

Intralesional corticosteroid injection as an effective treatment method for oral lesions: a meta-analysis

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Intralesional corticosteroid injection (ICSI) is known as one of the main methods used for treating a wide range of lesions. It also results in a high concentration of drugs at lesion sites, with minimal systemic absorption. Thus, this study aimed to provide a review of the intralesional corticosteroid injection (ICSI) indications in the treatment of oral lesions. To this end; relevant key words were searched in the databases of PubMed, Google Scholar, Scopus, ScienceDirect, and UpToDate in the present study. Accordingly, the results of a total number of 62 case reports or case series articles were used in this study and the positive therapeutic effects of intralesional corticosteroid injection (ICSI) in 23 common oral lesions were reported. The most common type of intralesional steroid in the treatment of oral lesions was triamcinolone. No significant difference was also observed in terms of pain in patients following the use of steroid alone or in combination with anesthetic agents; moreover, the reported side effects of this method were exceptionally rare and transient. It was concluded that the intralesional corticosteroid injection (ICSI) could be one of the effective therapeutic methods with no significant problems in many oral lesions such as inflammatory, immunologic, and vascular ones due to its higher therapeutic effects than other topical forms of steroids and fewer side effects than systemic corticosteroid.

Keywords: Intralesional corticosteroid injection. Triamcinolone. Betamethasone. Oral lesions. Oral disorders. Steroid injection.

INTRODUCTION

Intralesional corticosteroid injection (ICSI), introduced as a medical treatment in 1951, has become one of the main methods used alone or in combination with other procedures for treating a wide range of diseases as well as benign and malignant proliferations in the head and the neck (Egbert *et al.*, 2001; Buckmiller, Francis, Galde, 2008; Ffrooz, Tehranchia-Nia, Ahmed, 1995). The ICSI leads to a high concentration of drugs at lesion sites, with minimal systemic absorption; therefore, it has no common side effects of systemic form or even reduces them (Goldman, 1962; Saravanan *et al.*, 2014). However, in cases wherein high or repeated doses of injection are required, systemic corticosteroid considerations such as hypertension, heart failure, uncontrolled diabetes,

acute peptic ulcer, depression, severe psychosis, and active fungal and bacterial infections must be taken into account. In addition, the ICSI is preferable to the topical corticosteroids such as creams, ointments, mouthwashes, gels, and foams due to bypassing of mucous membranes, reduced risk of mucosal atrophy, higher drug concentrations, and longer durability in lesion sites (Laisuan *et al.*, 2017). Nowadays, various medications are available for the ICSIs; however, physicians commonly prescribe triamcinolone and betamethasone derivations. The most important point in this therapeutic approach is that the efficacy and the potential complications of the injection are dependent on its usage method (Ffrooz, Tehranchia-Nia, Ahmed, 1995). This injection is performed at offices without special supplies and equipment. Prior to injection; the history of any allergies, systemic problems, and the use of medications such as aspirin and warfarin must be taken from patients. Although the local anesthesia can be used at the site, it is not usually necessary because

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the pain created by the ICSI is similar to the injection of the anesthetic substance (Saravanan *et al.*, 2014). If the injectable material is a suspension, it must be shaken well before injection. Corticosteroids, either pure or diluted, with saline or anesthetics can be further applied. In most oral lesions, 0.1 to 0.2 mL of the substance is also injected into four sides of a lesion, and it is normally recommended not to increase the total dosage more than 2 mL in each session. For this purpose, insulin syringe is the most suitable injection device. Moreover, the forms used for the ICSI do not need to be kept in refrigerator thanks to their high shelf life (Richards, 2010).

Immediate side effects of the injection include pain, bleeding, infection, and allergic reaction, as well as delayed complications including atrophy of skin or mucous membranes, and hyper- or hypo-pigmentation of the lesion site (Saravanan *et al.*, 2014; Laisuan *et al.*, 2017). Although these indications are not very common, the possible cause of complications is the lymphogenous spread of corticosteroid suspension, which brings about dermal and epidermal changes such as thinning of the epithelium, loss of rete ridges, necrosis of epithelial and small blood vessels, interference with synthesis of melanin from melanocytes, reduction of mucopolysaccharides, and loss of elastic properties of tissues. In this line, the incidence of tissue atrophy depends on injection depth and local concentration obtained after injection (Hengge *et al.*, 2006; Friedman, Butler, Pittelkow, 1988; Schetman, Hambrick, Wilson, 1963). The ICSI in children can also cause abnormalities in their growth and immune system (Buckmiller, Francis, & Glade, 2008). Although the occurrence of these complications is very rare, it leads to some worries in some patients and reduces levels of collaboration in treatments. Therefore, the efficacy of this therapeutic approach depends on the effective communications by physicians with patients along with awareness concerning benefits and possible complications (Del Rosso, Friedlander, 2005). The ICSI is a safe and cost-effective process. Accordingly, the employment of this method in the treatment of skin lesions has been highly reported and approved. Nevertheless, no comprehensive review has been so far carried out on applying it in oral lesions, administration patterns, drug types and dosages, and treatment outcomes. Considering the relatively high prevalence rates of oral diseases and the potential of benefits of this method, it can be utilized in the treatment of numerous oral lesions. Thus, this study aimed to present a review of the ICSI indications and treatment details in oral lesions to provide more reliable evidence for clinicians.

