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Chapter in a Book

Haapasalo M, Qian W: Irrigants and Intracanal Medicaments. In: Ingle JI, Bakland LK: *Endodontics*. 6th Ed. BC Decker Inc, Hamilton; Ontario, Canada. 2008; Chapter 28: 997-9.

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Neville BW, Damm DD, Allen CM, Bouquot JE. *Oral and maxillofacial pathology*. 2nd ed. Philadelphia: W.B Saunders Co.; 2002. pp. 533–87.

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Oral leukoplakia: Diagnosis and treatment

*Marie Kjaergaard Larsen DDS¹, Jens Ahm Sørensen MD, PhD²,
Christian Godballe MD, PhD³, Torben Henrik Thygesen DDS, PhD⁴*

Review Article

Abstract

BACKGROUND AND AIM: Oral leukoplakia (OL) is a common premalignant lesion. The possible benefits of specific interventions in preventing a malignant transformation of OL are not well understood. This review assesses different invasive treatment techniques for OL and evaluate the optimal treatment possibilities.

METHODS: A Medline (PubMed) search was conducted and heterogeneity between the studies was found, e.g., with regard to the OL lesions, patient groups, follow-up time, and definition of recurrence.

RESULTS: The recurrence and malignant transformation rate after the different treatment methods were evaluated. The mean overall recurrence rate varied with the treatment method.

CONCLUSION: A surgical treatment appears to decrease the risk of transformation but does not fully eliminate it. Follow-up should be done regardless of the surgical treatment.

KEYWORDS: Oral Leukoplakia; Squamous Cell Carcinoma; Chemotherapy; Laser Ablation; Cryosurgery

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The incidence of oral cancer varies among countries and is generally increasing.¹⁻³ The most common type is the squamous cell carcinoma (SCC), which in the United States accounts for 96% of the oral cancers.¹ The etiological basis for the SCC is not known-human papilloma virus and the use of marijuana has been suggested.⁴ An increased focus on premalignant conditions, risk factors, and relevant treatment opportunities is imperative. In spite of decreasing the incidence of developing oral SCC, this review will base on the treatment of the premalignant condition and oral leukoplakia (OL).

A premalignant condition is a pathological process that possesses the ability to develop into a malignancy. In 1967, the World Health Organization (WHO) established a center for

characterizing and defining which oral lesions should be considered premalignant and to determine the risk of these lesions becoming malignant.⁵ One of the most common lesions is leukoplakia. OL was defined by the WHO in 1978 as: "a white patch or plaque that cannot be characterized clinically or pathologically as any other disease."⁵ The definition of OL has changed over the years and in 2005 it was defined as: "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer."⁶

OL has the potential risk of a malignant transformation into SCC. The prevalence of OL varies from 0.9 to 3%⁷⁻⁹ with a malignant transformation rate of 0.13-37%.⁹⁻¹⁵ The incidence of OL displays geographic and demographic variations thus resembling the

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incidence of oral cancer.¹⁶ The reported proportion of OL that transforms into carcinoma varies depending on several factors, e.g., the definition of OL, the study population, and the length of observation time. The main risk factors for developing OL are tobacco smoking, betel quid chewing, and alcohol consumptions.^{11,17-23} It is unclear whether these risk factors play a role in the malignant transformation of OL. The studies show that there is a higher risk of malignant transformation of OL in older persons than in younger persons when the OL is located on the lateral/ventral tongue, and non-homogenous lesions have a higher transformation rate than homogenous lesions.^{10-12,21,24,25}

The high-risk sites for developing SCC might be explained on the basis of a higher exposure to carcinogens than other areas of the oral cavity and the lower degree of keratinization.^{26,27} Holmstrup et al.²⁸ showed that the risk of non-homogenous OL undergoing malignant transformation was seven times greater than it was for homogenous OL. Furthermore, they showed a 5 times increased risk for malignant development when the size of the OL exceeded 20 cm².²⁸ Another study reported a higher potential for malignant development of widespread OL than for smaller, localized OLs.²⁷

The histological presence of epithelial dysplasia is often correlated with a higher risk of cancerous transformation.^{11,21,24,29} A meta-analysis from 2009 showed that the malignant transformation rate of lesions with oral dysplasia was 12.1%.³⁰ Holmstrup et al.²⁸

showed that 11-14% of lesions exhibiting slight epithelial dysplasia, developed into cancer.

Methods

This article focuses on OL treatment methods and their outcome. A web-based search was done using the National Center for Biotechnology Information (NCBI) to search Medline (PubMed). The use of PubMed was chosen according to the searching procedure and references. The keyword "OL" was used. A total number of 4315 titles were identified, and 252 titles and abstracts were recognized as potentially appropriate. The articles containing human immunodeficiency virus (HIV) and those not in English were excluded. Inclusion criteria were malignant transformation, diagnostic, treatment, and outcome. Furthermore, a thorough bibliographic hand search identified further studies. Due to the fact that only a few randomized clinical trials (RCTs) exist, retrospective non-RCTs were included.

Results

A full-text screening of 175 papers was performed according to the inclusion and exclusion criteria. 30 papers were included (Tables 1-4). Data from clinical articles were compared with regard to number of patients, clinical resolution of OL, follow-up, recurrence, and malignant transformation.

The clinical and histological appearance of OL

Clinically, OL varies in size, shape, and consistency. OL is often divided into homogenous and non-homogenous lesions.

Table 1. Results of observation in oral leukoplakia (OL) in the literature

| Author | Year | Number of patients | Follow-up (months) | Clinical resolution (%) | Malignant transformation (%) |
|---------------------------------|------|--------------------|--------------------|-------------------------|---|
| Silverman et al. ¹² | 1984 | 196 | 6-468 | NR | 17.5 (including 61 patients treated surgically) |
| Holmstrup et al. ²⁸ | 2006 | 175 | 18-223.2 | 16.0 | 4.00 |
| Banoczy and Csiba ³¹ | 1976 | 23 | 12-240 | 0.0 | 30.40 |
| Saito et al. ³² | 2001 | 51 | 7-192 | NR | 7.80 |
| Silverman et al. ³³ | 1976 | 4762 | 24 | 31.6 | 0.13 |
| 5 studies | | | 7-468 | 0-31.6 | 0-30.4 |

NR: Not report

Table 2. Results of surgical excision in oral leukoplakia (OL) in the literature

| Author | Year | Number of patients | Follow-up (months) | Recurrence (%) | Malignant transformation (%) |
|---------------------------------|------|--------------------|--------------------|----------------|---|
| Silverman et al. ¹² | 1984 | 61 | 6-468 | 34.4 | 17.5 (including 196 patients non-treated) |
| Holmstrup et al. ²⁸ | 2006 | 94 | 18-223.2 | 13.0 | 12.0 |
| Vedtofte et al. ³⁴ | 1987 | 46 | Average 46.8 | 17.4 | 6.5 |
| Pandey et al. ³⁵ | 2001 | 59 | 12-37 | 10.1 | 0.0 |
| Hogewind et al. ³⁶ | 1989 | 46 | 12-100 | 0.0 | 3.6 |
| Banoczy and Csiba ³¹ | 1976 | 45 | 12-240 | NR | 2.2 |
| Hsue et al. ³⁷ | 2007 | 166 | Mean 43.2 | NR | 4.8 |
| Saito et al. ³² | 2001 | 75 | 7-192 | NR | 1.3 |
| del Corso et al. ³⁸ | 2015 | 30 | 6-112 | 13.3 | 0.0 |
| 9 studies | | | 6-223.2 | 0-34.4 | 0-12 |

NR: Not report

Homogenous leukoplakia is flat and may exhibit superficial irregularities. The non-homogenous lesion is mostly white but can be white and red with an irregular texture that can be flat, nodular, or speckled. The homogenous lesion may be white, whitish yellow, or gray, and can vary greatly in size.^{5,57,58} Non-homogenous OL may compromise about 10% of all OL.⁵⁹ etiologic factors associated with OL, e.g., candidiasis, smoker's lesions, frictional lesions, and dental-restoration associated lesions and can show white plaques or patches and must be identified before making the diagnose of OL.^{58,60}

Histologically, OL shows variable degrees of hyperorthokeratosis, hyperparakeratosis, acanthosis, and atrophy. Furthermore, a diffuse chronic inflammatory infiltration in

the lamina propria is often seen. Dysplasia may be seen occasionally.⁵⁹ Apart from the nodular type of OL, there is not a strong correlation between clinical appearance and dysplasia.⁵ The presence of dysplasia may indicate an increased risk of the malignant transformation. The dysplasia is graded as mild, moderate and severe dysplasia and carcinoma in situ.^{13,59} Currently, no reproducible criteria exist that can be used to divide the dysplastic spectrum into mild, moderate or severe.⁶¹ The grade of dysplasia is subjective and dependent on the pathologist.^{24,61,62} Silverman et al.¹² showed that 8.6% of the patients with OL had a diagnosis of epithelial dysplasia. The benefit of a subdivision of epithelial dysplasia is not known.^{5,59,61}

Table 3. Results of cryosurgery in oral leukoplakia (OL) in the literature

| Author | Year | Therapy | Number of patients | Clinical resolution (%) | Follow-up (months) | Recurrence (%) | Malignant transformation (%) |
|-------------------------------------|------|--|--------------------|-------------------------|--------------------|----------------|------------------------------|
| Yeh ³⁹ | 2000 | Cryosurgery (open) (liquid nitrogen) | 25 | NR | 3-46 | 32.0 | NR |
| Kawczyk-Krupka et al. ⁴⁰ | 2013 | Cryosurgery (closed) (nitrous oxide) | 37 | 89.2 | 6 | 24.3 | 5.4 |
| Yu et al. ⁴¹ | 2009 | Cryosurgery (open) (liquid nitrogen) | 47 | All | 5-31 | 8.3 | 0.0 |
| Lin et al. ⁴² | 2012 | Cryosurgery (closed) (liquid nitrogen) | 54 | All | 7-38 | 8.3 | 0.0 |
| Saito et al. ³² | 2001 | Cryosurgery (closed) (liquid nitrogen) | 12 | All | 7-192 | 25.0 | 25.0 |
| 5 studies | | | | 89.2-100% | 3-192 | 8.3-32 | 0-25 |

NR: Not report

Table 4. Results of laser treatment in oral leukoplakia (OL) in the literature

| Author | Year | Therapy | Number of patients | Follow-up (months) | Recurrence (%) | Malignant transformation (%) |
|---|------|---|--------------------|--------------------|--|------------------------------|
| Yang et al. ²¹ | 2011 | CO ₂ | 114 | 21-110 | 17.5 | 11.4 |
| Chandu and Smith ²² | 2005 | CO ₂ | 43 | 2-102 | 28.9 | 7.3 |
| Schoelch et al. ⁴³ | 1999 | CO ₂ Nd: YAG | 70 (55) | 6-178 | 38.2 | 9.0 |
| Thomson and Wylie ⁴⁴ | 2002 | CO ₂ | 57 | 1-44 | 33.3 | 7.0 |
| Frame ⁴⁵ | 1985 | CO ₂ (vaporization or evaporation) | 75 | 3-45 | 8.0 | NR |
| Horch et al. ⁴⁶ | 1986 | CO ₂ (evaporation) | 32 | 37 | 22 | NR |
| Ishii et al. ⁴⁷ | 2003 | CO ₂ Nd: YAG | 82 | 6-288 | 29.3 | 1.2 |
| White et al. ⁴⁸ | 1998 | KTP | 17 | 1-36 | 23.5 | NR |
| | | CO ₂ | | | 27.2 | |
| López-Jornet and Camacho-Alonso ⁴⁹ | 2013 | CO ₂ Kirurgi | 48 | 1-40 | NR | 0 |
| Vivek et al. ⁵⁰ | 2008 | Nd: YAG | 28 | 60 | 7 | 3.5 |
| van der Hem et al. ⁵¹ | 2005 | CO ₂ | 200 | 1-219 | 9.9 | 1.1 |
| Flynn et al. ⁵² | 1988 | CO ₂ (vaporization) | 14 | 12-41 | 15 | NR |
| Chiesa et al. ⁵³ | 1990 | CO ₂ (vaporization or evaporation) | 145 | 12-36 | 10 (12 months) 21 (24 months) 27 (36 months) | 1.4 |
| Roodenburg et al. ⁵⁴ | 1991 | CO ₂ | 70 | 6-144 | 9.7 | NR |
| Lim et al. ⁵⁵ | 2010 | CO ₂ | 75 | 41-43 | 39.5 (CO ₂) | 4 (CO ₂) |
| | | KTP | | | 25 (KTP) | 5.4 (KTP) |
| Mogedas-Vegara et al. ⁵⁶ | 2015 | CO ₂ (vaporization) | 65 | 0.3-38.7 | 33.8 | 15.4 |
| del Corso et al. ³⁸ | 2015 | Nd: YAG | 47 | 6-112 | 38.3 | 3.9 |
| 17 studies | | | | 0.3-288 | 7-39.5 | 0-15.4 |

KTP: Potassium-titanyl-phosphate; Nd: YAG: Neodymium: yttrium-aluminum garnet; CO₂: Carbon dioxide; NR: Not report

Malignant transformation

Clinically, almost all oral cancers have two characteristic features: ulceration and an indurated margin, although these features may not be present in the early stages of oral cancers.⁵⁹ A diagnose of SCC is made histopathologically when the nests of epithelial cells have invaded the underlying lamina propria and deeper submucosa.^{5,59}

The most important predictor of recurrence and mortality in patients with SCC is the clinical stage at the time of diagnosis.^{13,59} The early detection and treatment of premalignant lesions can help

prevent transformation into oral carcinoma. Several methods are available for the screening of oral cancer and precancerous lesions. Unfortunately, most methods present limitations that make them more or less useful.^{13,59,63,64}

Conventional oral examination and palpation remain the standard method for screening of oral cancer and premalignant lesions.

Biopsy and histopathological examination are the gold standard in diagnosing and grading oral premalignant lesions.^{13,63,65-67} Invasive methods can be painful and can result in complications. Non-invasive tests

would be preferable as a diagnostic tool, and various tests are now being investigated. Toluidine blue (tolonium chloride) can be used to identify premalignant and carcinomatous lesions. The dye is a member of the thiazine group and it selectively stains acid tissue components such as DNA and RNA. Theoretically, dysplastic and malignant cells have a higher RNA and DNA content than normal cells, which is the rationale for its use.⁶³ Toluidine blue can help identify the presence of dysplastic or carcinomatous lesions, but due to a low specificity, it cannot replace biopsy.⁶⁸

Histological diagnosis of epithelial dysplasia has a disadvantage because the analysis is based on a static snapshot.^{13,62} The malignant transformation is a dynamic process in which several molecular changes are taking place simultaneously.

Optical imaging systems, saliva, and exfoliated cells can be used as a source for biomarker-based risk assessment.⁶³ Several studies have investigated changes as a method to identify when dysplastic lesions will develop into SCC.^{13,15,62,69-75} Many molecular changes are associated with the transformation from dysplasia to malignancy in OL and include loss of heterozygosity, aberrant DNA expression, dysregulation of apoptosis, and altered expression of tissue markers.^{58,62}

Treatment methods

Various treatment modalities for OL have been suggested. Overall, the treatments can be categorized as observation, chemotherapy, and surgical excision/ablation. Currently, the most appropriate treatment remains to be found. The outcome of the treatment modalities appears to vary, and long-term follow-up studies are few. A surgical excision has been considered the gold standard with regard to the treatment of small local lesions with severe dysplasia or carcinoma in situ.^{13,30} Recently, the use of cryosurgery, laser evaporation, and laser excision has been recommended in the literature.^{39-44,76-79} OL with a low to moderate malignant risk may

either be surgically removed or not.^{5,13} Non-dysplastic OL lesions have been shown to respond to changes in lifestyle factors such as reduction of alcohol and tobacco use.^{28,66,67} In addition, chemoprevention has shown a positive effect on precancerous lesions.⁶⁴

Non-surgical treatment/chemoprevention

Non-surgical treatment is a possibility when surgical removal is difficult because of, e.g., the location of the lesion, its size, or the patient's medical status.⁵⁷ Overall, the non-surgical treatment can be divided into carotenoids, vitamins, bleomycin, and photodynamic therapy. Ribeiro et al.⁶⁴ published a review in 2009 on the non-surgical treatment of OL. RCTs for chemotherapy of OL failed to demonstrate an effective treatment in preventing transformation to SCC and recurrence. No recommendation can be provided for specific non-invasive and invasive treatments of OL.

