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...
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-kB, 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 ISCI                                           | Dos of ISCI                  | Number of ISCI | Intervals of ISCI | Result of treatment | Follow up | Side effects                                                                 |
|----------------------------|----------------|--------------------------------------------------------|-----------------------------|----------------|-------------------|---------------------|-----------|----------------------------------------------------------------------------|
| Agha-Hosseini et al., 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/cm²        | 1-3                         | 6-25 w (12 w)  | 11 lesions complete resolution | 6 m                 | 4 Patients failure to thrive                                                |
| Meeuwis et al., 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 acetone (50 mg/5 mL) + Pingyangmycin 0.625 mg/mL | 5 mL                        | 2e4 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 Garcia, 2006    | PG              | Triamcinolone                                           | 5 mg                        | 3              | -                 | complete resolution | -         | none                                                                            |
| Adenis-Lamarre et al., 2009| PG              | Triamcinolone                                           | 5 mg                        | 3              | -                 | complete resolution | -         | None                                                                            |
| Dolannaz et al., 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 et al., 2010      | CGCG            | Triamcinolone (20 mg/mL) + 2% lidocaine                 | 0.1 mL/cm³                  | 6              | bweekly           | 15 complete resolution, 4 Partial recovery, 2 did not response | 4-8 y             | None                                                                            |
| Sezer et al., 2005         | CGCG            | Triamcinolone (10 mg/mL) + lidocaine 2%                 | 4 mL                        | 6              | Weekly            | complete resolution | 3 Y                 | None                                                                            |
| Da Silva Sampieri et al., 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        | 2                  | 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 ISCI                                          | Does of ISCI | Number of ISCI | Intervals of ISCI | 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 et al., 2012  | TMD                     | Triamcinolone hexacetonide, 20 mg/mL                  | 0/5-1 mL     | 1              | -                 | reduced signs and symptoms                                                          | 0.5 - 23 m | None                                |
| Alstergren et al., 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, Møystad, 2007 | TMD              | Betamethasone sodium phosphate + acetate             | 0/7-1 mL     | 2              | Biweekly          | reduce pain and improve function                                                    | 6 m       | Temporary pain after injections     |
| Lee et al., 2013     | Langerhans cell histiocytosis | methylprednisolone, 40 mg/mL                         | 3 mL         | 1              | -                 | complete resolution                                                                 | 35 mo     | None                                |
| Milián, 2001        | Langerhans cell histiocytosis | Triamcinolone acetonide                              | 25 mL        | 8              | every 3 weeks    | complete resolution                                                                 | 1 y       | none                                |
| Lee et al., 2013     | Langerhans cell histiocytosis | methylprednisolone succinate (40 mg/mL)             | 2 mL         | 3              | Every 4 month    | Near-complete resolution                                                            | 36 m      | None                                |
| Putters et al., 2005 | Langerhans cell histiocytosis | methylprednisolone succinate (40 mg/mL)             | 1-2 mL       | 1              | -                 | complete resolution                                                                 | 9 y       | None                                |
| Graham, Barret, Goltz, 1999 | Langerhans cell histiocytosis | Triamcinolone acetonide (10mg/mL)                  | 1.5 mL       | 1              | -                 | complete resolution                                                                 | 1 y       | None                                |
| Kaplow, 2012        | necrotizing sialometaplasia | Dexamethasone+ 2% lidocaine                          | 10 mg        | 1              | -                 | The lesion got worsened                                                             | 1 w       | None                                |
| Kojoh et al., 2004   | necrotizing sialometaplasia | Triamcinolone                                         | 10 mg        | 3              | Weekly            | There was no difference in the rate of healing                                      | 1 m       | None                                |
| Picciani et al., 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 et al., 2007 | GVHD                | 0.2% dexamethasone                                    | 0.5 mg/cm²   | 1              | -                 | drastically improving                                                               | -         | None                                |