MATERIAL AND METHODS

The data collection was fulfilled through searching in the databases of PubMed, Google Scholar, Scopus, ScienceDirect, and UpToDate using relevant keywords including corticosteroid injection, intralesional injection, triamcinolone injection, betamethasone injection, oral lesions, oral disorders, and steroid injection, alone or in combination. In this search, no time limit was considered, the last access to different platforms was in September 2018, and the search results were restricted to articles published in English. The inclusion criteria for the articles composed of:

- 1 - Clinical trial articles
- 2 - Case reports or case series articles
- 3 - Treatment of oral lesions or structures related to oral cavity; e.g. salivary glands, temporomandibular joint, lips, sinuses and oropharynx, no skin, or other sites of the body.
- 4 - Intralesional injection of steroids and no other forms of corticosteroids

RESULTS

Following the completion of the search process, 600 abstracts were obtained and about 200 relevant abstracts were reviewed and nearly 80 full-text articles in PDF format were selected. In total, 62 articles were included in this study.

DISCUSSION

The most common causes to use corticosteroid drugs in oral medicine are their anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive effects which appear to be largely mediated by several mechanisms such as functioning on stromal capillaries to decrease erythema, directing regulation of corticosteroid-responsive genes by steroid-receptor complex, having indirect control over transcription through blockage of effects of other transcription factors such as NF- κ B, inhibiting transcription of various pro-inflammatory cytokine genes including interleukin IL-1, IL-2, IL-6, interferon gamma (IFN- γ), and tumor necrosis factor-alpha, stimulating expression of anti-inflammatory cytokines genes such as transforming growth factor-B and IL-10, making shifts in T-helper type 1 (TH1) to TH2 ratio, and decreasing trafficking of lymphocytes to lesion sites by diminishing vascular permeability and inhibiting proliferation of various cell types including T lymphocytes (Norris, 2005). Therefore, steroids are mostly

employed in treatment of disorders that are inflammatory, hypersensitivity reactions against auto-antigens, as well as vascular lesions. It is noteworthy that the ICSI cannot alter the nature and the primary mechanisms that lead to the disease, but rather have palliative effects and suppress

the immune system (Saravanan *et al.*, 2014). In this study, it was proposed to provide a list of oral lesions that were likely to be treated by the ICSI. The details of the treatment protocol for each lesion along with treatment results were also reported in Table I.

TABLE I - List of articles that applied ICSI to treatment oral lesions

Author & Year	Type of Lesion	Type of ICSI	Dose of ICSI	Number of ICSI	Intervals of ICSI	Result of treatment	Follow up	Side effects
Agha-Hosseini <i>et al.</i> , 2016	CPLA	Triamcinolone 40 mg/mL		3	2 w	Complete regression	6 m	none
Buckmiller, Francis, Glade, 2008	hemangiomas	Triamcinolone and betamethasone	40 and 6 mg/cm ³	1-3	6-25 w (12 w)	11 lesions complete resolution	6 m	4 Patients failure to thrive
Meeuwis <i>et al.</i> , 1990	hemangiomas	Methylprednisolone	20-40 mg	1-5		Complete regression.	6 m to 5 y	Pneumonia, slight growth, acne Retardation, and fluffy Hair growth
Farmand, Kuttengerg, 1996	lymphangioma	Triamcinolone (instilled through the suction drain)	10 mg/kg (30-160 mg)	1-2		completely disappeared in 1 case, residual tumor excised	1-4 y	None
Luo, Gan, 2013	lymphatic malformations	Triamcinolone acetonide (50 mg/5 mL) + Pingyangmycin 0.625 mg/mL	5 mL	8	2-4 weeks	pingyangmycin with triamcinolone was more effective than pingyangmycin alone	-	None
Parisi, Glick, Glick, 2006	PG	Triamcinolone 40 mg/mL	(0.1 mL with 0.5 mL of 0.5% bupivacaine	6	1 & 2 inj weekly, and 4 inj bi-weekly	90% resolved	10 w	None
De La Rosa García, 2006	PG	Triamcinolone	5 mg	3	-	complete resolution	-	none
Adenis-Lamarre <i>et al.</i> , 2009	PG	Triamcinolone						
Dolanmaz <i>et al.</i> , 2016	CGCG	Triamcinolone + 0.5 % marcaine + epinephrine	3.5 mL	6	Weekly	4 complete resolution, 2 Partial recovery, 1 did not response	39 m	None
Nogueira <i>et al.</i> , 2010	CGCG	Triamcinolone (20 mg/mL) + 2% lidocaine	0.1 mL/cm ³	6	bweekly	15 complete resolution, 4 Partial recovery, 2 did not response	4-8 y	None
Sezer <i>et al.</i> , 2005	CGCG	Triamcinolone (10 mg/mL) + lidocaine 2%	4 mL	6	Weekly	complete resolution	3 Y	None
Da Silva Sampieri <i>et al.</i> , 2013	CGCG	Triamcinolone + Articaine	2 mL	6	Weekly	complete resolution	3 Y	None
Carlos, Sedano, 2002	CGCG	Triamcinolone (10 mg/mL, + Lidocaine 2% orBupivacaine 50%)	3-6 mL	4-20	every 15 days-every 3 weeks	complete resolution	2-7 y	None
Haldar, 1976	Cheilitis glandularis	Triamcinolone 1.5 mg/mL	2 to 3 mg in 10 to 15 Places	10	4 weekly and 2 biweekly, 2 monthly, 2 bimonthly	complete resolution	8 m	None
Sugaya, Migliari, 2018	Cheilitis glandularis	10 mg triamcinolone suspension 0.1% tacrolimus ointment)		2	Monthly Twice daily, 2 w	completely resolving	1 y	None