Surgery

The surgical excision of OL is defined as removal of the entire lesion. It is recommended that the lesion is excised with a margin of 3-5 mm of the clinical normal mucosa. The lesion is separated from the underlying tissue by blunt dissection. Subsequently, the defects are closed directly. This can be done by transposition of local mucosa flaps or with free mucosal grafts, depending on the size of the surgical defect.^{28,34}

Recurrence rates between 0 and 34.4% are reported following surgical excision,^{12,28,31,32,34-38} and 0-12% of surgically treated lesions develop carcinoma within a follow-up period of 7-223.2 months.^{12,28,31,32,34-38} No RCTs have been reported so far.⁸⁰ A retrospective study of 269 lesions investigated the long-term outcome of premalignant lesions after surgical excision and after a follow-up without surgery.²⁸ 94 lesions were surgically removed, and no surgical intervention was undertaken in 175 lesions. Malignant transformation was seen in 12% of the surgically treated lesions after a mean follow-

up period of 7.5 years, whereas 4% of the non-surgical treated lesions transformed malignantly after a mean follow-up period of 6.6 years. The two groups were not directly comparable due to a greater number of cases of non-homogenous OL, OL with epithelial dysplasia, and carcinoma in situ in the group that underwent surgical intervention. Thus, the study did demonstrate that surgical intervention of premalignant lesions did not prevent malignant development.²⁸

Post-operative complications after surgical excision of OL are described in the literature and include infections, nerve injuries, reduction in the mobility of the mouth, obstruction of salivary flow, etc.³⁴ In the treatment of large OL lesions, surgical excision can cause a considerable scar contraction during healing with both functional and aesthetic consequences.⁴⁵ In addition, the use of skin grafts can interfere with proper diagnosis and early signs of recurrence.^{34,45}

Cryosurgery

A cryosurgery is a treatment option for various skin and mucosal diseases. In the early 1960s, the method was used as a treatment for oral lesions such as hyperplasia, angiomas, and leukoplakia.^{81,82} Cryosurgery is a simple, weakly invasive technique in which rapid freezing destroys a lesion in situ.^{39,81}

The positive advantages of the therapy include a bloodless treatment and a relative lack of scarring and pain. In addition, a very low incidence of secondary infection has been noted.³⁹ Furthermore, it is very safe, relative inexpensive, and easy to perform. A disadvantage of the therapy is that a biopsy should be taken before the OL is treated because after treatment the true lesion is destroyed. It is non-specific in its destructive effects and due to lack of precision; it can be difficult to judge the volume of tissue necrosis afterward.^{39,40,67,81} Complications include pain, hyperemia, and edema.^{39-41,67} The treatment can be done with adjuvant

therapies and if there is no response to one freezing cycle, another cycle can be given.^{39,81}

In only a few studies has cryosurgery been used for the treatment of OL. One study treated 60 OL lesions with the use of cotton swabs and liquid nitrogen. All lesions showed a complete response after an average of 6.3 cryosurgeries, and 5 out of 60 OL recurred in the follow-up period of 1-5 months. The recurred lesions underwent cryosurgery again. The study demonstrated that OL with epithelial dysplasia required a significantly fewer number of cryosurgeries than lesions without dysplasia.⁴¹ The same authors investigated the use of cryogun cryosurgery in 60 OL lesions. All lesions showed complete regression after an average of 3.1 treatments. The cryogun therapy required fewer treatments to achieve complete regression than cryosurgery with cotton swabs. Perhaps this can be explained by the large amount of liquid nitrogen delivered by the cryogun, which maintains a constant low temperature, whereas the temperature increases quickly with the use of cotton swabs.⁴²

The recurrence of OL after cryosurgery has been reported to be 8.3-32.0% after a follow-up period of 3-192 months.^{32,39-42} Unfortunately, the malignancy rate following treatments has, unfortunately, only been reported in few studies with numbers varying from 0 to 25%.^{32,40-42}

Laser

Lasers have been increasingly used in oral and maxillofacial surgery since the 1970s, and it has become a well-accepted treatment of OL.^{76,77,83} Laser therapy for the treatment of OL was first described in 1978.⁸³ It can be used for evaporation, excision, and coagulation of tissue. The effect of various laser types is determined by their wavelength and the specific absorption in the tissue.

Different kinds of lasers have been used for oral surgery, including carbon dioxide (CO₂), neodymium:yttrium-aluminum garnet, and potassium-titanyl-phosphate (KTP) lasers. The most common and suitable for use in the

mouth is the CO₂ laser, which generates energy at a wavelength of 10.6 μm.^{22,46}

Laser excision is preferable because it allows histological examination, but some difficulty in the histopathological interpretation can occur because of collateral thermal damage.⁴⁵ Vaporization does not allow histological examination of the lesion, and there is a risk that small fragments of OL may not be completely eliminated by the beam.

In the literature, several advantages of the use of laser in the maxillofacial region have been described. The laser affords a hemostatic effect by sealing off the blood vessels, creating a virtually bloodless field. Incision of the oral mucosa can be made with minimal bleeding.^{45,47,78} This is very useful in highly vascularized areas. The risk of damage to the tissues is small, which reduces acute inflammatory reactions and post-operative pain, swelling, edema, and infection owing to the cauterization of nerve endings and blood vessels.^{45,47,78,84} Wound healing after laser treatment is good because of limited tissue contraction and produces satisfactory mobility of the oral mucosa.^{47-49,84} There is no need for sutures with the laser technique, which shortens the surgical time.^{48,78}

One of the disadvantages with laser evaporation is that the lesion is not available for histological study. Therefore, an incisional biopsy must always be obtained before the treatment.⁶⁷ Wound healing is delayed compared with surgical excision and closure with sutures because of secondary healing with epithelial regeneration. Complete healing is described to take around 2-3 weeks.⁴⁶ Safety precautions are another consideration.^{78,82}

Post-operative complications after laser treatment include pain, bleeding, difficulties with speech, paresthesia, difficulty swallowing, obstructive swelling of the submandibular gland and tethering of the tongue. In one study, 78% of patients treated by laser reported one or more of these complications.^{50,85}

The recurrence rate of OL after laser

treatment is 7.0-39.5% within a mean follow-up period of 1-288 months.^{21,22,38,43-48,50-56,76} Recurrence of OL is more likely, especially in deeper tissue layers, which are not completely eradicated.³³ The malignant transformation rate has been reported to be 0-11.4% after a follow-up period of 1-288 months.^{21,22,38,43-48,50-56,76}

Few studies have compared the different types of lasers. Lim et al.⁵⁵ compared the use of the KTP and CO₂ laser in the treatment of OL in a retrospectively study of 75 patients. No significant difference was found between the two groups treated either by KTP or CO₂ laser. A statistically significant reduction in recurrence rate was demonstrated in the patients treated with the KTP laser (P = 0.049). The recurrence rates for the KTP and CO₂ laser groups were 25.0 and 39.5%. The reduction in recurrence might be explained by the greater thermal damage from the KTP laser.

Discussion

One of the approaches for diagnosing SCC is to detect premalignant lesions and prevent their malignant transformation either by invasive or non-invasive treatment methods. It seems redundant to treat all OL lesions surgically, as only 0.13-37% develop into SCC.⁹⁻¹⁵ Furthermore, several studies have shown that some OL lesions can regress spontaneously without any treatment.^{28,34} It is, therefore, important to determine the risk for malignant transformation of each OL lesion.

It is possible to identify lesions with a high risk of developing malignancy using the clinical and histological picture.^{11,12,21,24,25,34,79} Carcinomas may develop in OL lesions with no signs of epithelial dysplasia.^{12,28,32} A study showed malignant development in 11-14% of lesions exhibiting slight epithelial dysplasia.²⁸ Instead, clinical characteristics like the location, size, and homogeneity of the OL may be used to identify risk.^{11-13,21,24,25,28,62,79}

Another important factor is the reliability of the biopsy that is taken for histological evaluation. Lack of correlation between

histological features and outcome of the lesions can probably be explained by the site and size of the biopsy. Vedtofte et al.³⁴ found that four of 61 OL lesions had superficial carcinomas in the excision specimen that were undiagnosed in the incisional, pre-operative biopsy. Lee et al.⁸⁶ investigated the reliability of incisional biopsies. In 200 cases receiving a single-site biopsy, 29.5% of the patients were underdiagnosed (the definitive diagnosis was more serious). Also, overdiagnosis (the definitive diagnosis was less serious) did occur in 32.9% (with CO₂ laser) and 20.0% (with KTP laser) of their biopsies. In 12.0% of the cases, resection specimen showed malignancy undetected by incisional biopsy. Thus, the study showed that incisional biopsies have limitations regarding the assessment of OL. Patients receiving multiple-site biopsies had significantly lower rates of under diagnosis and unexpected carcinomas. It is possible to histopathologically examine the entire OL lesion with an excisional biopsy, but this entails the risk of incomplete treatment of malignant lesions and overtreatment of benign lesions. In general, excisional biopsy is not cost-effective.⁸⁶ Other methods for predicting the potential for malignant transformation are needed. The use of gene markers seems promising as a method of assessing the prognosis with regards to malignant transformation. Currently, no studies have demonstrated methods that are applicable for routine diagnostic work.^{13,15,62,69-75}

Several treatment options to prevent OL developing into SCC are described in the literature. Invasive techniques such as surgical excision, cryosurgery, laser excision, and laser ablation have been investigated with regard to preventing OL from developing into carcinoma. Few studies have compared the recurrence and malignant transformation after treatment between the different treatment options.^{32,40} Significant heterogeneity between follow-up studies is seen in the literature, which makes it difficult

to compare the trials.^{30,62} The definition of recurrence differs in different studies, which results in different rates of recurrence. Thus, it is not possible to determine the influence of exposure to causative agents in treated patients, and the selection of the proper treatment method remains difficult.

A Cochrane review failed to show a high level of evidence regarding an effective treatment in preventing OL from transforming into carcinomas. Treatments of OL can be effective but recurrence and adverse effects are common.⁸⁰ Holmstrup et al.²⁸ showed that surgical interventions did not prevent all premalignant lesions from malignant development. Further, they showed a higher rate of malignant development of surgically treated OL (13%) compared with non-surgically treated lesions (4%), which is in contrast to other reported study results.^{12,30-32,34} The two groups in the study of Holmstrup et al.²⁸ were not completely comparable due to the retrospective nature of the study and because the groups were not randomized. However, they still showed that surgical interventions could not prevent OL lesions from developing into carcinomas. Further investigations are needed.

Saito et al.³² investigated patients with OL who underwent surgical excision, cryosurgery, cryosurgery followed by surgical excision and observation. The malignant transformation rate was lower among patients that received surgical excision (1.3%) than among patients who underwent cryosurgery (25.0%) and among patients who did not receive any treatment (7.8%). The study groups were not completely comparable because of the unequal numbers of patients in each group, the number of severe dysplasia was higher in the group that underwent surgical excision, and the location of OL was different between the groups. However, their data still indicate that the rate of malignant transformation is higher in patients that undergo cryosurgery than among patients who receive surgical excision in those in whom

surgical excision is performed.

The time for the occurrence of malignant transformation in OL is not clear. Pandey et al.³⁵ did not show any carcinoma after surgical excision 1 year after treatment. Holmstrup et al.²⁸ showed that carcinomas developed 2.7-15.1 years after surgical intervention. In 257 patients with OL, Silverman et al.¹² found the greatest occurrence of malignant transformation in the second follow-up year (24%). The malignant transformation was also seen 20-39 years after the initial diagnosis of OL. There is currently no consensus regarding the treatment and follow-up required for patients with OL. Reported follow-up periods vary from immediate discharge to lifetime follow-up.⁸⁷ However, in general, the literature suggests a close and prolonged follow-up of patients who have undergone surgical treatment.^{12,22,28,34,54}

Yang et al.²¹ investigated the risk for recurrence after laser surgery. Patients with non-homogenous OL had a higher risk for recurrence compared to patients with homogenous OL. Lifestyle factors such as cigarette smoking and betel quid chewing affected the outcome. Patients who did not quit smoking cigarettes or chewing betel quid were 9.6 and 19.5 times more likely to develop recurrence than those who did quit. Thus, the curative effect of the treatment is not only dependent on the treatment method, but also the lifestyle factors, that might serve as causative agents.

In tables 2-4, the recurrence and malignancy rates reported in several studies of invasive treatments are listed. The rates vary between the studies, and as mentioned, the study outcomes are not completely comparable. The main studies are retrospective with small patient groups. It is not possible to give specific evidence-based recommendations regarding the surgical treatment of OL lesions because of a lack of RCTs in the literature. In non-RCTs, the effectiveness of various surgical interventions has resulted in various outcomes.

Furthermore, the literature contains no studies of sufficient quality for evidence-based recommendations for the use of non-surgical treatment modalities.

OL lesions are not lethal in themselves and the risk of developing carcinomas is low. Therefore, adverse effects and complications in the proposed treatment must be kept very low. Non-invasive treatments are often preferable for the patient. Side effects such as headache, muscular pain, erythema, and erosions have been reported.⁸⁰ No study has compared the recurrence, the malignancy rate, and the objective and subjective (patients) side effects and complications of chemotherapy with the invasive treatment modalities.

López-Jornet and Camacho-Alonso⁴⁹ compared the pain and swelling after removal of OL with CO₂ laser and a cold knife. They found statistically significant differences during the first 3 days after treatment. The patients treated with CO₂ laser showed a lower level of post-operative pain ($P = 0.021$) and swelling ($P = 0.019$) compared with the patients treated with surgery. The study group was small and the follow-up period was brief, but their results were interesting and showed that the CO₂ laser could be an interesting alternative to conventional surgery, considering the apparent reduction of side effects. Furthermore, another study showed a significant difference in the use of post-operative analgesic. 90% of the patients treated with a conventional surgery used analgesics postoperatively, compared to 29% patients treated with CO₂ laser used them ($P < 0.001$).⁷⁸ Chee and Sasaki⁷⁷ compared the operating time and blood loss between surgical excision and CO₂ laser excision in 45 patients. The visualization of the operative field was better in the CO₂ group, but there was no improvement in operating time. Another study reported shorter surgical time when CO₂ laser was used compared to that associated with surgical excision because of less bleeding and no need for sutures.⁷⁸ Thus, CO₂ laser can be a good alternative to

surgical excision owing to its favorable features like a clearer surgical field because of its hemostatic effect and probably also reduced post-operative pain and swelling.⁴⁹

So far no study reveals any evidence that non-surgical and surgical treatments are protective against the malignant transformation of OL. There is no evidence of the opposite effect either. It appears that recurrence and malignant transformation of OL might be independent of the treatment regime. The number of OL lesions that are prevented from development into cancer is unknown. A follow-up by the clinician responsible for the treatment should be done regardless of the treatment. No strict guidelines can be given with regard to follow-up, but lifelong follow-up is recommended at intervals of < 6 months.⁸⁸

Conclusion

The detection, diagnosis, and management of OL remain complex. The risk of malignant transformation of OL varies from 0.13 to 37% depending on location, etiological factors, clinical features, and degree of dysplasia. Promising technologies for determining the

risk of malignant transformation are currently being investigated. Several medical and surgical treatment protocols have been recommended. However, no high-level, evidence-based study exists that recommends one specific treatment. Some treatments of OL may be effective in healing but no treatments have been shown to be able to prevent recurrence and malignant transformation. Surgical treatment appears to decrease the risk of transformation but does not eliminate it. Future research is needed to identify better prognostic markers for the progression from OL to SCC, a more effective and less invasive treatments, and the length of follow-up periods.

Conflict of Interests

Authors have no conflict of interest.

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Effect of levamisole on treatment of recurrent aphthous stomatitis: A systematic review and meta-analysis

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Review Article

Abstract

BACKGROUND AND AIM: The aim of this study was to systematically analyze the effect of levamisole on treatment of recurrent aphthous stomatitis (RAS).

METHODS: An electronic search was executed in PubMed, Cochrane, and Scopus after determining the research question using the appropriate Medical Subject Heading (MeSH) term covering the period from 1975 to 2015. Additional publications from hand searching and the reference section of each relevant article enriched the article list. Finally, 9 articles that have assessed the effect of levamisole on the treatment of RAS and had suitable qualifications for the accomplishment of systematic review and meta-analysis were included.

RESULTS: The results showed that the chance of improvement in patients taking levamisole was 6 [odds ratio (OR) = 5.67, 95% confidence interval (CI)] times more than in patients not taking this drug.

CONCLUSION: It appears that levamisole is an effective drug for the treatment of RAS, but further appropriate studies should carryout in this context.