| De Oliveira et al., 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 et al., 2015   | mTOR inhibitor stomatitis | Triamcinolone acetonide                              | -            | 1-4            | Weekly (4-15d)    | immediate symptomatic improvement, complete resolution 2 to 70 days                | -         | None                                |
| Xia et al., 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 et al., 2013     | OLP                    | Triamcinolone acetonide                              | 0.5 mL       | 5              | 4 weekly and 1 biweekly            | significantly improve in pain and burning mouth                                    | 1 y       | cushingoid features.                |
| Liu et al., 2013     | OLP                    | Betamethasone                                        | 1.4 mg        | 8 mg           | 2 weekly          | Betamethasone was better than triamcinolone                                       | 3m        | None                                |
| Borahan, Fisekioglu, Alpay, 2014 | Erosive OLP            | Methylprednisolone acetate                          | 0.1 cc        | 5              | biweekly           | significantly improvement                                                            | Abscess formation Mucosal atrophy              |
| Metwalli et al., 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 ISCI | Does of ISCI | Number of ISCI | Intervals of ISCI | 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 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                                |
| Nguyen, Ahmed, 2014| Pemphigus vulgaris | Triamcinolone acetonide | 10-15 mg | 4             | Every three weeks | Lesions resolved within five to seven days.                  | 18 m      | None                                |
| Abbas et al., 2014 | Pemphigus vulgaris | Triamcinolone + 2% xylocaine 2 mL | 10 mg/mL + daily | 2             | Resolving within 2 months.                                 | 1 year    | None                                |
| Mignogna et al., 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 et al., 2016 | MMP | Triamcinolone | 0.3 – 2 mL per erosion | 2-18 | - | Remission                                                  | 6-10 m | None                                |
| Leroux et al., 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 et al., 2016   | Cluster headache | Triamcinolone and bupivacaine | 10 mg | 1             | - | Steroid injections an easy, safe and effective              | 60 days   | None                                |
| Sinha R, 2016       | Mucocele       | Betamethasone 4 mg/mL | 1 mL | 2-4 weekly | 18 case complete resolved, 2 case Reduced in size          | 6 m       | Mild discomfort                       |
| Mortazavi et al., 2017 | Mucocele | Dexamethasone (8 mg/2 mL + silk sutures) | 3 | weekly | Complete healing                                           | 6 m       | None                                |
| Baharvand et al., 2014 | Mucocele | Triamcinolone acetonide | 8 mg/mL Dexamethasone | 1 mL | 3 weekly | 7 case complete resolved 2 case Reduced in size              | (6-20 m) | Mild discomfort                       |
| Mignogna et al., 2004 | Oral Granulomatosis | Triamcinolone | 40 mg/mL | 1 mL (4 mg) | 2-3 weekly | Lip swelling settle in all patients with 3 recurrences    | 3-30 m | Hypopigmentation of the upper lip skin |
| Ravindran, Karunakaran, 2013 | Oral Granulomatosis | Triamcinolone acetonide | - | 2 biweekly | Improvement with no recurrences                           | 1 y       | None                                |
| van der Waal et al., 2002 | Oral Granulomatosis | Triamcinolone acetonide | - | Within 2-6 m biweekly to monthly | Patients responded to ICSI                                    | 8.2 y | None                                |
| Yang et al., 2005   | Plasma Cell Cheilitis | Triamcinolone acetonide | 5.0-4.0 mg/mL | 2-4 weekly | Lesions healed completely                                      | -         | None                                |
| Tseng et al., 2008  | Plasma Cell Cheilitis | Triamcinolone acetonide (2.5 mg/mL) | 0.1 mL | 2 biweekly | Healed completely                                           | 1 y       | None                                |
| Kaur et al., 2001   | Plasma Cell Cheilitis | Triamcinolone acetonide 10 mg/mL | 3 | biweekly | Healed completely                                           | 3 m       | None                                |
| Ebrahimi, Nader, Kendall, 2016 | Trigeminal neuralgia | Triamcinolone acetonide | - | - | Excellent pain relief                                      | -         | None                                |
**TABLE I - List of articles that applied ICSI to treatment oral lesions (cont.)**

| Author & Year | Type of Lesion | Type of ISCI |Does of ISCI | Number of Intervals of Does of ISCI | 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).

Uregulating 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 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 lyzosomal 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 supplicative and deep supplicative (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, Sheykhbahaei, 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; Bjornland, Gjaerum, Moystad, 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 idiopath 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 rapamycin 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, Fiseckioglu, 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).

**Mucocoele**

Mucocoele 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 also be present in acute phases as non-specific ulcers or 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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