TABLE I - List of articles that applied ICSI to treatment oral lesions (cont.)

Author & Year	Type of Lesion	Type of ICSI	Dose of ICSI	Number of ICSI	Intervals of ICSI	Result of treatment	Follow up	Side effects
Samiee, 2011	TMD	Triamcinolone acetonide, 40 mg/mL	0/5 mL	1	-	reduced signs and symptoms	1 w	temporary facial palsy
Stoll <i>et al.</i> , 2012	TMD	Triamcinolone hexacetonide, 20 mg/mL	0/5-1 mL	1	-	reduced signs and symptoms	0.5 - 23 m	None
Alstergren <i>et al.</i> , 1996	TMD	methylprednisolone 40 mg/mL + lidocaine	0/5-0/7 mL	1	-	reduced signs and symptoms and NPY-LI	6 w	None
Bjørnland, Gjaerum, Moystad, 2007	TMD	Betamethasone sodium phosphate+ acetate	0/7-1 mL	2	Biweekly	reduce pain and improve function	6 m	Temporary pain after injections
Lee <i>et al.</i> , 2013	Langerhans cell histiocytosis	methylprednisolone, 40 mg/mL	3 mL	1	-	complete resolution	35 mo	None
Milián, 2001	Langerhans cell histiocytosis	Triamcinolone acetonide	25 mg	8	every 3 weeks	complete resolution	1 y	none
Esen <i>et al.</i> , 2010	Langerhans cell histiocytosis	methylprednisolone succinate (40 mg/mL)	2 mL	3	Every 4 month	Near-complete resolution	36 m	None
Putters <i>et al.</i> , 2005	Langerhans cell histiocytosis	methylprednisolone succinate (40 mg/mL)	1-2 mL	1	-	complete resolution	9 y	None
Graham, Barret, Goltz, 1999	Nodular fasciitis	Triamcinolone acetonide (10mg/mL)	1.5 mL.	1	-	completeresolution	1 y	None
Kaplan, 2012	necrotizing sialometaplasia	Dexamethasone+ 2% lidocaine	10 mg	1	-	The lesion got worsen.	1 w	None
Keogh <i>et al.</i> , 2004	necrotizing sialometaplasia	Triamcinolone	10 mg	3	Weekly	There was no difference in the rate of healing	1 m	None
Piccianni <i>et al.</i> , 2010	RAS	Betamethasone dipropionate+ disodiumphosphate	5 mg/mL + 2 mg/mL	1	-	partial regression in first week. No recurrence in 6 months	6 m	None
Ohbayashi <i>et al.</i> , 2007	GVHD	0.2% dexamethasone	0.5 mg/cm ²	1	-	drastically improving	-	None
De Oliveira <i>et al.</i> , 2011	mTOR inhibitor stomatitis	Triamcinolone 40 mg/mL (4 case clobetasol gel 0.05%	8 to 24 mg	1-9	biweekly	drastically improving	-	None
Villa <i>et al.</i> , 2015	mTOR inhibitor stomatitis	Triamcinolone acetonide	-	1-4	Weekly (4-15d)	immediate symptomatic improvement, complete resolution 2 to 70 days	-	None
Xia <i>et al.</i> , 2006	Ulcerative OLP	Triamcinolone (40 mg/mL)	0/5 mL	1 and 2	biweek	Relief of sign & symptoms and reduction in size	4 week	None
Lee <i>et al.</i> , 2013	OLP	(40 mg/mL) Triamcinolone acetonide	0.5 mL	5	4 weekly and 1 biweekly	significantly improve in pain and burning mouth	1 y	cushingoid features.
Liu <i>et al.</i> , 2013	OLP	Betamethasone Triamcinolone	1.4 mg 8 mg	2	weekly	Betamethasone wes better than triamcinolone	3m	None
Borahan, Fisekcioglu, Alpay, 2014	Erosive OLP	Methylprednisolone acetate	0.1 cc	5	biweekly	significantly improvement	Abscess formation Mucosal atrophy	
Metwalli <i>et al.</i> , 2018	OLP	Triamcinolone acetonide	20 mg/mL	2	weekly	significantly improvement but no statistically significant differences with BCG-PSN	2 w	2 case atrophy and persistent \ erythema
Tilakaratne, 2016	OSF	Methylprednisolone	40 mg	6	monthly	improving mouth opening	1 y	None