KEYWORDS: Levamisole; Treatment; Aphthous; Recurrent; Stomatitis

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Recurrent aphthous stomatitis (RAS) is the most common type of an inflammatory lesion of the oral cavity, affecting 5-25% of the general population.^{1,2} The most characteristic symptom of the disease is the recurrent onset of single or multiple painful rounded or oval ulcers that appear mainly on non-keratinized oral mucosa of the lips, cheeks, and tongue.¹

The etiology of RAS remains unknown.¹⁻³ The suggested triggering factors include genetic predisposition, infection with microorganisms, food allergies, vitamin and

microelement deficiencies, increased oxidative stresses, endocrine alterations (menstrual cycle), smoking cessation, certain chemical products, mechanical injuries, and anxiety.^{1,2,4} Immune changes occur in RAS, beginning with an unclear antigenic stimulation of keratinocytes, and induce the activation of T-lymphocytes, the release of cytokines [including tumor necrosis factor-alpha (TNF- α) and leukocyte chemotaxis].²

Since the cause of the disease is unclear, many drugs have been evaluated in an attempt to relieve the symptoms. A treatment

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is multidimensional and varies according to the predisposing factors. In all the cases, management is symptomatic with attempts to reduce inflammation and pain of the aphthae using topical or systemic treatments.² The choice of drug depends on the severity of the disease, the number of ulcers, their location and duration and the magnitude of pain.⁴

The use of systemic corticosteroids and immunomodulating agents has been the mainstay of the treatment for recurrent aphthous ulcers (RAU).⁵ Corticosteroids are the first choice systemic treatment and immune modulators may be useful as the second line treatment.² One of the most effective systemic immunomodulators to be used in cases of RAU is levamisole.³

Steroids have been shown to provide symptomatic relief, whereas levamisole seems to provide symptomatic relief and alter the disease course.⁶ It was found that in patients with RAS, the immune system's function becomes disrupted in response to some types of trigger factors. Both types of the immune response, natural and acquired (humoral and cellular), may become disturbed in patients with RAS, which is manifested with neutrophil reactivation and hyper-reactivity, elevated concentration of the complement ingredients and cytokines, increased number of natural killer (NK) cells and B-lymphocytes, and disrupted CD4/CD8 ratio.¹

One of the agents used for systemic treatment of RAS is levamisole because it has a wide variety of immunological effects. Previously, it was used as an anti-helminthic drug. It can provide the normal phagocytic activity of macrophages and neutrophils, regulate T-cell activity, modulate the activity of human interferons (IFNs), and the serum levels of interleukin (IL-6) and IL-8. In the cases of RAU, it helps in normalization of CD4⁺/CD8⁺ cell ratio and increased level of serum immunoglobulin A (IgA) and IgM.³

This drug has commonly been used as monotherapy and an adjunct to treatment in

a variety of diseases by gastroenterologists and dermatologists due to its wide range of immunomodulatory actions.⁴ Many studies have done to evaluate the effect of levamisole in the treatment of RAS and reported varied results with different success rates.⁷⁻¹²

The present review was conducted to assess the effect of levamisole on aphthous lesions via a systematic and meta-analysis approach.

Methods

Search methodology and study selection

Our clinical question included four elements: population, intervention, comparison, and treatment outcomes. This research was designed to answer the question whether levamisole could be effective in improving clinical signs of recurrent aphthous patients or not. An electronic search of the PubMed, Cochrane, and Scopus databases was performed covering the period from 1975 to 2015. The following appropriate Medical Subject Heading (MeSH) terms for search were used: aphthous (aphthae, canker sore, periadenitis mucosa), recurrent (recurrence, relapse, recrudescences), stomatitis (stomatitis, oral mucositis, oromucositis), treatment (therapy, therapeutic, management), levamisole, and combination of these terms by the conjunctive operator AND and OR (Tables 1 and 2). A hand search as well as reference section of each relevant article was accomplished. Text files of the searched data from the above-mentioned databases were imported into the EndNote X7.1 for Windows & Mac, Reference management. (Thomson Reuters) software.¹³ Then, after excluding duplicate records, 2365 records remained. Exclusion of the irrelevant articles was performed in the three steps of title, summary and the main text, and 29 articles remained at the end of this step. The full texts of all the related studies were evaluated by two authors separately. If there was any disagreement between these two reviewers, agreement was achieved by consulting with the third reviewer/epidemiologist and statistical advisor.

Table 1. Description of trials

| Author | Year | Sample size | | | Number of improvement | | Index of improvement | Side effect | Dosage |
|------------------------------------|------|-------------|------------|---------|-----------------------|---------|---|--|---|
| | | Total | Levamisole | Placebo | Levamisole | Placebo | | | |
| Lehner et al. ¹⁹ | 1976 | 47 | 26 | 21 | 21 | 6 | Number of ulcers Duration of ulcers | Nausea, Influenza | 50 mg tid 2 days/week |
| van De Heyning ¹⁵ | 1978 | 13 | 7 | 6 | 6 | 1 | Number of ulcers Duration of ulcers Pain of ulcers | No side effect | Weekly 150 mg 3 days/week Every other week |
| de Cree et al. ¹⁷ | 1978 | 18 | 9 | 9 | 7 | 2 | Frequency of ulcers Duration of ulcers Pain of ulcers | Headache, Nausea | 150 mg 3 days/week Interval of 2 weeks |
| Olson and Silverman ¹⁸ | 1978 | 48 | 23 | 25 | 15 | 7 | Frequency of ulcers Duration of ulcers Pain of ulcers | Dysgeusia, Hyperosmia, Headache | 150 mg 3 days/week Weekly |
| Miller et al. ²⁰ | 1978 | 20 | 10 | 10 | 9 | 3 | Frequency of ulcers Number of ulcers Duration of ulcers | Nausea/diarrhea, Dysgeusia, Sleeplessness | 150 mg 3 days/week Every other week |
| Kaplan et al. ¹⁴ | 1978 | 65 | 34 | 31 | 19 | 5 | Number of ulcers Duration of ulcers Pain of ulcers | Dysgeusia, Hyperosmia, Headache, Nausea/vomiting | 150 mg 3 days/week Every other week |
| Drinnan and Fischman ¹⁶ | 1978 | 30 | 15 | 15 | 6 | 5 | Frequency of ulcers Number of ulcers Duration of ulcers Pain of ulcers | Cacogeusia, Nausea | 150 mg 3 days/week Every other week |
| Weckx et al. ²¹ | 2009 | 25 | 15 | 10 | 7 | 7 | Frequency of ulcers Number of ulcers Duration of ulcers Size of ulcers | No side effect | 150 mg 3 days/week Every other week |
| Sharda et al. ⁶ | 2014 | 30 | 20 | 10 | 12 | 2 | Number of ulcers Duration of ulcers Pain of ulcers Frequency of ulcers Size of ulcers | No side effect | 150 mg 3 days/week Weekly for 3 weeks |

Table 2. The Medical Subject Heading (MeSH) terms and their synonyms

| Levamisole | Treatment | Aphthous | Recurrent | Stomatitis |
|--------------------------|-------------|---------------------|----------------|--------------|
| Tetramisole | Therapy | Aphthae | Recurrence | Mucositis |
| Levamisole | Therapeutic | Canker sore | Relapse | Oromucositis |
| Decaris | Management | Sore canker | Recrudescences | Stomatitides |
| Dekaris | | Ulcer, aphthous | | |
| Levamisole hydrochloride | | Periadenitis mucosa | | |

The quality evaluation of articles was performed using Critical Appraisal Skills Program (CASP) according to the Public Health Resource Unit (PHRU) (England 2006).¹³

All the articles were rated according to this checklist and the articles with desirable quality were determined. Articles rating 6 and more were included in the present study. In this step, 20 articles were excluded and 9 articles^{6,14-21} were included in the study. Subsequently, the required data were extracted and imported into an Excel (version 2007) sheet. The main author's name, publication date of the article, quality assessment rating of each study, type of study, sampling method, sample size, study groups' assignment, treatment period duration, dose of the drug used, age (range, average), male and female ratio, the patients' response to the treatment, clinical outcomes, and side effects were systematically recorded.

The review of literature was confined to English papers with randomized clinical trial studies. The meta-analysis was carried out on the clinical outcomes.

An estimation of each treatment effect was

reported as odds ratio (OR) index. In fact, OR was measured for every study and then pooled using a fixed-effect model. The investigation of total variation between findings of studies (the estimations of treatment/intervention effects from final studies) was carried out using Cochran's test for heterogeneity and I^2 index. This index shows what percentage of differences observed between the indexes of the study are due to the heterogeneity between the studies.

The Cochrane guidelines for classification of this index are as follows:

Cochrane Handbook 2008 categories:

- 0-40%: might not be important
- 30-60%: moderate heterogeneity
- 50-90%: substantial heterogeneity
- 75-100%: considerable heterogeneity.

Results

Initially, 3837 articles were found using the electronic search and hand search. Repetitive 2365 articles were omitted. Based on the title, abstract and full text 1443 irrelevant articles were discarded, leaving 29 studies (Figure 1).

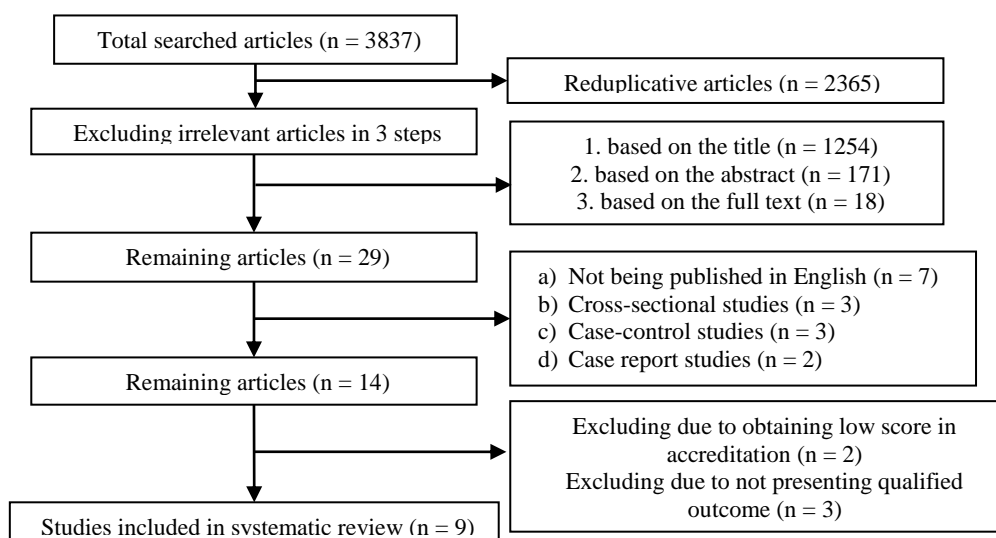
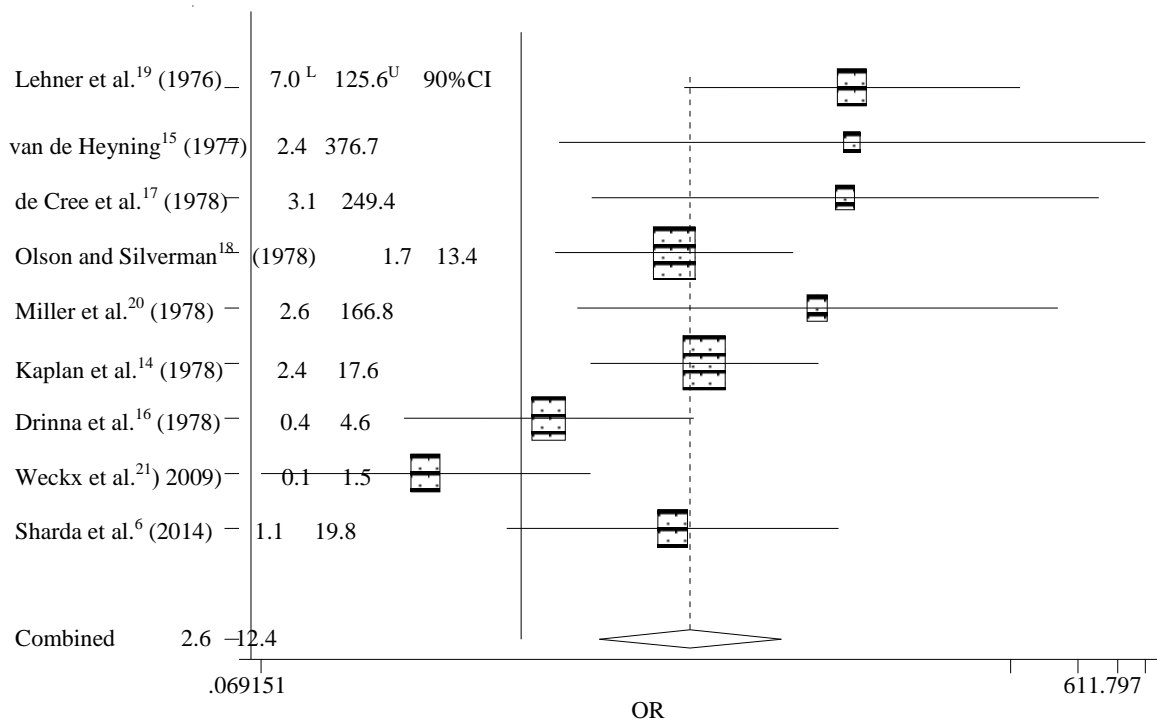
**Figure 1.** Flow diagram of studies

Table 3. The combination of key words

| Levamisole and treatment | Treatment and recurrent and aphthous |
|---|--|
| Levamisole and aphthous | Treatment and recurrent and stomatitis |
| Levamisole and recurrent and aphthous | Treatment and stomatitis |
| Levamisole and recurrent and stomatitis | Treatment and recurrent and aphthous and stomatitis |
| Levamisole and stomatitis | Levamisole and recurrent and aphthous and stomatitis |
| Treatment and aphthous | Levamisole and treatment and recurrent and aphthous and stomatitis |

**Figure 2.** The overall odds ratio (OR) in a fixed model

Two case reports, 3 case-control, 3 cross-sectional, and 7 non-English articles were separated. Quality assessment of the 14 studies was executed according to the PHRU and 9 articles had suitable qualifications (Score 6 or more) for the accomplishment of systematic review and meta-analysis. Table 3 shows the basic information of these 9 studies.

Meta-analysis results of levamisole are presented in figure 2. The chance of improvement in patients taking levamisole was 6 [OR = 5.67, 95% confidence interval (CI)] times more than in patients not taking this drug, and the difference was significant ($P = 0.001$).

In this study, heterogeneity of chi-squared results was $Q = 20.732$ on 8 degrees of

freedom ($P = 0.008$), which was significant at 5% level of significance. Therefore, the study results were heterogenic.

Discussion

This study was performed based on Cochrane systematic review and meta-analysis. The research question was designed to answer whether levamisole is effective in improving clinical signs and symptoms of RAS or not. According to the results of meta-analysis, levamisole improves the clinical signs of RAS. RAS is a common disease and despite many research studies in this field, the etiology of this condition is unknown and there is no definitive treatment for it.²

As the mentioned earlier, the use of

systemic corticosteroids and immunomodulating agents has been the mainstay of treatment for RAU.⁵ One of the most effective systemic immunomodulators to be used in cases of RAU is levamisole.³

The exact mode of action of levamisole remains unclear. Levamisole reportedly decreases the frequency, duration and number of oral ulcers. Levamisole has been found to immunomodulate T-cell-mediated immunity. Normalization of the decreased CD4⁺/CD8⁺ cell ratio and increased serum levels of IgA and IgM has been found in RAU patients after levamisole treatment.³ The serum TNF- α level may be associated with the severity of RAS. It has been concluded that levamisole can modulate serum TNF- α levels in RAS patients.²² IL-6 and IL-8 are pro-inflammatory cytokines that affect cellular and humoral immunities and levamisole can modulate the serum level of these cytokines.^{3,23}

This drug has proven to increase hemoglobin concentration of the patient along with regulating immune system of RAS patients.⁴ Based on evidence available, it seems that levamisole could be effective in the treatment of RAS.^{2,5,22,23} Many studies have evaluated this subject. Outcomes of some of these studies confirm the effect of levamisole on improving clinical signs of aphthous lesions including reduction of frequency, number, duration, size, and pain of ulcers.^{6,14-21}

We assess the results of 9 selected articles in different dimensions.

Levamisole and frequency of ulcers

Six articles showed that levamisole could reduce the frequency of aphthous periods and increase the interval of episodes.^{6,14-18}

Levamisole and duration of ulcers

All the 9 articles supported the effect of levamisole on decreasing duration of ulcers in the mouth and accelerating recovery of ulcers.^{6,14-21}

Levamisole and the number of ulcers

Seven studies demonstrated a decrease in the

number of lesions in different sites by levamisole.^{6,14-16,19-21}

Levamisole and size of ulcers

In two investigations, the diameter of ulcers were measured and a reduction in ulcer sizes was noted after taking levamisole.^{6,21}

Levamisole and pain of ulcers

The results of six trials confirmed the effect of levamisole on decreasing pain of aphthous ulcers.^{6,14-18}

Levamisole and types of aphthous lesions

Two studies described their results based on the classification of aphthous lesions including minor, major, and herpetic form. Olson and Silverman¹⁸ reported that levamisole had more effects on improvement of minor aphthous than major aphthous ulcers, whereas Lehner et al.'s study¹⁹ showed that the efficacy of levamisole in recovery of major aphthous ulcers was more significant than minor aphthous ulcers.

