoj pulpi CD146+ mogu proizvesti stanice koje se mogu diferencirati u odontoblaste za popravak oštećenja dentina i za rekonstrukciju stanične populacije pulpe. FA inicira mineralizaciju DPC-a i ima potencijalnu ulogu u popravljanju oštećenog tkiva pulpe. FA može poboljšati zarastanje intraoralnih ozljeda poticanjem proljećenja i regeneracije stanica oralne sluznice. Potrebna su dodatna istraživanja o upotrebi FA u poticanju cijeljenja stanica oralne sluznice induciranjem ekspresije različitih citokina koji reguliraju molekule uključene u staničnu adheziju i formiranje izvanstančnog matriksa (ECM) za učinkovito liječenje teških i tvrdokornih bolesti oralne sluznice.

**Zaključak**

FAO/FAS, u koncentraciji 0,1 %, učinkovit je u liječenju OLP-a, OLR, oralnog pemphigusa i HAEM-a. FAO/FAS 0,1 % brzo smanjuje bol i upalu. Taj topikalni steroid je jeftin i bez ozbiljnih nuspojava, osim pseudomembranozne kandidi jaze koja se jednostavno liječi. Nadalje, FAO/FAS 0,1 % pokazao se sigurnim u liječenju pacijenata s višestrukim i različitim sistemskim bolestima te trudnica.

**Conclusion**

FAO/FAS 0.1% is effective in the treatment of OLP, OLDR, oral pemphigus, and HAEM. FAO/FAS 0.1% rapidly reduces pain and inflammation. This topical steroid is low-cost (2 US$/5 gm pack) with no serious side-effects other than easily treated pseudomembranous candidiasis. Moreover, FAO/FAS 0.1% was safe when used in treating patients with multiple or various systemic diseases and a pregnant patient.
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Abstract

Topical steroids have been widely used in the treatment of symptomatic oral lichen planus to reduce pain and inflammation. Potent topical steroids such as clobetasol propionate, fluocinolone acetonide (FA), and fluocinonide have been widely used in the treatment of severe oral mucosal lesions. Many reports have demonstrated that these steroids were effective in treating oral lesions with only minor side-effects. This review describes the effectiveness and side-effects of using FA 0.1% in the treatment of symptomatic oral lichen planus (OLP), oral lichenoid drug reaction (OLDR), oral pemphigus, and herpes associated erythema multiforme (HAEM). FA 0.1% was effective and safe in the treatment of patients with multiple systemic diseases and a pregnant patient with HAEM. Moreover, this topical steroid rapidly reduced pain, inflammation, and enhanced lesion healing with no serious side-effects other than pseudomembranous candidiasis, which is easily treated. In some cases, a long-term treatment with FA 0.1% resulted in hyperpigmentation at the areas of previously healed oral lesions; however, this hyperpigmentation was gradually resolved after discontinuing topical steroid treatment.

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