TABLE I - List of articles that applied ICSI to treatment oral lesions (cont.)

Author & Year	Type of Lesion	Type of ICSI	Dose of ICSI	Number of ICSI	Intervals of ICSI	Result of treatment	Follow up	Side effects
Singh, 2014	OSF	Betamethasone Lycopene	4 mg	16	Twice weekly	Lycopene is better than betamethasone.	4 m	None
James, 2015	OSF	Dexamethasone+ Hyaluronidase + Lignocaine HCL	1.5 mL 1500 IU 0.5 mL	2	biweekly	Improvement in mouth opening Reduction in burning sensation and ulceration	9 m	None
Kumar, 2007	OSF	Betamethasone + Lycopene	2 1-mL ampules of 4 mg	4	biweekly	Mouth opening was increased more in steroid group.	6 m	None
Singh, 2010	OSF	Hydrocortisone acetate+ Hyaluronidase	1.5 mL 1500 IU	22	Weekly	Biweekly injections was more convenient because of number of visits and cost	3 m	None
Triamcinolone+ Hyaluronidase	10 mg 1500 IU	11	Biweekly					
Nguyen, Ahmed, 2014	Pemphigus vulgaris	Triamcinolone acetonidein 2% xylocaine	10-15 mg	4	Every three weeks	lesions resolved within five to sevendays.	18 m	None
Abbas <i>et al.</i> , 2014	Pemphigus vulgaris	Triamcinolone + 2g cellcept	10 mg/mL +daily	2		Resolving within 2 months.	1 year	None
Mignogna <i>et al.</i> , 2010	Pemphigus vulgaris	Triamcinolone acetonide	40 mg/mL diluted 2 : 1 with saline (i.e. 25 mg/mL) per four lesions	2-8	weekly	Reducing time of remission and total number of corticosteroids	5.3 years	Gingival pellets and Candidiasis
Kalinska-Bienias <i>et al.</i> , 2016	MMP	Triamcinolone	0.3 – 2 mL per erosion	2- 18	-	remission	6-10 m	None
Leroux <i>et al.</i> , 2011	Cluster headache	Cortivazol+ verapamil	3.75 mg in 1.5 mL	3	48-72 hours	Rapidly relief was seen in steroid group	3-11 m	None
Gaul <i>et al.</i> , 2016	Cluster headache	Triamcinolone and bupivacaine	10mg	1	-	Steroid ijectiois an easy, safe and effective	60 days	None
Sinha R, 2016	Mucocele	Betamethason 4 mg/ mL	1 mL	2-4	weekly	18 case complete resolved, 2 case Reduced in size	6 m	Mild discomfort
Mortazavi <i>et al.</i> , 2017	M ucocele	dexamethasone (8 mg/2 mL + silk sutures)		3	weekly	Complete healing	6 m	None
Baharvand <i>et al.</i> , 2014	Mucocele	8 mg/mL Dexamethasone	1 mL	3	weekly	7 case complete resolved 2 case Reduced in size	(6-20 m)	Mild discomfort
Mignogna <i>et al.</i> , 2004	orofacial granulomatosis	Triamcinolone 40 mg/mL	1 mL (4 mg)	2-3	weekly	lip swellingsettle in all patients with 3 recurrences	3-30 m	Hypopigmentation of the upper lip skin
Ravindran, Karunakaran, 2013	orofacial granulomatosis	Triamcinolone acetonide	-	2	biweekly	Improvement with no recurrences	1 y	None
van der Waal <i>et al.</i> , 2002	orofacial granulomatosis	Triamcinolone acetonide		Within 2-6 m	biweekly to monthly	Patients responded to ICSI.	8.2 y	None
Yang <i>et al.</i> , 2005	Plasma Cell Cheilitis	Triamcinolone acetonide	5.0-4.0 mg/mL	2-4	biweekly	lesions healedcompletely	-	None
Tseng <i>et al.</i> , 2008	Plasma Cell Cheilitis	Triamcinolone acetonide (2.5 mg/mL).	0.1 mL	2	biweekly	healedcompletely	1 y	None
Kaur <i>et al.</i> , 2001	Plasma Cell Cheilitis	triamicinolone acetonide 10 mg/mL		3	biweekly	healedcompletely	3 m	None
Ebrahimi, Nader, Kendall, 2016	trigeminal neuralgia			2		excellent pain relief		

TABLE I - List of articles that applied ICSI to treatment oral lesions (cont.)