Method of administration

Five methods had been used in the articles reviewed.

A. 150 mg daily for 3 consecutive days/weeks¹⁸

B. 150 mg for 3 consecutive days every other week^{14-16,20,21}

C. 50 mg 3 times daily for 2 consecutive days every week¹⁹

D. 150 mg three times daily for 3 consecutive days/weeks⁶

E. 150 mg daily for 3 consecutive days/weeks with an interval of 2 weeks¹⁷

The duration of trials and follow-up periods of patients were different in different studies, from 2 to 6 months but all of them reported that no clinical changes were seen 1 month after initiation of treatment. Differences in methods of administration and trial protocols in a wide range of duration resulted in differences between the results of studies.

Adverse effects of levamisole are mild and infrequent and include rash, nausea, abdominal cramps, alopecia, arthralgia, hyperosmia, dysgeusia and a flu-like

syndrome and rarely agranulocytosis.^{3,4} The most common adverse effects of levamisole in the mentioned studies were headache, nausea, dysgeusia, and hyperosmia.^{14,16-20}

Overall, 6 articles confirmed the efficacy of levamisole in improving clinical signs of RAS,^{6,14,15,17-19} while 3 articles did not support the influence of levamisole for recovery of clinical signs of aphthous stomatitis.^{16,20,21}

In general, the study results show that studies were heterogenic. The heterogeneity was attributed to differences in methods of administration of levamisole (differences in doses and duration), carrying out the trials in different years and lack of a standard index for improvement between different studies. Moreover, this review showed that there is a time lag between the studies. Most studies conducted in the years 1976-1978 and only two studies recently conducted (2009 and 2014).^{6,21} However, despite the effectiveness of levamisole in the improving of clinical signs of RAS that in most older studies referenced,^{14,15,17-19} the reason of this time lag is not specified. Therefore, further studies are necessary on this topic.

Limitations

The most important factor was the number of appropriate studies carried out in this context; therefore, further studies are necessary on this topic. Since levamisole was administered at different doses using different protocols in different studies, it is difficult to evaluate discrepancies between studies with differences in their data. It is suggested that future studies use

standardized variables and similar conditions including evaluation of size, number, duration, frequency and pain of ulcers, to facilitate comparisons between the results of different studies. The types of aphthous ulcers (minor, major and herpetic form) should be considered for more accurate assessment of the influence of levamisole. Administration of an equal dose of levamisole with the same prescription order and similar period of follow-up make it possible to compare the results of different studies.

Conclusion

Many studies have been undertaken to find an appropriate treatment for RAS and numerous topical and systemic interventions have been used.^{24,25} Administration of levamisole is one of the systemic interventions for the treatment of RAS because of its immunomodulatory action. The results of this study showed that the chance of improvement in patients taking levamisole was 6 times more than that in patients not taking it. Although several studies supported its efficacy, further studies are necessary in this field.

Conflict of Interests

Authors have no conflict of interest.

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Denture-related oral mucosal lesions among removable denture wearers referred to clinics of Kerman, Iran

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Original Article

Abstract

BACKGROUND AND AIM: Since increasing the proportion of elderly in the world, so oral lesions related to removable denture-wearing are an important issue. The aim of this study was to evaluate the prevalence of denture-related oral mucosal lesions (DMLs) in removable denture wearers referred to clinics of Kerman, Iran.

METHODS: This cross-sectional study was conducted on 350 removable denture wearer, with mean age 58.52 ± 10.78 years old, that had been selected by multistage clustering sample from individuals who referred to Kerman clinics. The data were obtained by a checklist consist of demographic characteristics (sex, age, and educational level) self-reported daily denture hygiene frequency, age of prosthesis and clinical examination. Data were analyzed in SPSS using chi-square and t-tests. P value was considered at 5% significant level.

RESULTS: The results showed 71.8% of the denture wearers had denture related mucosal lesions. The most common lesion was denture stomatitis 36.6% followed by traumatic ulcer 26.5% and angular cheilitis 8.7%. There were significant differences between night wearing denture and age of prosthesis and denture-related mucosal lesions ($P < 0.001$).

CONCLUSION: The finding of this study showed the prevalence of denture-related mucosal lesions is common. Dentists should be instruct the patients for removing the denture at night and routine follow-up visits.

KEYWORDS: Removable Denture; Oral; Denture-related Lesion; Stomatitis; Traumatic Ulcer; Angular Cheilitis

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Life expectancy is increasing in the world and the proportion of elderly is also increasing, so the number of elderly who need denture has increased.¹ Iran's population is about 74 millions. The elderly people were 3.9% of the whole population in 1965 and had reached 5.1% by 2006. It is expected that the portion of population over 65 years in Iran will increase to 20-25% by 2050.² Good oral health is essential for maintaining general health, especially among the elderly population.³ It is shown that replacement removable dentures

have a positive effect on individuals' oral health.⁴

Conditions, such as denture stomatitis, traumatic ulcer, and angular cheilitis, have been reported in denture wearer.⁵

Denture stomatitis is an inflammatory process of oral mucosa, occur beneath of a removable denture. Association between denture stomatitis and oral Candida infection, poor denture hygiene, night wearing denture,⁶ endothelial dysfunction,⁷ and vitamin A deficiency, cigarette smoking⁸ have been reported.

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It is also shown denture plaque, *Candida* infection, poor denture retention, and mechanical trauma are associated with DMLs.⁹

Pentenero et al.¹⁰ showed prevalence of oral mucosal lesions were greater in denture wearer. Denture stomatitis was the most common oral lesions in Venezuelan aged populations.¹¹ DMLs among Brazilian farmers were 50% and the most common lesions were denture stomatitis.⁹ Dundar and Ilhan¹² showed 40.7% of patients older than 60 years had lesions due to dentures.

Singh et al.¹³ reported that denture stomatitis is the most common DMLs followed by burning mouth syndrome, superimposed infection, and angular cheilitis.¹³ Denture stomatitis and traumatic ulcers were reported in 35.8 and 29.0% of patients, respectively, in Turkey by Baran and Nalcaci.¹ Jainkittivong et al.¹⁴ found 45.0% of the patients with denture mucosal lesions and the most common DMLs were traumatic ulcer (19.5%) and denture stomatitis (18.1%). The prevalence of denture stomatitis in Greece' denture users reported high.¹⁵ The three most common lesions in an old population in Spain were angular cheilitis (34%), traumatic ulcers (15%), and denture stomatitis (14%), respectively.⁵ In Jafarian et al.¹⁶ study in Hamadan, 78.7% of denture wearer had at least one type of denture-related oral mucosal.

Since the differences between the prevalence of DMLs in different studies¹⁷ and there is not similar study in Kerman, Iran, the aim of this study was to study the prevalence of DMLs in removable denture wearers referred to clinics of Kerman.

Methods

This cross-sectional study was conducted on 384 participants (counted based on sample size formula) with removable dentures attending to private and government clinics in Kerman with multistage sampling method. City divided into five area: North, South, East, West, and Central. Then from each area two clinics selected (about 40 participants in each clinic). Researcher

attended 3 times a week in the morning and afternoon shifts to the selected clinics, participants were selected accidentally among patients who attended to clinic. Sampling continued until reaching the sample size. Finally, data analyzed on 350 samples. Data were obtained from a checklist consisting of demographic characteristics (age, sex, educational level, kind of prosthesis, age of prosthesis, night wearing, daily frequency of denture cleaning), and clinical examination. The clinical examination was done by a last year dental student who was trained about oral mucosal lesions. Denture wearers were divided into complete denture wearer and partial removable denture wearer groups. The age of denture use was categorized into five groups: (1) 1-5 years of use, (2) 5-10 years, (3) 11-15 years, (4) 16-20 years, and (5) greater of 20 years of use.¹⁸ The educational level of participant was divided into four groups: (1) illiterate, (2) below of diploma, (3) diploma, and (4) university. Soft tissue examination was undertaken using a mouth mirror and gauze compresses. Denture stomatitis was defined when the mucosa under the base of denture was shiny erythematous and was diagnosed according to the Newton criteria.^{7,9} Angular cheilitis was defined as erythematous cracks or fissuring at commissure of the lip/s. Traumatic ulcer was defined as a round or oval lesion with well-defined borders in contact with the denture.⁵

Patients who had a history of antifungal therapy in the previous 2 weeks and uncontrolled diabetes based on physician examination, and any systemic diseases that can effect on oral mucosa were excluded. All of the participants provided written informed consent. Data were analyzed in SPSS software (version 18, SPSS Inc., Chicago, IL, USA) using chi-square and t-tests. P value was considered at 5% significant level.

Results

Of the 350 users of dentures, 247 (70.6%) were female and 103 (29.4%) were male with the mean age 58.52 ± 10.78 years old. 274

(70.57%) had complete denture and the length year of using prosthesis over 20 years was 14.0% (Table 1). 55.1% had nocturnal use of their denture. 64.0% cleaning their denture 3 times a day. The prevalence of denture-related oral lesions was 71.8%. The most common lesion was denture stomatitis 36.6% followed by traumatic ulcer 26.5% and angular cheilitis 8.7%. There were no significant differences between type of denture-related oral lesions and sex ($P = 0.820$). There were significant differences between educational level and denture-related lesions ($P < 0.001$). Denture wearer, who had higher education, had lower denture-related lesions. Based on the time-length of denture usage, the patients who have denture-related oral lesions were using dentures statistically significantly longer ($P < 0.001$). There were significant differences between wearing prosthesis at night ($P < 0.001$), frequency of denture cleaning ($P = 0.040$) and denture stomatitis. The type of removable prosthesis (complete or partial

denture) and denture stomatitis had significant difference ($P = 0.030$). Table 2 shows correlation between denture stomatitis, traumatic ulcer and angular cheilitis according to demographic variables and self-report denture cleaning and wearing denture at night.

Table 1. Distribution of socio-demographic parameters

| Variable | n (%) | Total number |
|------------------------|------------|--------------|
| Sex | | |
| Men | 103 (29.4) | 350 |
| Female | 247 (70.6) | |
| Educational level | | |
| Illiterate | 150 (42.8) | 350 |
| Below diploma | 130 (26.0) | |
| Diploma | 59 (16.8) | |
| university | 11 (3.1) | |
| Type of denture | | |
| Complete | 247 (70.6) | 350 |
| Partial | 103 (29.4) | |
| Age of current denture | | |
| < 5 years | 145 (41.4) | 350 |
| 6-10 years | 76 (21.7) | |
| 11-15 years | 28 (8.00) | |
| 16-20 years | 52 (14.85) | |
| > 20 years | 49 (14.00) | |

Table 2. Correlation between demographic variable and frequency of denture cleaning and denture stomatitis, traumatic ulcer and angular cheilitis

| Variable | Denture stomatitis | Traumatic ulcer | Angular cheilitis |
|-------------------------------|--------------------|-----------------|-------------------|
| | n (%) | n (%) | n (%) |
| Denture | | | |
| Complete denture | 146 (41.7) | 90 (25.6) | 58 (16.6) |
| Partial denture | 109 (31.6) | 96 (27.4) | 3 (0.9) |
| P | < 0.001 | NS | < 0.001 |
| Sex | | | |
| Male | 146 (41.7) | 56 (15.9) | 38 (10.8) |
| Female | 104 (31.6) | 34 (9.6) | 23 (6.7) |
| P | NS | < 0.001 | NS |
| Age of prosthesis | | | |
| < 5 years | 121 (34.8) | 138 (39.5) | 7 (2.1) |
| 6-10 years | 152 (43.4) | 36 (10.8) | 23 (6.6) |
| 11-15 years | 175 (50.0) | 89 (25.1) | 0 (0.0) |
| 16-20 years | 71 (20.4) | 54 (15.4) | 81 (23.1) |
| > 20 year | 257 (73.5) | 78 (22.4) | 186 (53.1) |
| P | < 0.001 | < 0.001 | < 0.001 |
| Use denture at night | | | |
| Yes | 228 (65.3) | 201 (57.6) | 184 (52.9) |
| No | 122 (34.7) | 149 (42.4) | 166 (47.1) |
| P | < 0.001 | NS | NS |
| Frequency of denture cleaning | | | |
| Once a day | 159 (45.7) | 120 (34.3) | 145 (41.5) |
| Twice a day | 114 (32.5) | 117 (33.5) | 123 (35.3) |
| 3 times a day | 77 (21.8) | 113 (33.2) | 82 (23.2) |
| P | < 0.001 | NS | < 0.001 |

*Significant, NS: Not significant

Discussion

Access to dental care is improving in the most countries, and many people are able to maintain their natural teeth longer than the past, but there also people who are edentulous and need use denture.

Oral lesions such as denture stomatitis, traumatic ulcers, and angular cheilitis are related to removable denture use.^{14,18} In this study, denture stomatitis was the most common oral lesions related to denture, that is compatible with Baran and Nalcaci,¹ Kossioni¹⁵ studies in Turkey and Greece.

In this study, 36.6% of individuals had denture stomatitis. This finding is similar to Evren et al.,¹⁹ Marchini et al.,²⁰ Baran and Nalcaci¹ who reported prevalence of denture stomatitis 44.8, 42.2 and 35.8 percent respectively, but is lesser than da Silva et al.⁹ who reported 71.4% of denture wearer had denture stomatitis. The range of denture stomatitis is reported between 15.0 and 70.0% in different studies.²¹ Denture stomatitis is a result of local factors, such as ill-fitting dentures and biofilm formation on the prosthetic surface.²²

There were not significant differences between prevalence of DML and sex. In this study, that is similar to Evren et al.¹⁹ This finding is not similar to da Silva et al. study.⁹ Some studies reported DML is more prevalent in women.²³⁻²⁵ This difference may be due to sample size, clinical examination, and type of removable denture.

In this study, the prevalence of traumatic ulcer and angular cheilitis was 26.5 and 8.7%, respectively. In the Martori et al.⁶ study were 15.0 and 34.0%, that is not similar to our study, and da Silva et al.⁹ showed 5.4% traumatic ulcer and 4.4% angular cheilitis, studies have showed a prevalence rate of 10-25%, similar to that found in the present study.^{1,6,12} Traumatic ulcer is associated to non-adapted denture, and resorbed residual ridge, since the age of denture in 14.0% participants in the present study were > 20 years, so this difference is justifiable. Angular cheilitis is associated to decrease the

vertical dimension.⁹

We found 55.1% were wearied their denture at night. de Castellucci Barbosa et al.²⁵ and da Silva et al.⁹ showed that 64.0 and 53.4% of denture wearer and did not remove their prosthesis at night, respectively, that is similar to our study.

There was significant difference between use of denture at night and DML. Kossioni¹⁵ concluded the most important factor for denture stomatitis was continuous use of denture. Martori et al.⁶ showed the patients who wore their denture at night, had higher incidence of stomatitis than those who did not. Navabi et al.¹⁷ also showed denture wearing at night and age of denture were major factors for denture stomatitis.

We found significant difference between educational level and DML. This finding is similar to Marchini et al.²⁰ may be due to individual with higher educational level have better job situation and better convenience to dental services.

In this study, significant differences between the DML and the age of denture. This finding is similar to da Silva et al.⁹ and Ercalik-Yalcinkaya and Ozcan²⁶ and Mandali et al.²⁷ that showed denture age had significant impact on frequency of DML. Emami et al.²⁸ showed wearing the dentures at night can reduce the protective effect of saliva, and good oxygenation of the mucosa, so microbiological aggression cannot remove from oral cavity.

In this study, there were significant differences between type of prosthesis and denture-related lesions. Patients who had partial removable denture had lower lesions. In agreement with some studies have reported that there is a greater prevalence of lesions among complete removable denture wearer,^{14,21} since this type of denture covers a greater area of oral mucosa than partial removable denture and, therefore, a greater chance of plaque retention as well as mechanical injury is expected.

Conclusion

The most factor for denture related oral

mucosa lesions were using the denture at night, age of prosthesis, and educational level. Dentists can help to prevent DML through making high quality denture and train the patients about methods and materials for denture cleaning and maintaining the prosthesis. Dentists should be instruct the patients for removing the denture at night and routine follow-up visits.

Limitations

Although the research has reached its aims, there were some limitations.

First: This study was conducted only on patients who were attending to Kerman clinics. Therefore to generalize the results, the study should have involved more participants at different level.

Second: The lesions that were studied in

the present study were limited to a group of lesions that examiner was train about their diagnosis. Therefore for further study, all of denture related lesions should be mentioned.

Third: Demographic variables such as age of denture were collected based on patients' reports, because lack of patients records, therefore to better data interpretation for further study, data should be gathered from patients records.

Conflict of Interests

Authors have no conflict of interest.