Author & Year	Type of Lesion	Type of ICSI	Dose of ICSI	Number of ICSI	Intervals of ICSI	Result of treatment	Follow up	Side effects
Elshiek, Amr, 2016	trigeminal neuralgia	Methylprednisolone	40 mg	1	-	Calcitonin was better than steroid	2w to 12m	None
Hannon, 1983	Foreign-body Granuloma	Triamcinolone diacetate	0.7 mL and 0.5 mL	2	biweekly	healed completely	6 w	None
Anjomshoaa et al., 2013	Follicular Lymphoid Hyperplasia	Triamcinolone acetonide	40 mg in 1 mL	4	weekly	completely resolved.	7 m	none

Caliber-Persistent Labial-Artery (CPLA)

This lesion is an initial arterial branch that, without dividing and decreasing the diameter, can penetrate into subcutaneous tissue of the lips and create a noticeable palpable lesion. In 2016, Agha-Hosseini *et al.* reported a complete improvement of a lesion in the upper lip of patients following three triamcinolone injections (Agha-Hosseini, Sheykhbahaei, 2016).

Hemangioma

Hemangioma is known as the most common neonatal tumor that occurs at birth or during the first few weeks of birth in the head and the neck. The occurrence of this lesion in the oral mucosa is relatively rare and can affect the lips, cheeks, tongue, gums, mucous membranes, jawbones, and salivary glands (Chen, Yeong, & Horng, 2000; Dilip, Madhukar, & Prithviraj, 2016). Two studies in 1990 and 2008 also showed the significant effects of the ICSI treatment on parotid gland hemangiomas and subglottic hemangiomas (Meeuwis *et al.*, 1990; Buckmiller, Francis, & Glade, 2008).

Lymphangioma

Lymphangioma is a developmental tumor of the lymphatic origin. Lymphangioma is covered by endothelial cells and it often contains high vascular contents. Therefore, it can be treated with a similar mechanism of hemangioma (Farmand, Kuttenberger, 1996). A number of reports have been further registered on triamcinolone successful injection in the treatment of cystic hygroma and vascular malformations of the face and the head (Luo, Gan, 2013; Farmand, Kuttenberger, 1996).

Upregulating vasaconstrictor receptors on the vascular smooth muscle cells, increased production of angiotensin, augmented angiotensin converting enzyme (ACE) performance on vascular smooth muscles and endothelium, increased protein concentration of signal

transmission from receptors, strengthened connection of signal transmission to receptor, increased intracellular vasaconstrictor production such as endothelin and decreased intracellular vasodilator production (Agha-Hosseini, Sheykhbahaei, 2016), tightened precapillary sphincters, and competition for estrogen receptors have been the proposed mechanisms for the effects of corticosteroids in the improvement of vascular lesions (Dilip, Madhukar, Prithviraj, 2016).

Pyogenic Granuloma (PG)

It is a benign, usually single, vascular lesion within the mouth that is found most commonly in the gum and the upper anterior teeth, but other areas of the mouth, such as the lips, tongue, and cheeks may also be involved. In this regard, two studies revealed the therapeutic effects of corticosteroid injection in recurrent PG as well as PG in patients with GVHD; respectively (Parisi, Glick, Glick, 2006; de la Rosa-Garcia *et al.*, 2006; Adenis-Lamarre *et al.*, 2009). It seems that both anti-inflammatory effects and the above-mentioned mechanisms for the improvement of vascular lesions are helpful in improving PG.

Central Giant Cell Granuloma (CGCG)

This benign lesion in the jaw is limited to tooth-bearing areas, which sometimes shows a behavior similar to neoplasm (Motamedi *et al.*, 2007). In cases wherein the lesion size is large and surgery can lead to functional or cosmetic defects and even bleeding during surgery, the ICSI can be much more effective. There have been also numerous recent reports of the beneficial impacts of the ICSI on the treatment of these lesions (Nogueira *et al.*, 2010; Carlos, Sedano, 2002; Sezer *et al.*, 2005; da Silva Sampieri *et al.*, 2013; Dolanmaz *et al.*, 2016). The use of the ICSI to treat this lesion was first proposed by Jacovay *et al.* (Rajeevan, Soumithran, 1998). Santos *et al.*, in 2018, also reported the treatment of brown tumor

associated with hyper-parathyroidism as a lesion which is clinicopathologically similar to CGCG (Dos Santos *et al.*, 2018). Stimulated proliferation and differentiation of precursor cells into osteoclasts, inhibited activity of mature osteoclast cells, induced apoptosis of osteoclast-like cells, and the impeded extracellular production of lysosomal proteases are the proposed mechanisms of the ICSI effect in the treatment of CGCG (Nogueira *et al.*, 2010; Carlos, Sedano, 2002; da Silva Sampieri *et al.*, 2013). It seems that the given method can be also employed to treat similar lesions with too much bleeding, such as peripheral giant-cell granuloma (PGCG) and aneurysmal bone cyst (ABC). However, there have been no reports on the efficacy of this method in the treatment of these intra-oral lesions, although there are few reports about the treatment of ABC in other bones using the ICSI (Fraser, Coates, Cole, 1992; Gladden Jr *et al.*, 2000).

Glandular Cheilitis (GC)

This is a chronic inflammatory process that involves the mucus salivary glands and their ducts which frequently occurs in the lower lip of adult males. It is not a naturally pre-malignant lesion (Haldar, 1976) and its clinical forms are simple, superficial suppurative and deep suppurative (Carrington, Horn, 2006). In 1976, complete treatment of this lesion was reported by the ICSI method (Haldar, 1976). In 2018, Sugaya demonstrated complete improvement of GC following two triamcinolone injections and 0.1% tacrolimus ointment application (Sugaya, Migliari, 2018).

Temporomandibular Disorder (TMD)

A group of patients with temporomandibular joint disorders experience pain, tenderness, and long-term motor limitations despite conservative treatments. In these situations, intra-articular corticosteroid injection is considered to improve the disease symptoms (Kopp *et al.*, 1987). In this regard, different studies have examined the effects of this method on a variety of subjective symptoms, radiographic symptoms, as well as histological changes in the articulated tissues (El-Hakim, Abdel-Hamid, Bader, 2005). The anti-inflammatory effects of corticosteroids are also manifested through their effects on the release of neuropeptides from the end of neural fibers, inhibitory effects on the production of inflammatory mediators such as prostaglandin and leukotriene, and corticosteroid through the synthesis of lipoprotein as an inhibitory protein on phospholipase A2 (Agha-Hosseini, Sheykhabaei, 2016; Alstergren *et al.*, 1996). The potential side effects of intra-articular corticosteroid therapy include joint destruction,

infection, and sometimes disease progression (El-Hakim, Abdel-Hamid, Bader, 2005; Kopp *et al.*, 1985). Various investigations have further highlighted the benefits of the ICSI treatment in a variety of TMDs (Alstergren *et al.*, 1996; Samiee *et al.*, 2011; Stoll *et al.*, 2012; Bjørnland, Gjaerum, Møystad, 2007).

Granulomatosis disorder

Orofacial granulomatous lesions are uncommon chronic conditions with multifactorial etiology and unexplained pathogenesis that mostly occur due to systemic conditions such as Crohn's disease, sarcoidosis, tuberculosis, or local causes such as chronic infections, foreign bodies, and allergies (Ravindran, Karunakaran, 2013). Clinically, they are usually in the form of a persistent or recurrent swelling that affects the lips. In addition, conditions such as Melkersson-Rosenthal syndrome and Miescher's cheilitis should be also considered among these lesions (Miest, Bruce, Rogers, 2016). A few recent studies on the positive effects of using the ICSI in treating such lesions were mentioned in Table (Ravindran, Karunakaran, 2013; Mignogna *et al.*, 2004; Van Der Waal *et al.*, 2002).

Plasma-cell cheilitis

This lesion is a benign idiopathic inflammatory condition, which is represented by dense infiltration of plasma cells in mucous and is usually shown as a plaque or patch with an eroded, flattened, or slightly raised and round surface. In patients with plasma-cell cheilitis, the degree of induced acanthosis in tissue appears to be an important factor determining the outcomes of treatment by topical corticosteroids (Yang *et al.*, 2005; Tseng *et al.*, 2009; Kaur *et al.*, 2001).

Lymphoid hyperplasia

The lymphoid hyperplasia lesions are basically a propagation of benign lymphocytic reactivity with unclear etiology, usually seen as an exophytic mass of soft tissues with an intact surface in the areas of the mouth that have lymphoid tissues, such as the Waldeyer's tonsillar ring and the lateral border of the tongue and the palate. Follicular types are usually the same as the normal mucosal in color appearance; otherwise, they may be blue-black or purple-red. These lesions have been often treated by a surgical procedure and through removal of the lesion with many complications, especially in the posterior regions of the mouth. However, one study in 2013 showed that the ICSI

with the probable mechanism of inductions of apoptosis in activated T lymphocytes could easily treat these types of lesions with no complications (Anjomshoaa *et al.*, 2013).

Vesiculobullous disorder

Vesiculobullous lesions are a category of chronic mucosal ulcers. In this respect, pemphigus vulgaris and benign mucous membrane pemphigoid (BMMMP) is one of the most common lesions in the mouth. The primary treatment of these lesions is using the systemic corticosteroid, which can be employed in combination with immunosuppressive drugs. The ICSI in these lesions is not recommended during relapse/flare periods due to inadequate effects. It seems that the given method is the most effective one in the maintenance phase; as more than 70% of the lesions are improved and the systemic corticosteroid is getting tapered (Fortuna & Mignogna, 2011; Mignogna *et al.*, 2010; Nguyen & Ahmed, 2014; Abbas *et al.*, 2014; Kalinska-Bienias *et al.*, 2016). In this respect, a study in 2018 demonstrated that the ICSI in combination with immunosuppressive drugs could lead to reduced dose of corticosteroids and shortened time of clinical improvements (Mignogna *et al.*, 2010).