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Arch dimensional changes following orthodontic treatment with extraction of four first premolars

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Original Article

Abstract

BACKGROUND AND AIM: Tooth extraction as a part of orthodontic treatment plan to create space for leveling and aligning teeth or causing tooth movement leads to changes in arch width and length. The outcome of these changes is important for the clinicians and affects the treatment and retention plans. Despite some previous studies, data in this regard are still scarce and further investigation is required on this subject. The purpose of this study was to evaluate dental arch dimensional changes following four first premolars extraction orthodontic treatment.

METHODS: In this study, 100 pairs of dental casts and respective patient records that fulfilled the inclusion criteria were randomly selected from the archives of the Department of Orthodontics, School of Dentistry in Shahid Beheshti University of Medical Sciences, Tehran, Iran. Length and width of dental arch were measured on the initial and final casts of patients using a digital caliper with 0.1 mm precision. The mean, standard deviation (SD) and standard error of variables were determined, and the data were analyzed using SPSS software. Paired t-test was applied to compare changes before and after treatment.

RESULTS: The obtained results showed that the maxillary and mandibular inter-canine widths significantly increased as the result of fixed appliance therapy with the extraction of four first premolars. The arch width at the second premolar and molar at mesiobuccal cusp tip and distobuccal cusp tip regions in the maxilla and mandible showed a significant reduction ($P < 0.001$). In this study, arch length at different points was measured. In the maxilla, the incisor-canine distance in both quadrants experienced a significant increase ($P < 0.001$). Furthermore, the canine-molar distance and the incisor-molar distance in both quadrants and the total arch length showed a significant reduction ($P < 0.001$). In the mandible, the incisor-canine distance in the right quadrant significantly increased ($P < 0.050$), but the reduction in the incisor-canine distance in the left quadrant was not statistically significant. Moreover, the canine-molar and the incisor-molar distance in both quadrants and the total arch length all decreased significantly ($P < 0.001$).

CONCLUSION: Orthodontic treatment with extraction of four first premolars significantly increased the inter-canine width and incisor-canine distance in both jaws; but, the inter-premolar and inter-molar widths, canine-molar distance, incisor-molar distance, and total arch length significantly decreased.

KEYWORDS: Dental Arch Length; Dental Arch Width; Extraction Orthodontic Treatment

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Arch dimensional changes following extraction orthodontic treatments are important for orthodontists. A better understanding of these changes is essential for treatment and planning for the retention period.¹ Edward H Angle was a pioneer in describing normal

occlusion and was in favor of a full complement of teeth. In 1940, Tweed by extraction of first premolars in a group of patients previously treated non-extraction, noticed that their occlusion became much more stable.^{2,3} Furthermore, in 1974, Shapiro found that the inter-molar width was

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significantly different in extraction and non-extraction cases.⁴ A high number of clinicians believe that tooth extraction narrows the dental arch, decreases the arch width, and increases the buccal corridor display when smiling.³ Not evaluating arch dimensional changes as the result of tooth extraction leads to inappropriate treatment planning and not meeting patient expectations.⁵⁻⁷ Thus, it is a research priority to evaluate and measure the maxillary and mandibular arch width and length before and after orthodontic treatment of patients with the extraction of first premolars. The effect of tooth extraction on length and width of dental arch, facial vertical height, soft tissue profile, and prevention of relapse in orthodontic treatments is still a matter of great controversy among researchers and to date; the effect of tooth extraction in this respect has not been well documented.⁸⁻¹⁰ The purpose of this study was to evaluate dental arch dimensional changes following four first premolars extraction orthodontic treatment.

Methods

This retrospective, descriptive, analytical study was conducted on dental records of 100 patients with class I angle malocclusion and 200 pairs of casts that met the inclusion criteria and selected from the archives of the Department of Orthodontics, School of Dentistry in Shahid Beheshti University of Medical Sciences, Tehran, Iran, using systematic random sampling. The inclusion criteria were (1) class I malocclusion, (2) presence of a complete permanent dentition, (3) acceptable treatment outcome at the end of treatment, (4) extraction of four first premolars, and (5) availability of pre- and post-treatment orthodontic casts. The exclusion criteria were (1) congenital missing and (2) facial asymmetry.

Measurements were made using a digital caliper (NEIKO/014007A/CHAINA) with 0.1 mm readability and repeated twice for each variable with a 2-day time interval. In cases where the difference between the two

measurements was > 0.1 mm, the measurement was repeated for the third time, and the mean of three measurements was calculated and recorded.

Understudy variables were:

1. Intercanine width: defined as the linear distance between the cusp tips of the right and left canines in one arch

2. Inter-second premolar width: defined as the linear distance between the buccal cusp tips of the right and left second premolars in one arch

3. Inter-first molar width at mesiobuccal cusp tip (MBCT): defined as the linear distance between the MBCTs of first molars in one arch

4. Inter-first molar width at distobuccal cusp tip (DBCT): defined as the linear distance between the DBCTs of first molars in one arch

5. Incisor-canine distance: defined as the linear distance between the midpoint of the incisal edge of central incisor and cusp tip of canine tooth in the right and left quadrants

6. Canine-molar distance: defined as the linear distance between the canine cusp tip and DBCT of the first molar in the same quadrants

7. Incisor-molar distance: defined as the linear distance between the midpoint of the incisal edge of the central incisor and the DBCT of the first molar in the right and left quadrants

8. Total arch length: defined as the sum of incisor-canine and canine-molar distances of both quadrants of one jaw.

Data were analyzed using SPSS software (version 18, SPSS Inc., Chicago, IL, USA). Mean and standard deviation (SD) were calculated for each variable. Kolmogorov-Smirnov test was used to determine data distribution. Paired t-test was applied to compare changes before and after treatment.

Results

After the primary evaluation of dental records and pre- and post-treatment casts, the following results were obtained. As observed

in table 1, the inter-canine width significantly increased in the maxilla and mandible. The inter-premolar width after the extraction treatment significantly decreased in both jaws. The inter-molar width at MBCT and DBCT significantly decreased in the maxilla and mandible. As observed in table 1, incisor-canine distance in both maxillary quadrants and right mandibular quadrant significantly increased but experienced a significant reduction in the left mandible. As expected,

canine-molar distance in both quadrants of the maxilla and mandible experienced a significant reduction. Incisor-molar distance in both quadrants of the maxilla and mandible significantly decreased. A total arch length in the maxilla and mandible significantly decreased after treatment as well.

In the next step, the pre- and post-treatment images were superimposed, and overall changes in the arch form were evaluated as observed in figure 1 (A and B).

Table 1. Changes in width and length of dental arch following extraction orthodontic treatment in millimeter

| Variable | Pre-treatment | Post-treatment | Difference | P |
|-----------------------------|---------------|----------------|---------------|----------|
| | Mean ± SD | Mean ± SD | Mean ± SD | |
| Inter-canine width | | | | |
| Maxilla | 33.95 ± 2.69 | 35.49 ± 1.76 | 1.54 ± 2.28 | 0.001*** |
| Mandible | 26.43 ± 2.39 | 27.01 ± 1.75 | 0.57 ± 2.42 | 0.019* |
| Inter-second premolar width | | | | |
| Maxilla | 43.60 ± 3.50 | 42.58 ± 2.08 | -1.02 ± 3.19 | 0.002** |
| Mandible | 37.28 ± 3.80 | 34.41 ± 1.97 | -2.87 ± 3.69 | 0.001*** |
| Inter-molar width at MBCT | | | | |
| Maxilla | 49.47 ± 2.20 | 47.30 ± 2.86 | -2.16 ± 3.97 | 0.001*** |
| Mandible | 43.22 ± 3.17 | 40.36 ± 2.58 | -2.86 ± 2.30 | 0.001*** |
| Inter-molar width at DBCT | | | | |
| Maxilla | 51.86 ± 2.89 | 50.13 ± 2.75 | -1.73 ± 1.94 | 0.001*** |
| Mandible | 46.10 ± 3.19 | 43.66 ± 2.77 | -2.44 ± 2.15 | 0.001*** |
| Incisor-canine distance | | | | |
| Maxilla | | | | |
| R | 15.31 ± 1.62 | 16.24 ± 1.01 | 0.91 ± 1.49 | 0.001*** |
| L | 15.14 ± 1.49 | 16.14 ± 1.21 | 1.00 ± 1.32 | 0.001*** |
| Mandible | | | | |
| R | 11.51 ± 1.53 | 12.04 ± 1.26 | 0.53 ± 1.71 | 0.003** |
| L | 12.41 ± 1.82 | 12.08 ± 0.79 | -0.32 ± 1.80 | 0.001** |
| Canine-molar distance | | | | |
| Maxilla | | | | |
| R | 26.60 ± 1.71 | 19.64 ± 1.53 | -6.95 ± 1.77 | 0.001*** |
| L | 26.48 ± 1.80 | 19.53 ± 1.29 | -6.94 ± 1.73 | 0.001*** |
| Mandible | | | | |
| R | 24.95 ± 3.14 | 19.03 ± 1.29 | -5.91 ± 2.82 | 0.001*** |
| L | 25.50 ± 2.32 | 19.10 ± 1.31 | -6.39 ± 1.83 | 0.001*** |
| Incisor-molar distance | | | | |
| Maxilla | | | | |
| R | 42.22 ± 2.90 | 37.56 ± 1.67 | -4.66 ± 2.16 | 0.001*** |
| L | 42.21 ± 2.51 | 37.58 ± 1.81 | -4.62 ± 1.95 | 0.001*** |
| Mandible | | | | |
| R | 36.34 ± 3.17 | 32.03 ± 1.72 | -4.31 ± 2.74 | 0.001*** |
| L | 36.60 ± 2.51 | 32.19 ± 1.79 | -4.41 ± 1.65 | 0.001*** |
| Arch length | | | | |
| Maxilla | 83.56 ± 4.66 | 71.57 ± 3.24 | -11.99 ± 3.36 | 0.001*** |
| Mandible | 73.52 ± 5.23 | 62.34 ± 3.24 | -11.18 ± 4.00 | 0.001*** |

*P ≤ 0.050, **P ≤ 0.010, ***P ≤ 0.001

MBCT: Mesio Buccal cusp tip; DBCT: Distobuccal cusp tip

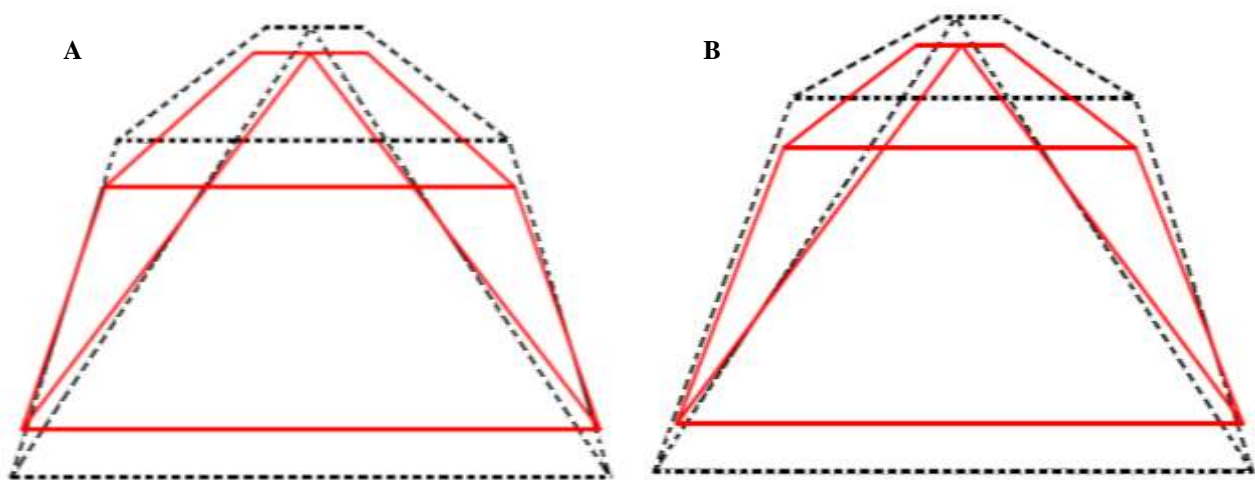


Figure 1. Schematic view of the changes in length and width of dental arch before and after treatment, (A) Maxilla before: Dotted, after: Red line, (B) mandible before Dotted, after: Red line

Discussion

Several studies have discussed changes in arch dimensions as the result of fixed orthodontic treatment along with tooth extraction. This study sought to assess changes in length and width of dental arch following orthodontic treatment with extraction of four first premolars in class I malocclusion patients. This method has been previously used by Kim and Gianelly,⁹ Isik et al.,¹¹ and Al-Sayagh.¹² The obtained results showed that maxillary and mandibular inter-canine width significantly increased following fixed orthodontic treatment with tooth extraction. Inter-second premolar width and inter-molar width at the MBCT and DBCT experienced a significant reduction in both the maxilla and mandible. Similar results were reported by Bishara et al.,^{1,8} Gianelly,¹³ Kim and Gianelly,⁹ Isik et al.,¹¹ Aksu and Kocadereli,¹⁰ and Al-Sayagh.¹²

Kim and Gianelly⁹ compared 30 patients undergoing orthodontic treatment with tooth extraction with 30 patients treated non-extraction treatment plan. Dental arch widths after completion of the treatment significantly changed in both groups with and without extraction except for maxillary inter-canine width that did not change in the non-extraction group compared to the baseline value. After treatment, the inter-canine width in the maxilla and mandible

slightly increased in both groups. These changes were statistically non-significant. The inter-molar and inter-premolar widths decreased in both jaws in the extraction group.

The only difference between the two studies is the inter-canine width that although increased in the maxilla and mandible in both studies; this difference in our study was not statistically significant in the mandible. Kim and Gianelly concluded that extraction treatment does not cause narrowing of dental arch and this treatment does not have a negative effect on smile esthetics.⁹ In another study, Aksu and Kocadereli,¹⁰ evaluated changes in dental arch width in 30 patients who underwent extraction treatment and 30 patients treated non-extraction and demonstrated a significant increase in inter-canine width in the maxilla and mandible after treatment in both groups. Inter-molar width in the mandible significantly decreased in the extraction group. Reduction in the inter-molar width in the maxilla in the extraction group was not statistically significant;¹⁰ but, this reduction was statistically significant in our study. This difference may be due to the larger sample size in our study. Isik et al. in their study,¹¹ revealed that the maxillary and mandibular inter-canine width increased in the extraction group. However, this increase only in the maxilla was statistically

significant. Furthermore, similar to our findings, the inter-premolar and inter-molar widths significantly decreased.

In the study by Bishara et al.¹ the inter-canine width increased in the extraction group due to the alignment of crowded anterior teeth. The inter-molar width in their study decreased in the extraction group. Their findings are in agreement with our study results. The only difference is that our study patients had class I malocclusion, whereas Bishara et al.'s understudy subjects had class II division I malocclusion.¹

Gianelly found that the mandibular inter-canine width significantly increased by 1.39 mm in the extraction group but changes in maxillary inter-canine width and inter-molar width in both jaws were not statistically significant.¹³

The difference between our study and Gianelly's¹³ may be attributed to the small sample size in both groups in his study (25 patients) and measurement of inter-second molar dimension instead of inter-first molar width. We evaluated arch length at different areas and found that in the maxilla, the incisor-canine distance in both quadrants significantly increased. Furthermore, the canine-molar distance in the right and left quadrants, incisor-molar distance in both quadrants and total arch length all experienced a significant reduction. In the mandible, the incisor-canine distance in the right quadrant significantly increased but change in incisor-canine distance in the left quadrant was not statistically significant. A statistically significant reduction was also detected in the canine-molar distance in both quadrants, incisor-molar distance in both quadrants and total arch length. Similar results were obtained by Bishara et al.⁸ They compared 45 patients treated with tooth extraction and 46 treated non-extraction in the two groups of males and females. In their study, a significant reduction occurred in the posterior arch length in the maxilla and mandible after treatment in the tooth extraction group. The total arch length did not

significantly change in all groups post-treatment. The anterior and posterior arch lengths decreased post-treatment in all groups.

In general, their results were similar to our findings. The only difference was that our study subjects had class malocclusion; whereas, Bishara et al.'s patients had class II division I malocclusion and were evaluated in two groups of males and females.⁸ Furthermore, Bishara et al. found that changes in width and length of dental arch were similar in the two groups of males and females.⁸ In another study by Heiser et al.⁷ arch length significantly decreased in both jaws. This finding was similar to our obtained result.

Al-Sayagh¹² conducted a study on 20 patients with tooth extraction (10 males and 10 females) and 20 patients treated non-extraction (10 males and 10 females). Only the maxillary arch was evaluated, and a significant reduction in the following parameters was observed in both maxillary quadrants of males and females in the extraction group: inter-molar width, incisor-molar distance, canine-molar distance, molar vertical distance, and arch length. The inter-canine width significantly increased in females in the extraction group. Moreover, the incisor-canine distance increased in females in the extraction group; but this increase was not statistically significant. In males, this distance decreased but this reduction only in the right maxilla was statistically significant. The difference between findings by Al-Sayagh study¹² and our conclusions could be explained by the small sample size in the aforementioned study especially in the two groups of males and females that decreased the internal consistency of the obtained results.