Trigeminal neuralgia

Trigeminal neuralgia is known as one of the most common causes of facial pains, which usually occurs as one-side sudden, severe, pulsating, recurrent, and diffused pain in one or more trigeminal branches. The ICSI is one of the proposed therapies in this painful disorder particularly in the trigger point of pain or involved neural branch blocks (Gronseth *et al.*, 2008). There are also contradictory reports on the effectiveness of this method (Ebrahimi, Nader, Kendall, 2016; Elsheikh, Amr, 2016).

Cluster headache

Cluster headache is one of the most severe and debilitating types of primary headaches. Corticosteroid injection in the greater occipital nerve is also recognized as one of the therapeutic options. Some of the reports on the positive effects of this treatment were presented in this study (Gaul *et al.*, 2016; Leroux *et al.*, 2011).

Necrotizing sialometaplasia

This is a rare inflammatory disease of the minor salivary gland that, in most cases, affects multiple glands in the hard palate due to an ischemic event. The lesion

is self-limiting within 3 to 12 weeks and the supporting and symptomatic methods are considered as the basis for its treatment. Two studies in 2004 and 2012 showed that intralesional triamcinolone had no significant effect on the improvement of the lesion and, in some cases; it had exacerbated the necrosis (Kaplan *et al.*, 2012; Keogh *et al.*, 2004). It seems that trauma of drug injection, high doses of injectable substance, and lower keratinized tissue nature could reduce the acceptability of the substance and lead to more necrosis in this site or even no improvements. Accordingly, the ICSI was not recommended as a suitable method for the treatment of these lesions.

Recurrent Aphthous Stomatitis (RAS)

This is one of the most common oral ulcers with an approximate incidence rate of 5-50% (Pakfetrat *et al.*, 2010). In this respect, the ICSI reduces the symptoms, the course of the disease, and the period of normal mucus repair; but it does not affect the rate and the frequency of its recurrence (Picciani *et al.*, 2010).

The role of the immune system in producing the RAS has been largely proven. The reduction in the proportion of T helper cells relative to T-cytotoxic cells and the special role of some types of human leukocyte antigens (HLAs) such as IL-1B and IL-6 have been well-illustrated. Steroids, through inhibition of lymphocyte B and effector T cells, can thus cut the response of these cells to accelerators such as allergies, trauma, and stress; and ultimately inflammatory processes can have palliative effects in improving symptoms in patients (Saravanan *et al.*, 2014).

Langerhans Cell Histiocytosis (LCD)

This is a rare disease with unclear etiology, characterized by monoclonal proliferation of langerhans cells. Some believe that the LCD is a neoplastic process. These lesions inside the mouth can also affect soft tissues, hard tissues, or both (Esen *et al.*, 2010). Routine treatment of this disease is also a major surgery with radiotherapy and chemotherapy, although in some cases self-healing has been also reported. The beneficial therapeutic benefits of the ICSI in the treatment of these lesions have been frequently reported (Esen *et al.*, 2010; Putters *et al.*, 2005; Lee, Yoon, 2013; Merglová *et al.*, 2014). Even some studies have regarded it as the first line of treatment for the LCD due to fewer invasions as well as easier and cheaper prescriptions (Lee & Yoon, 2013). Suppressing the langerhans cells, T lymphocytes, eosinophils, and osteoclast-like cells are the suggested mechanisms for

the effect of this method on the treatment of these lesions (Esen *et al.*, 2010).

Nodular fasciitis

This is a benign inflammatory fibroblastic lesion. It also has a relatively benign clinical behavior but it is similar to sarcoma in terms of histopathologic evaluations. Due to the rapid growth and infiltration in the muscles, radical surgery approach is needed. In this respect, a study (1999) reported the successful treatment of this lesion using the ICSI (Graham, Barret, Goltz, 1999).

Mamelian target of rapamycine inhibitor-associated stomatitis

Mamelian target of rapamycin (mTOR) is a serine/threonine kinase that is essential for regulating cell growth and proliferation. Inhibition of this enzyme is one of the relatively new approaches in cancer management, as a target therapy. The side effects of this treatment include stomatitis, dermatitis, anorexia, nausea, and vomiting. Stomatitis is seen in the form of lesions that are quite similar to the RAS in the mouth (de Oliveira *et al.*, 2011). Unlike mucositis caused by chemotherapy and radiotherapy, steroids are not good treatments for it, so the use of a variety of local, intralesional or systemic corticosteroids can be effective in the treatment of stomatitis induced by the mTOR inhibitor (de Oliveira *et al.*, 2011; Peterson *et al.*, 2016; Villa *et al.*, 2015), even though some studies have reported self-improvements without any interventions and treatments (Dominguez *et al.*, 2000).