Conclusion

Orthodontic treatment with extraction of four first premolars:

1. Caused a significant increase in the inter-canine width and incisor-canine distance in both jaws

2. Caused a significant reduction in inter-premolar width, inter-molar width, canine-molar distance, incisor-molar distance, and total arch length

3. Caused forward (mesial) movement of the posterior teeth toward the anterior (narrower) region of the arch.

Conflict of Interests

Authors have no conflict of interest.

Acknowledgments

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Frequency of recurrent caries in bitewing radiographies in patients who attended Kerman dental radiology centers, Iran

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Original Article

Abstract

BACKGROUND AND AIM: Recurrent caries is defined as caries in the marginal edges of filled teeth and is the most common reason for restoration replacement. The aim of this study was to evaluation of recurrent caries in amalgam, resin-based restorations and crowns in bitewing radiographies in patients who attended Kerman dental radiology centers, Iran.

METHODS: This cross-sectional study conducted on 3000 bitewing radiographies. Data were gathered by a checklist consist of sex, age, age of restorations (patients reported), and evaluation of radiographies consist of type of restorations, teeth number, existence recurrent caries. Radiographies examination was done by a last year dental student who was trained. Data were analyzed by SPSS software using chi-square and t-tests. $P < 0.050$ was considered significant.

RESULTS: The rate of the recurrent caries was 8.4%. The rate of recurrent caries in amalgam and resin-based composite was 3.1 and 42.5%, respectively. Resin-based composite material had higher recurrent caries with significant difference ($P = 0.001$). There was also significant differences between age of restorations and recurrent caries ($P = 0.030$). Multi-surfaces restorations had more recurrent caries ($P = 0.020$). There was no significant correlation between sex, number of teeth, mandible or maxilla, and recurrent caries.

CONCLUSION: According to the results of this study, resin-based composite, older and complex restorations had a higher rate of recurrent caries.

KEYWORDS: Recurrent Caries; Bitewing; Radiography; Restoration

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Dental caries is a microbial multi-factorial disease that leads to the destruction and loss of tooth mineral structures.¹ This process can change from early lesion to a clinical cavity during 6 ± 18 months in smooth surfaces.² Recurrent caries is defined as caries in the marginal edges of filled teeth.³ Dental plaque accumulation and incomplete caries removal during cavity preparation are factors for recurrent carries development.⁴ Recurrent

caries is the most common reason for restoration replacement.⁵ Kidd et al.⁶ reported that about 75% of restorative treatments are the replacement of existent restorative, and the main reason is recurrent caries. By the same token, other studies also indicate that recurrent caries is the main reason of replacement restoration.^{7,8} In a study by Chestnut et al.,⁹ the frequency of recurrent carries on 4294 Scottish patients in the age 12-13 years was 8%.

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Chrysanthakopoulos¹⁰ showed that recurrent caries was the most common reason for the replacement of old restoration with resin-based restorations. Clinical examination, radiographic pictures and using dental floss are diagnostic methods to detect recurrent caries.¹¹ Bitewing radiography is a reliable method for detecting recurrent caries. It is shown that intraoral bitewings are better than panoramic and extra oral bitewings in the diagnosis of recurrent caries.¹² In addition, there are no differences between digital and analog accuracy in the detection of recurrent caries.¹³ Since dentists spend a significant amount of their time each year replacing failed restorations, and this process has economic cost for patients and as there are not a similar study about the frequency of recurrent caries in Kerman, Iran, the aim of this study was to assess the frequency of recurrent caries in patients referring to Kerman dental radiology clinics.

Methods

In this cross-sectional study, 3000 bitewing radiographies were selected among patients referring to Kerman dental radiology clinics from October 2014 to February 2015. Written consent was obtained from all subjects. A trained last year dental student was appointed to refer to four dental radiology centers (four visits in a week) and evaluate bitewing radiographies. These centers had similar radiographic apparatus. Radiolucencies in filled teeth or crowns were considered to be recurrent caries. If there was any doubt in diagnosis of recurrent caries that radiography was checked by radiologist.

Data were gathered according to upper or lower jaw, number of teeth (molars or premolars), types of restoration [occlusal, mesio-occlusal, disto-occlusal, mesio-occluso-distal (MOD)], types of filling material (resin-based composite and amalgam), vital or root canal teeth, and crown recorded (Figure 1). We also gathered data regarding sex, age, and age of restoration from patients. The age of restoration was recorded based on patients'

report. Radiographies with close contact and defect in processing were excluded. Data were analyzed by SPSS software (version 21, SPSS Inc., Chicago, IL, USA) using chi-square and t-tests. $P < 0.050$ was considered significant. All radiographies were prescribed by dentists. This study was approved by the Ethics Committee of Kerman University of Medical Sciences (ethic code: k/93/478).

Results

This cross-sectional study was conducted on 3000 bitewing radiographies. In this study, 4297 restorations were evaluated. The age range of participants was 18-46 years with the mean age of 35.12 ± 11.63 years. The age range of restoration was 3-12 years with the mean age of 4.67 ± 2.17 years. The number of filled teeth with amalgam and resin-based composite was 3698 and 280, respectively. In addition, 319 restorations were crown and 359 (8.4%) restorations had recurrent caries. The rate of recurrent caries in amalgam and resin-based composite was 3.1% and 42.5%, respectively. The frequency of recurrent caries according to type of restorations and teeth is shown in figure 1.

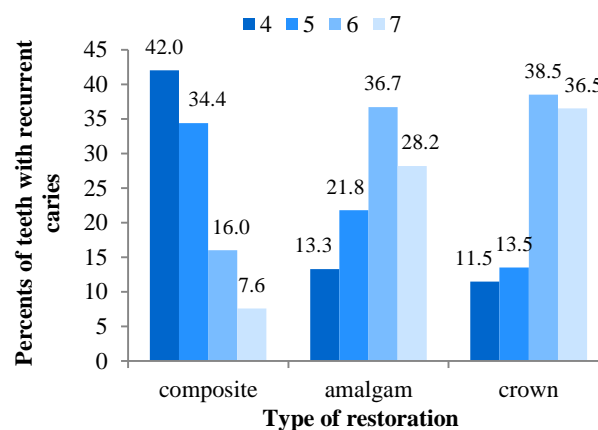


Figure 1. Percents of recurrent caries according to type of restorations and teeth

Table 1 shows the frequency of recurrent caries according to the type of restoration. There were significant differences between different types of restorations and recurrent caries ($P = 0.001$).

Table 1. Correlation between type of restoration materials and recurrent caries

| Type of restoration | Number of total restorations | Number of recurrent caries | Percentage of recurrent caries | P |
|---------------------|------------------------------|----------------------------|--------------------------------|-------|
| Amalgam | 3598 | 188 | 5.2 | 0.001 |
| Composite | 280 | 119 | 42.4 | |
| Crown | 320 | 52 | 15.5 | |

There was not a significant difference between sex and the frequency of recurrent caries ($P = 0.190$). The frequency of recurrent caries was higher in two and three surfaces of restoration than one surface restorations, with significant differences, $P = 0.020$ (Table 2). 182 (51.0%) of recurrent caries were in maxilla and 177 (49.0%) were in mandible. There were no significant differences between two arches ($P = 0.230$). Older restoration showed higher recurrent caries. Significant correlation was found between the age of restoration and recurrent caries ($P = 0.030$).

Discussion

In this study, we used bitewing radiographies to assess the frequency of

recurrent caries in patients. Kamburoglu et al. showed that intraoral bitewing has the more accuracy to detect recurrent caries in comparison to extraoral bitewing and panoramic radiography.¹² Fitzgerald et al.¹³ expressed that bitewing had an accuracy of 59% for amalgam in the diagnosis of recurrent caries. In another study, the accuracy rate of bitewing in the diagnosis of recurrent caries for amalgam and composite restorations was 51 and 68%, respectively.¹⁴ Based on similar studies bitewing radiographies in the diagnosis of recurrent caries in this study is acceptable.^{12,14,15}

In this study, the rate of recurrent caries was 8.4%. This finding is similar to a study by Otto and Rule¹⁶ in which recurrent caries was 10%.

Table 2. Correlation between variables and recurrent caries

| Variables | Number of recurrent caries | Percentage of recurrent caries | P |
|-------------------------------|----------------------------|--------------------------------|-------|
| Sex | | | |
| Men | 168 | 46.9 | NS |
| Women | 191 | 53.1 | |
| Type of restoration materials | | | |
| Amalgam | 188 | 5.2 | 0.001 |
| Composite | 119 | 42.4 | |
| Crown | 52 | 15.5 | |
| Type of filling | | | |
| Class 1 | 39 | 10.8 | 0.020 |
| MO | 105 | 29.2 | |
| DO | 114 | 31.7 | |
| MOD | 101 | 28.1 | |
| Root canal therapy | | | |
| Yes | 177 | 49.2 | NS |
| No | 182 | 50.7 | |
| Type of teeth | | | |
| 4 | 81 | 22.5 | NS |
| 5 | 89 | 24.7 | |
| 6 | 108 | 30.0 | |
| 7 | 81 | 22.5 | |
| Age of restorations | | | |
| 1-4 years | 73 | 20.3 | 0.030 |
| 5-8 years | 112 | 31.1 | |
| 8 and more | 174 | 48.4 | |

NS: Not significant; S: Significant; MO: Mesio-occlusal; DO: Disto-occlusal; MOD: Mesio-occluso-distal

Chestnut et al.⁹ also found a 10% rate for recurrent caries in their study. In a similar vein, Davari et al.¹⁷ also reported a 15% rate for recurrent caries on CL II amalgam restorations failure at dental school in Yazd, Iran. Jaber Ansari and Valizadeh Haghi¹⁸ also showed the rate of 26% for recurrent caries. The difference in percentages could be related to differences in the patient population, caries susceptibility, oral hygiene, diet, and study design. It is shown that cusp fractures and recurrent caries are the most common factors for amalgam restorations failure.¹⁹

In one study regarding the placement or replacement of filling, it was shown that the reason for replacement of filling with resin-based composite was recurrent caries in 43% of cases.²⁰ In our study, recurrent caries in composited filling was significantly higher. This finding is in line with other studies in which significant differences were observed between types of restoration material and recurrent caries.^{6,21} The same finding was also found in a study by Jaber Ansari and Valizadeh Haghi,¹⁸ in which composite fillings had significant higher recurrent caries. They studied recurrent caries in posterior teeth. Resin-based composite is the most common aesthetic alternative to dental amalgam. Moderate to large posterior composite restorations have higher failure rates, more recurrent caries, and increased frequency of replacement.²² Simecek et al.²³ showed that the number of resin-based composite restorations requiring replacement was significantly higher than amalgam restorations.

Some authors have suggested that differences between longevity of composite and amalgam may be more operator-related rather than material-related.²⁴ Factors such as patient's caries risk, tooth position, patient habits, number of restored surfaces, the quality of the tooth-restoration bond, and the ability of the restorative material can have an impact on a sealed tooth-restoration interface.²² In this study, recurrent caries was higher in proximal surfaces of restoration.

This finding is in congruence with the study of Jaber Ansari and Valizadeh Haghi¹⁸ in which recurrent caries was significantly higher in MOD restorations.

Laccabue et al.²⁵ showed that when restorations increased from a single occlusal surface to additional surfaces, a significant higher caries risk status was seen in elevating replacement rates for both amalgam and composite restorations. It may be due to proximal overhang which can lead to periodontal problems and recurrent caries. It may also avoid the use of wedges and contouring of matrix bands by dentists and patients cannot clean the contact of restoration properly. In this study, there was a significant correlation between the age of restorations and recurrent caries, older restorations had more recurrent caries. Bernardo et al.²⁶ in a 7 years evaluation of amalgam and composite restoration found that recurrent caries was the main factor of treatment failure. Chrysanthakopoulos²⁰ reported the mean age of composite restorations were 4 years. In this study, recurrent caries was seen in 14.5% of crowns. Behr et al.²⁷ showed that in the first 5 years of crown restoration, recurrent caries was 1.3%. This difference can be due to the differences between types of restorations or the age of restorations.

Conclusion

Based on the findings of the present study, the frequency of recurrent caries in amalgam, resin-based composite, and crown restoration was 8.4%. The rate of recurrent caries in amalgam and resin-based composite was 3.1 and 42.5%, respectively. Resin-based material composite, older restorations and complex restorations had higher rate of recurrent caries.

Regular follow-up visits especially in high-risk patients and meticulous removal of caries lesions during restorative procedures are recommended. We also suggest oral hygiene instruction to the patients, especially in crown and two or more surfaces restorations by dentists.

Conflict of Interests

Authors have no conflict of interest.

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Epidemiology of oral and pharyngeal cancers: A retrospective study in Kermanshah, Iran

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Original Article

Abstract

BACKGROUND AND AIM: The aim of this study was to determine the incidence and relative frequency of oral and pharyngeal cancers in Kermanshah, Iran, from March 1993 until March 2006.

METHODS: The data used in this epidemiologic study were extracted directly from pathology records registered in 12 (all) public and private pathology centers of Kermanshah province during the 13-year study period. The medical data of 13,323 cases of cancer were studied.

RESULTS: During the 13-year period of this study, 350 new malignant cases occurred in the oral cavity and pharynx. 247 (70%) were men and 103 (30%) were women. The mean age for oral and pharyngeal cancers was 57 [standard deviation (SD) = 17.09] with male to female ratio 2.39:1. The most common oral and pharyngeal cancers were squamous cell carcinoma (SCC) with 283 patients. 211 (74.6%) of the patients were men and 72 (25.4%) of them were women; the mean age of SCC was 60 (SD = 16) with male to female ratio 2.93:1. The two most common sites of involvement were lips [166 (47.5%)] and tongue [25 (7.14%)]. The overall incidence rate of oral and pharyngeal cancers was 1.47 per 100000 populations.

CONCLUSION: In summary, the incidence risk of oral and pharyngeal cancers in people living in Kermanshah province is similar to the most other provinces of Iran. However, this study showed that the rank of oral and pharyngeal cancers among males (9th most common cancer) is low when compared to other regions of Iran and other countries such as India, Australia, and France.

KEYWORDS: Epidemiology; Oral Cancer; Pharyngeal Cancer; Iran

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Oropharyngeal cancers (OPCs), globally, are the sixth most common cancer.^{1,2} OPC includes tumors of the lips, tongue, gingiva (gums), floor of the mouth, soft and hard palate, tonsils, salivary glands, oropharynx, nasopharynx, hypopharynx, and other less frequent sites.³⁻⁶ Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the oral cavity and represents

about 90% of all oral malignancies.^{7,8} It is necessary to remind that variation of OPCs per geographic region around the world is large. The incidence rate is higher in developed countries than in developing countries. However, in countries of Southern Asia, such as India, oral cancer is the most common cancer affecting males and third cancer affecting females, after breast and cervix uteri tumors.⁹

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OPCs are resulted mainly due to the widespread use of tobacco and alcohol.^{2,10} Other risk factors such as viral infection (human papilloma virus, Epstein-Barr virus, and human T-cell lymphotropic virus), nutritional deficiency (iron, vitamin A and C), environmental factors, familial aggregation, and genetic susceptibility, could also have specific effect on the incidence of oral and pharyngeal cancers.^{2,4,9,11,12} OPCs can be seen in places where tobacco is consumed (chewing or smoking) with alcohol or without it. The incidence of OPCs depends on gender, age, culture, and even in developed countries.^{1,2} For example, the use of betel quid is common in parts of Asia that the major risk factor for oral cancer and cancer incidence there are high.¹¹ In the majority of studies in Iran, smoking including cigarette, hookah, and tobacco consumption was found to be a risk factor.¹³

Due to the high level of morbidity and mortality oral cancer in the world and the variety of its incidence in different geographical areas and even in some cases in an area due to different age groups, gender, habits, is very variable.^{2,7,11} Hence, should be highlighted to epidemiology of it to catch data that is required for effective programs and interventions. Considering lack of epidemiological study in Kermanshah, the researchers conducted this study.

Kermanshah is located in the western part of the Islamic Republic of Iran, bordering by Iraq and has a large population of Kurdish ethnics. The total population of the province is 1800000, nearly half living in the provincial capital, Kermanshah city.¹⁴

Methods

Based on nature of research and due to principles highlighting in Medline, this is cross-sectional study that surveyed for the first time in Kermanshah province from 1993 to 2006 in one of the above-mentioned sites.

As shown in table 1, all tumors were categorized according to the International Classification of Diseases (ICD-10) codes for

morphology.¹⁵ The case selection for this study included any diagnosed oral SCC (OSCC) and other malignant neoplasms. Tumors of the skin of the lip, hematologic malignancies, and metastatic tumors to the jaws or oral mucosa were excluded from this study. Since there was no comprehensive cancer registry in Kermanshah province until 2002, the data used in this epidemiological study were extracted directly from pathology records registered in 12 public and private pathology centers of Kermanshah province by oral medicine assistant. The cases with grossly incomplete information and double registered cases were carefully reviewed and excluded from the study.

The method applied is a description of variables including sex, age, and histological type. Population estimates were derived based on data obtained from 1996 census and population growth rate, provided by the Iranian Census Bureau. The crude and age-adjusted incidence rates for oral and pharyngeal cancers, standardized to the world population, were calculated and expressed per 1 million populations. Meanwhile, the frequency and ranking of the 10 most common body cancers were calculated. To assess the effects of age and sex and also checking the time variation, the risks ratio was estimated using negative binomial method. The 95% confidence intervals (CI) were estimated for incidence risks ratio. The 95% CI of all rates were analyzed using STATA data analysis and statistical software (version 8, StataCorp LP, Texas, USA)

Results

In Kermanshah, during the study period from 1993 to 2006, a total number of 13323 new cancer cases were diagnosed. The most common cancer was skin malignancy [16.7% (n = 2235)]. The 19 most common OPCs are presented in table 1. Among males, the first two outstanding cancers were stomach (10.0%) and bladder (6.3%), whereas in females these ranked third and ninth, respectively.

Table 1. Site description of the oral cavity and pharynx

| ICD-10 | Site | Includes |
|--------|----------------------------------|--|
| C00 | Lip | External upper and lower lip, inner aspect of upper and lower lip, commissure of lip |
| C01 | Tongue | Base of tongue |
| C02 | Tongue | Dorsal surface of tongue, border of tongue, ventral surface of tongue, anterior two-thirds of tongue |
| C03 | Gum | Upper and lower gum, alveolar (ridge) mucosa gingiva |
| C04 | Floor of mouth | Anterior floor of mouth, lateral floor of mouth |
| C05 | Palate | Hard and soft palate, uvula |
| C06 | Mouth unspecified | Buccal mucosa, vestibule of mouth, retromolar area |
| C07 | Parotid gland | Parotid gland |
| C08 | Unspecified major salivary gland | Submandibular gland, sublingual gland |
| C09 | Tonsil | Tonsillar fossa, tonsillar pillar (anterior) (posterior) |
| C10 | Oropharynx | Vallecula, anterior surface of epiglottis, lateral and posterior wall of oropharynx, branchial cleft |
| C11 | Nasopharynx | Anterior and posterior wall of nasopharynx, superior and lateral wall of nasopharynx |
| C12 | Pyriform sinus | Pyriform fossa |
| C13 | Hypopharynx | Postcricoid region, aryepiglottic fold, hypopharyngeal aspect, posterior wall of hypopharynx |
| C14 | Other and ill-defined sites | Pharynx, waldeyer's ring |

ICD: International Classification of Diseases

In females, breast cancer was the most common malignancy (8.5%). During the 13-year period of this study, 350 (2.6%) new malignant cases occurred in the oral cavity and pharynx. The majority of oral and pharyngeal cancers (80.9%) were OSCCs group; approximately, 19.1% of cancers were other tumors. 67.0% of cancers occurred in the oral cavity, 22.0% in the pharyngeal region, and 11.0% in the salivary glands. Other tumors histological types included: lymphomas (7.4%), nasopharyngeal carcinoma (4.3%), mucoepidermoid carcinoma (3.7%), adenoid cystic carcinoma (3.4%), and adenocarcinomas (2.6%) (Table 2). The male to female ratio for OSCC and other

tumors are 2.93:1 and 3:1, respectively.

About 268 cases (76.6%) were SCC (excluding 15 cases of nasopharyngeal carcinoma) (Table 2). The most common site for this histologic type in the oral cavity was the lip [(62.0%), n = 166] followed by the tongue [(9.3%), n = 25] (Table 3).

In this study, OPCs occurred in patients between 1 and 96 years of age. The mean age for OPCs was 57 [standard deviation (SD) = 17.09]. The mean age of OPCs was 60 among males (SD = 16) and 54 in females (SD = 18). Statistically significant differences were found in the risk of OPCs between male and female (P = 0.001); the incidence of OPCs was 1.47 per 100000 populations (Figures 1 and 2).

Table 2. Distribution of oral cavity and pharynx cancers classified by sex and histological types

| Histology | Male | Female | Total |
|--------------------------|------------|-----------|------------|
| | n (%) | n (%) | n (%) |
| SCC | 199 (74.3) | 69 (25.7) | 268 (76.6) |
| Lymphoma | 16 (61.5) | 10 (38.5) | 26 (7.4) |
| Nasopharyngeal carcinoma | 12 (80.0) | 3 (20.0) | 15 (4.3) |
| Mucoepidermoid carcinoma | 7 (53.8) | 6 (46.2) | 13 (3.7) |
| Adenoid cystic carcinoma | 4 (33.3) | 8 (66.7) | 12 (3.4) |
| Adenocarcinoma | 5 (55.6) | 4 (44.4) | 9 (2.6) |
| Acinic cell tumor | 1 (50.0) | 1 (50.0) | 2 (0.6) |
| Malignant melanoma | 0 (0.0) | 1 (100) | 1 (0.3) |

SCC: Squamous cell carcinoma

Table 3. Mean age and sex distribution of oral squamous cell carcinoma (SCC) classified by location

| Site | Mean age (year) | | Male | Female | Total | M/F ratio |
|-------------------|-----------------|--------|-----------|----------|-----------|-----------|
| | Male | Female | n (%) | n (%) | n (%) | |
| Upper lip | 68 | 59 | 4 (2) | 10 (20) | 14 (7) | 0.4 |
| Lower lip | 65 | 57 | 102 (63) | 18 (35) | 120 (56) | 5.7 |
| Lip unspecified | 62 | 64 | 29 (18) | 3 (3) | 32 (15) | 9.6 |
| Lip, total | 65 | 60 | 135 (83) | 31 (61) | 166 (78) | 4.35 |
| Tongue | 63 | 69 | 14 (9) | 11 (22) | 25 (12) | 1.3 |
| Gingiva | 60 | 82 | 4 (3) | 1 (2) | 5 (2) | 4 |
| Floor of mouth | 81 | 58 | 2 (1) | 2 (4) | 4 (2) | 1 |
| Palate | 65 | 33 | 3 (2) | 3 (6) | 6 (3) | 1 |
| Buccal mucosa | 40 | 0 | 1 (1) | 0 (0) | 0 (1) | - |
| Oral, unspecified | 58 | 58 | 3 (2) | 3 (6) | 6 (3) | 1 |
| Total | 62 | 60 | 162 (100) | 51 (100) | 213 (100) | 3.17 |

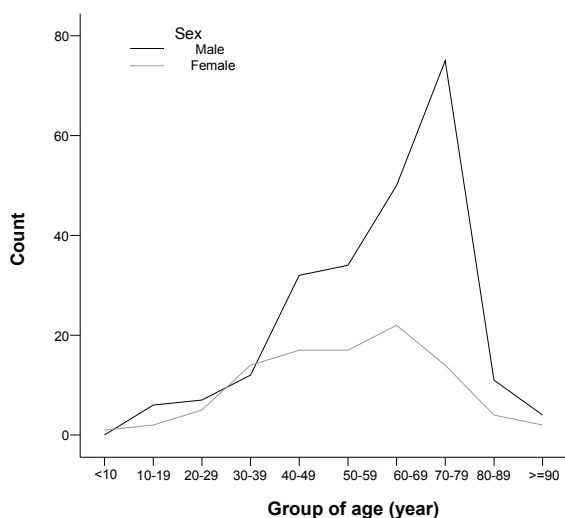


Figure 1. The temporal variation of the annual incidence of pharyngeal and oral cancers among males and females

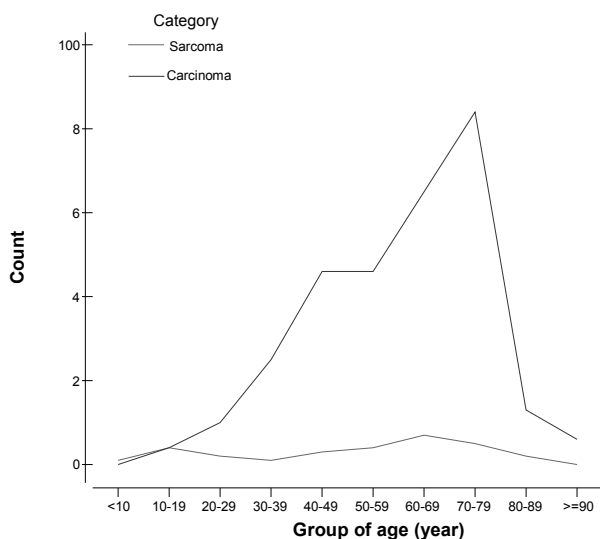


Figure 2. Age distribution of oral and pharyngeal cancers divided by category

It is necessary to highlight OPCs were the 12th common cancers of the body (the 9th in the male and the 13th in females). After age and sex adjustment, the incidence increased in both genders types and location (Figures 3 and 4). The increasing risks affected male population more than the double. The most common type of OPCs was SCC [80.9% (n = 283)]. SCC of the oral cavity and pharynx occurred in patient between 15 and 96 years of age. The mean age of oral and pharyngeal cases was 60.34 (SD = 16); although the age of 20 cases was not recorded. Of the 263 remaining patients, 38 cases (14.5%) were young adults (< 40 years of age) (Table 4). Considering the annual incidence, overall, average annual incidence rate for 1993-2006 was 1.2 cases per 100000 persons.

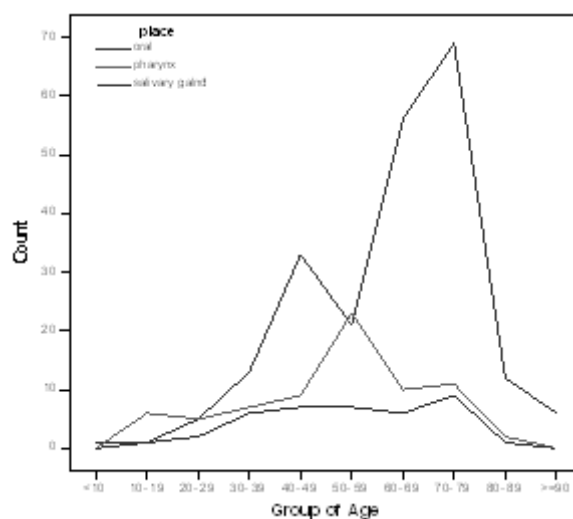


Figure 3. The temporal variation of the annual incidence of pharyngeal and oral cancers divided by place

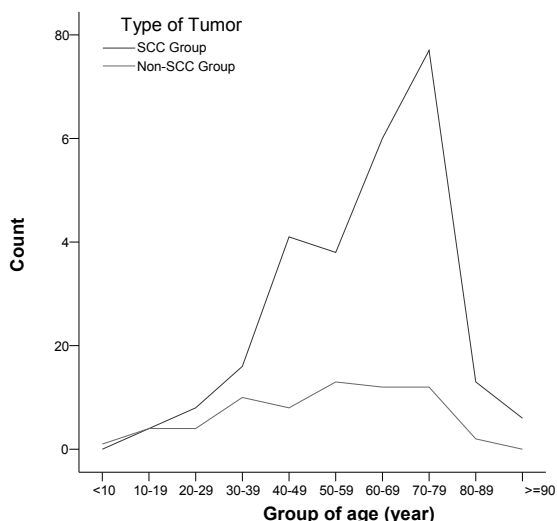


Figure 4. Age distribution of oral and pharyngeal cancers divided by type of tumor

There was no regular pattern in the incidence rate of oral and pharyngeal SCC during this period.

The incidence of oral SCC was 0.9 per 100000 populations. Considering population, the highest incidence rate was recorded in 2000 (1.51 per 100000) and the lowest

incidence rate in the years 1995 and 1997 (0.33 per 100000). In this study, the most common site of oral SCC was a lip (in 166 patients), representing 78.0% of all oral SCC of these. 135 cases (81.32%) were found among males and 31 cases (18.7%) in females. Lower lip was affected in 120 cases (72.3%) and upper lip in 14 cases (8.4%), the exact site of 32 (19.0%) cases of lip cancer was unspecified. It was observed that the upper lip was more frequently affected among women than among men (19.6 vs. 2.4%), while lesions of the lower lip predominated among men (63.0 vs. 35.2%). All new lip cancers diagnosed in the period 1993-2006 were considered that lower lip cancer was almost 8.06 times than the upper lip cancers. The overall male to female ratio was 4.3:1. However, when specific subsite data were analyzed by gender, the male to female ratio was 0.5:1 for the upper lip and 5.7:1 for the lower lip. Considering the age factor, the patient's age at the time of diagnosis ranged from 22 to 96 years.

Table 4. Crude and relative frequency of oropharyngeal from March 1993 to March 2006

| Group of age | Sex | Oral | Pharynx | Salivary gland | Total |
|--------------|--------|--------------|--------------|----------------|-------|
| | | Count [n(%)] | Count [n(%)] | Count [n(%)] | Count |
| < 10 years | Female | 1 (100) | - | - | 1 |
| 10-19 years | Male | 1 (17) | 5 (83) | - | 6 |
| 20-29 years | Female | - | 1 (50) | 1 (50) | 2 |
| | Male | 2 (29) | 4 (57) | 1 (14) | 7 |
| 30-39 years | Female | 3 (60) | 1 (20) | 1 (20) | 5 |
| | Male | 6 (50) | 5 (42) | 1 (8) | 12 |
| 40-49 years | Female | 7 (50) | 2 (14) | 5 (36) | 14 |
| | Male | 23 (72) | 6 (19) | 3 (9) | 32 |
| 50-59 years | Female | 10 (59) | 3 (18) | 4 (24) | 17 |
| | Male | 14 (41) | 16 (47) | 4 (12) | 34 |
| 60-69 years | Female | 7 (41) | 7 (41) | 3 (18) | 17 |
| | Male | 40 (80) | 7 (14) | 3 (6) | 50 |
| 70-79 years | Female | 16 (73) | 3 (14) | 3 (14) | 22 |
| | Male | 61 (81) | 7 (9) | 7 (9) | 75 |
| 80-89 years | Female | 8 (57) | 4 (29) | 2 (14) | 14 |
| | Male | 9 (82) | 1 (9) | 1 (9) | 11 |
| 90-99 years | Female | 3 (75) | 1 (25) | - | 4 |
| | Male | 4 (100) | - | - | 4 |
| Unknown | Female | 2 (100) | - | - | 2 |
| | Male | 13 (81) | 2 (13) | 1 (6) | 16 |
| Total | Female | 3 (60) | 2 (40) | - | 5 |
| | Male | 173 (70) | 53 (21) | 21 (8) | 247 |
| | Female | 60 (58) | 24 (23) | 19 (18) | 103 |

SCC of the tongue was next to that of the lip. 25 patients suffered from tongue SCC represented 7.7% of all oral SCC cases. The male to female ratio was 1.25:1 (Table 5).

Table 5. Distribution of location of oropharyngeal cancers (OPCs) classified by sex

| Site | Male | Female |
|----------------------------------|------|--------|
| Upper lip | 5 | 10 |
| Lower lip | 103 | 18 |
| Lip unspecified | 29 | 3 |
| Tongue | 14 | 11 |
| Gum | 5 | 2 |
| Floor of the mouth | 2 | 3 |
| Palate | 7 | 6 |
| Buccal mucosa and vestibule | 2 | - |
| Parotid gland | 13 | 9 |
| Submandibular gland | 5 | 1 |
| Sublingual gland | - | 3 |
| Unspecified major salivary gland | 3 | 4 |
| Tonsil | 9 | 3 |
| Oropharynx | 1 | 3 |
| Nasopharynx | 23 | 8 |
| Piriform sinus | 5 | 1 |
| Hypopharynx | 9 | 6 |
| Oral unspecified | 4 | 5 |
| Pharynx unspecified | 5 | 5 |
| Total | 247 | 103 |

In this study, cancer of gingiva represented 2.0% of all oral cancers. The male to female ratio was 2.5:1. The total number of OPC and oral SCC in the other sites show on tables 3 and 5, respectively.

Discussion

In this study, skin cancer was the most common form (16.7%) of all cancers. The male to female ratio was 1.48:1. As a comparison, an epidemiological study in Kerman, Iran, showed that skin cancer had been the most common form (19.1%) of all cases.¹⁶ In another study in Tehran, Iran, skin cancer was the most common form, 23.0% of all cases. The male to female ratio was 2:1.¹⁷

Other geographic areas with high incidences are eastern, Western and Southern Europe, Australia, New Zealand, and Malaysia.⁹ In this study, the incidence of oral and pharyngeal cancers in Kermanshah province was 1.47/100000. The annual incidence of oral and

pharyngeal cancers showed a little change during the period of study.