Oral Lichen Planus (OLP)

The OLP is known as one of the most common chronic inflammatory lesions within the mouth that can also affect skin, nails, hair, and other mucous membranes. Oral lesions are more resistant to treatments. In addition, lichenoid lesions with similar clinical manifestations can be created inside the mouth due to the use of drugs as well as contact with restorative or prosthetic materials. Regarding the role of immune system and autoreactive reactions in the etiopathogenesis of this disease, the use of various types of corticosteroids has been accepted as the first line treatment of this lesion (Agha-Hosseini *et al.*, 2016). The use of the ICSI in the treatment of these lesions, especially those areas with more inflammations and manifestations such as erosion and ulcers, can be very effective in controlling the symptoms in patients (Lee *et al.*, 2013; Xia *et al.*, 2006; Borahan, Fisekcioglu,

Alpay, 2014; Liu *et al.*, 2013). The effect of the ICSI in the treatment of the OLP in children has been also reported with no certain complications (De Moraes *et al.*, 2011). In 2018, Metwalli reported the same effects of Bacillus Calmette-Guerin polysaccharide nucleic acid extract versus triamcinolone acetonide intralesional injection in the treatment of OLP (Metwalli *et al.*, 2018).

Mucocele

Mucocell may occur through extravasation and retention phenomena in the salivary glands. Extravasation is caused due to salivary glandular duct rupture and retention is caused due to dilation of the gland duct. Non-surgical therapies include cryosurgery, ICSI, sclerosing materials, lasers, and micro-crystallization. In this respect, corticosteroids seem to result in accumulation and contraction of the expanded duct of the salivary glands or induction of freezing similar to sclerosing agents (Agha-Hosseini, Sheykhbahaei, 2016; Mortazavi *et al.*, 2014; Baharvand, Sabounchi, Mortazavi, 2014).

Foreign Body Granuloma

Entrance of any foreign materials into the oral mucosa such as suturing, restorative and abrasive materials, denture, anesthetic needle, injection of facial beauty gels or even bristles of toothbrushes can lead to chronic or acute inflammatory infiltration which produce granulomatous reactions. In this regard, a number of reports have been published about the beneficial effects of the ICSI in the treatment of granulomas in the lips (Shahrabi-Farahani *et al.*, 2014; Jham *et al.*, 2009).

Lupus Erythematosus

This is a multi-system inflammatory disease with rare oral manifestations (Netto *et al.*, 2017). The oral manifestations in these patients can be seen as non-specific ulcers or white and red plaques with discoid manifestations in different oral areas such as palate, cheeks, tongue, and gums. Although several studies have reported successful treatments of lupus skin lesions using the ICSI (Yaşar *et al.*, 2017; Callen, 2006), no report was found on the use of oral lesion treatment via this method to be reviewed in this study.

Graft-versus-Host Disease (GvHD)

This is one of the main complaints following allogeneic transplant of hematopoietic stem cells. More

than 80% of cases of this disorder can affect oral mucosa, in addition to involvement of several organs. Oral symptoms can be also present in acute phases as non-specific ulcers but they can be similar to OLP, scleroderma, Sjögren syndrome, and dysgeusia in chronic phases. One of the therapeutic options for oral GvHD lesions is corticosteroid. In this respect, one study was found reporting the use of the ICSI method in the treatment of the GvHD (Ohbayashi *et al.*, 2007).

Other Uses

In addition to the above-mentioned applications of the ICSI for the treatment of intraoral lesions, corticosteroid injection is further employed in other dental conditions; e.g., controlling postoperative pain and swelling, increasing teeth movements in orthodontic treatments, and preventing esophageal stenosis after endoscopic dissection and joint stiffness after trauma (Zerener *et al.*, 2015; Abtahi *et al.*, 2014; Ohki *et al.*, 2012; Efird *et al.*, 2014).

CONCLUSION

The ICSI can be considered as one of the effective therapeutic methods with no significant problems in the treatment of many oral lesions such as inflammatory, immunologic, and vascular disorders. It can also have higher therapeutic effects than other topical forms of steroids and fewer side effects than systemic corticosteroids. According to the results of this study, further research studies are recommended to be conducted about the effects of this therapeutic approach in many common oral lesions.

AUTHORSHIP

Narges Gholizadeh: Conceived, planned, and carried out the experiments presented in the manuscript, or interpreted the data, or both.

Nafiseh Sheykhbahaei: Wrote the paper, or reviewed its successive drafts.

Maryam-Sadat Sadrzadeh-Afshar: Collected and assembled the data, and then approved the final draft.

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Received for publication on 07th February 2018

Accepted for publication on 10th October 2018