The highest incidence was in the year 2000 (2.22/100000, M = 1.51, F = 0.71) and the lowest incidence in the year 1995 (0.56/100000, M = 0.45, F = 0.11). Overall, the incidence rate was low compared to other countries in the world, such as France (12.4 per 100000),¹⁸ Finland (M = 12.5, F = 3.9 per 100000),¹⁹ United States (8.3 per 100000),³ and Australian (Men = 17.5/100000).²⁰

Among eastern European countries, the highest combined rates among males were observed in Slovakia (19.7/100000) and Slovenia (18.9/100000).¹⁸ Asia showed the broadest range in incidence rates of OPCs compared to this study. Some countries, such as India (20 per 100000) and Philippines (7.1 per 100000), were the highest recorded countries.¹⁸ In Iran, the incidence of OPCs was found to be 1.13/100000 in Shiraz, Iran,²¹ 1.19/100000 in Kerman.²²

In Iran, 9% of the patients had a history of opium abuse, but more than half of the patients did not have any recognized risk factors. The incidence and stage of cancer had a significant relationship with cigarette smoking ($P = 0.013$).²³ The highest incidence is observed in India and Philippines, with a clear predominance of the oral cavity. Therein, the habit of chewing betel quid is equally common among the two sexes. In India, Bengaluru, the incidence rate of oral cancer among women exceeded that of males.¹⁸ Similar to other studies, this series showed men preponderance with male to female ratio of 2.39:1. In this study, there was male predominance in some age groups (60-69, 70-79 years). In 30-39 age groups, females were more predominated. As with malignant tumors in other parts of the body, OPC is a disease that is more common with advancing age, usually showing a sharply rising incidence after the age of 40 or 50.²⁴

This study showed that OPC was more common in the age groups of 60-69 and 70-79. The mean age of oral and pharyngeal cases in Kermanshah province was 57

(SD = 17.09). The mean age of patients suffering from OPCs in other studies was as follows: Iran (Kerman 55.36, Fars 55, and Khuzestan province 55 ± 16 years),²⁵ Basque country (60.5 years),²⁶ and Jordan (62.5 years).²⁴

The finding also showed the most common OPC was SCC (80%). This finding was in agreement with the report of the amount of this cancer in South America, Europe, Asia and especially in Iran.^{2,3,4,7,13,20-23,25,27,28} Other cancers of the oral and pharyngeal were as follows: Malignant salivary gland tumors (10.6%), lymphoma (7.4%), sarcoma (1.1%), and malignant melanoma (0.3%). These findings are in agreement with other studies. Elter et al.²⁹ analyzed a group of 7422 North Carolina patients with OPCs and observed the vast majority (93.0%) of cases were SCC and salivary gland tumor, including adenocarcinomas, accounted for 6.2% of all oral cancers. Canto and Devesa³ reviewed, 65130 cases of oral and pharyngeal cancers in the United States and found that the majority (83.0%) were SCC. Adenocarcinomas accounted for 9% of all oral and pharyngeal cancers; they occurred mainly in the major salivary glands. In an epidemiological study of oral and pharyngeal cancers in Kerman, SCC was the most frequent histological type (78.9%), followed by malignant salivary gland tumors (4.9%), lymphoma (3.4%), melanoma (3.4%), and sarcoma (3.0%).²⁷ Another study conducted in Iran showed that 97% of all types of oral cancers were SCC in Fars²¹ and this percent was about 75.0% in Khuzestan,²⁵ which is similar to the present results.

SCCs, accounting for an average of 70.0%, were the most common among all types of oral cancer and the epidemiological pattern of oral cancer in Iran is somewhat similar to that of other countries.¹³ Lip cancer has a variable incidence worldwide, with the highest rates reported in the south of Australia and in some regions of Canada and Spain.³⁰ In North America, the incidence recorded in the USA for men varies from 0.4 to 4.4 per 100000 inhabitants per year,

whereas in the Newfoundland region of Canada it ranges from 12.7 to 27.1 cases per 100000. The literature reviews also point out that the vast majority of lip cancer cases occur in the lower lip.³¹

In this study, it was found that lips were the most common site of OPCs with a male to female ratio of 4.3:1. Lips SCC occurred in 166 patients, representing 78% of all SCCs. This finding was comparable to other reports from UK, India, Fars, Kerman, and Khuzestan province in Iran.^{13,23,22,25,27,28,32} In this study, lower lip was affected in 120 cases (72%) and upper lip in 14 cases (9%). The exact sites of 32 (19%) cases of lip cancer were unspecified. Likewise, it was observed that upper lip was more frequently affected among women than among men (19.6 vs. 2.4%). These results are comparable to other retrospective study of cancer of the lip in the Mexico where lower lip was mostly common affected site in both sexes, but the upper lip was affected more frequently among women than among men (50.0 vs. 25.8%).³¹

In another study conducted in Iran, it was found that lower lip was the most frequently involved site cases 90%.^{21,27} Compared to SCC of the oral cavity, lip cancer has a distinct analytical epidemiology. Potential etiological agents or carcinogens that might contribute to the onset of lip cancer may be independent or multifactorial and require a number of exposures before manifestation.³³ Since particularly the lower lip is involved in lip cancer, which receives considerably more direct sunlight than the upper lip, this observation has also been used as support for the actinic radiation-lip cancer association. The markedly lower incidence of lower lip cancer among women has been attributed to the more frequent use of protective sun screening agents, such as lipstick and shading devices and less outdoor activity.^{24,33}

Since lip cancer is the most common in fair-skinned men with an outdoor employment and rural residence, occupational factor has been linked to the elevated risk of lip cancer. The higher risk of

developing lip cancer in rural compared to urban areas holds true for both sexes. Fishing, farming, forestry, agriculture, works involving exposure to creosote and work in greenhouses are strongly associated with lip cancer as compared to typical indoor occupations and urban dwelling. Despite the overwhelming number of data, the definitive pathogenic pathway remains unclear.³³ The cases of the high incidence rate of lower lip cancer in Kermanshah are probably from outdoor exposure because most people in the province are farmers.

The tongue has been the most common site of oral SCC in USA, Australia, Brazil, France, UK and Denmark.^{24,34} Tongue cancer among males is most common in India (9.4:100000 in Bombay), Brazil (7.4:100000 in Sao Paulo), and France (7.9:100000 in Doubs) and in females (although rates are much lower) the rate in Bombay (3.4:100000), and among Indians in Singapore (3.3:100000) are considerably higher than those reported from cancer registries in other countries.³⁵ In Iran, studies showed that OSCC was the most common malignancy in the tongue and buccal mucosa.^{23,28}

In our study, the tongue was the second most common site affected. The male to female ratio was 1.3:1 with a mean age of 65 years). Tongue SCC occurred in 25 patients, representing 12% of all oral SCC cases. This figure is low, compared to other countries, such as USA, Brazil, France, UK, and Denmark.^{24,34} Of all 67 cases of oropharyngeal non-squamous cell malignant tumor (excluding metastatic tumors), giving an

incidence of 2.7 per million populations.

The other most common tumors cancer was salivary gland tumor (n = 36), followed by lymphoma (n = 26), sarcoma (n = 4) and melanoma (n = 1). These findings are in accordance with those reported by others.^{22,36} There were 36 new cases of salivary gland tumor in this study population resulted in an incidence rate of 1.9 per million populations. Mucoepidermoid carcinoma was the most common malignant tumor of salivary glands in our series accounted for 36.1% of cases. Palate and parotid were the most common sites of involvement. This finding is in agreement with some other reports.^{37,38} There were 26 cases of oral lymphoma in our series accounted for 7.4 of all oral and pharyngeal cancers. This is higher compared to the figure of 3.5-4% reported from other countries.^{24,39}

Conclusions

In summary, the incidence risk OPCs in the people of Kermanshah province are similar to the other reports from Iran. However, the study showed that the frequency of OPCs among males (9th most common cancer) is higher compared to other investigation from other regions of Iran.

Conflict of Interests

Authors have no conflict of interest.

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Quality appraisal of published qualitative dental, medical and health researches in Iranian Persian language journals

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Original Article

Abstract

BACKGROUND AND AIM: This study aimed to determine the rate of published qualitative research in the field of public health including dental researches in Iran and to appraise their quality.

METHODS: A total of 165 articles which published in 170 Iranian Medical Journals between years 2000 and 2014 were found eligible to the study. 48 papers were selected randomly. The papers were appraised by two calibrated reviewer using the Critical Appraisal Skills Programme (CASP) appraisal framework for qualitative research.

RESULTS: Only 2 studies (about 4%) were on dental topics. About 82% (38-48) studies had sufficient reporting regarding aims, study design, recruitment and data collection, data analysis, finding and implication of research. Only 12 articles (25%) had an adequate discussion of the study limitations. Overall, the assessment showed that 27 papers (about 56%) of studies were well conducted.

CONCLUSION: Qualitative methods are underutilized on dentistry topics, and the quality of qualitative research on health topics in medical journals of Iran is mediocre.

KEYWORDS: Qualitative Research; Critical Appraisal; Oral Health; Iran

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Qualitative researches provide appropriate understanding of people's experiences, perspectives and histories in the context of their personal circumstances or settings, and answering "what," "how," and "why" questions.¹

The popularity of qualitative methodologies have increased over the past decades,^{2,3} especially it is now widespread within health services research programs.⁴ A lot of examples of qualitative research can be identified within the health research field.⁴⁻⁶ The importance of qualitative research

should not be discounted^{7,8} because it has a significant place in public health for problem definition, hypothesis generation, and evaluation. The qualitative studies that are poorly designed or have inadequate reporting can lead to inappropriate application of qualitative research in decision-making, health care, health policy, and future research.⁹

However, qualitative researches have been criticized because their procedures and processes are not transparent enough.² Reading critically and analyzing the quality of articles are skills that help to design valid

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and reliable research studies.¹⁰ Critical appraisal skills of research literature are essential for all members of the health-care team, to develop models of evidence-based practice that focus on optimal outcomes. Improvement of the quality and safety of health care depends on the measurement of these outcomes, so there is an extra need for clinicians to have a comprehension of research methodologies so that they can design and implement effective quality assurance programs using valid and reliable methods^{10,11} as well as quality appraisal is an important issue in systematic reviews.¹² There is considerable debate over using which quality criteria are appropriate to assess qualitative studies. Assessment of the quality in qualitative research can be done using the same large concepts of validity (or trustworthiness) used for quantitative research, but these need to be put in a different contextual framework according the aims of qualitative research.¹³ Consequently, skills of critical appraisal are included in formal postgraduate research training.¹⁰

There are no mechanical or “easy” solutions to restrict the likelihood of existing errors in qualitative research. However, there are some ways of improving validity; each of these ways requires the exercise of judgment on the parts related to researcher and reader.¹⁴

Considerable disagreement about the characteristics of good quality qualitative research caused producing guidelines such as checklists.¹⁵ By using these guidelines, the review of qualitative research can be done systematically and scientifically, so the quality of analyzing and reporting qualitative evaluation findings of research undertaken will be improved.^{5,16} Another benefit of guidelines is the contribution of them to the ongoing process of trying to achieve a consensus on what supposes as quality in qualitative research.³

This study aimed to determine the rate of published qualitative dental, medical and health researches in Iranian Persian language journals and appraise their quality.

Methods

A list of scientific databases which included Iranmedex, SID database, Medilab, Magiran, and Google search engine in Persian and English for qualitative studies in Iran was prepared. About 170 Persian-language medical and dental journals have been indexed between 2000 and 2014 in these databases. All articles with qualitative research keyword were extracted. 165 full text articles were available. All these articles were summarized by two experts who were trained and calibrated (90% agreement) in qualitative research methods to choose the articles that have been done by qualitative method certainly. The readers had consensus about the qualitative method of all available full text articles. Then, according to 170 journals and 165 qualitative papers, a pilot study was conducted through appraising 10 articles to know how many papers are enough to reach the aim of the study. It was concluded that 48 articles ($\alpha = 5\%$ and $1-\beta = 85\%$) are the right sample size, which they were selected randomly for evaluation by numbering through a blind selection process. A flow diagram summarizing this process is shown in figure 1.

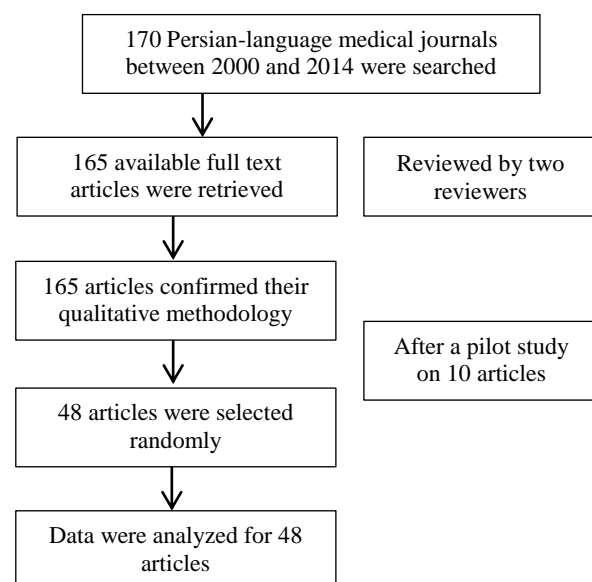


Figure 1. Flow chart of the study

Critical appraisal tool

There is considerable variability in intent,

components, construction, and psychometric characteristics of published critical appraisal tools to report research. There is no “gold standard” critical appraisal tool for any study design, nor is there any widely accepted generic tool that can be applied equally well across study types. No tool was specific to allied health research requirements. Thus, interpretation of the critical appraisal of research reports currently needs to be considered in light of the properties and intent of the critical appraisal tool chosen for the task¹⁷ but numbers of appraisal frameworks are available for the assessment of qualitative research and easy-to-use, study design-specific checklists to guide the reader through a research article.^{1,17} We used Appendix H Methodology checklist designed for qualitative studies. This qualitative checklist is planned based on accepted principles of implementing qualitative research and that may affect its quality. Using this qualitative checklist is appropriate for people with basic understanding of qualitative methodology.¹⁸

The criteria used in this checklist are adapted from: The Qualitative Research and

Health Working Group, Liverpool School of Tropical Medicine and National Critical Appraisal Skills Programme (CASP) Collaboration for Qualitative Methodologies, CASP 10 questions to help you make sense of qualitative research. The checklist contains 13 questions grouped into six themes include aims of the research, study design, recruitment and data collection, data analysis, findings/interpretations, implementation of research and then overall assessment of the study (Table 1) and it also has provided hints for completing.¹⁸ Rigor, credibility, and relevance have been considered in the framework. Initial questions are about clear statement of the study aims and the appropriateness of a qualitative approach.

Two qualitative methodologies trained researcher were selected to appraise each article independently. Kappa (90%) was calculated for evaluating inter-rater reliability of the researcher. Five studies were selected randomly by both researcher and appraise 2 weeks later to test the reliability of their work, and there was 85% agreement for intra-examiner by test-retest evaluation.

Table 1. Frequency of articles that met the H Methodology criteria

| Criteria | n (%) |
|--|---------------|
| Aims of the research | |
| Are the aims and objectives of the research clearly stated? | 48 (100) |
| Is a qualitative approach appropriate? | 48 (100) |
| Study design | |
| Is (are) the research question(s) clearly defined and focused? | 38 (82) |
| Are the methods used appropriate to the research question(s)? | 38 (82) |
| Recruitment and data collection | |
| Is the recruitment or sampling strategy appropriate to the aims of the research? | 41 (87) |
| Are methods of data collection adequate to answer the research question? | 44 (93) |
| Are the roles of researchers clearly described? | 29 (62) |
| Have ethical issues been addressed adequately? | 14 (31) |
| Data analysis | |
| Is the data analysis sufficiently rigorous? | 44 (93) |
| Findings/interpretation | |
| Are the findings internally coherent, credible (valid)? | 47 (98) |
| Are the findings relevant? | 47 (98) |
| Implications of research | |
| Are the implications of the study clearly reported? | 44 (93) |
| Is there adequate discussion of the study limitations? | 12 (25) |
| Overall assessment of the study | + ++ + ++ |
| How well was the study conducted? Code ++, + or – | 21 27 44% 56% |

By an administrator, the journal title, date and authors' names were masked and each article was identified by a unique code. The researcher appraised each article independently and then discussed to reach a consensus. If there was disagreement between them about some qualitative items, consultation with a third expert researcher was implemented.

For overall, assessment of the study according to the notes of the framework, if all or most of the criteria have been fulfilled or where they have not been fulfilled the conclusions of the study or review were thought very unlikely to alter, we assigned ++ to the article. If some of the criteria have been fulfilled or those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions, we assigned + to the article; if few or no criteria fulfilled, the conclusions of the study are thought likely or very likely to alter the assigned code was negative (-).

Results

Out of 48 papers, 12 (25%) were published in medical journals, 34 (70%) papers in nursing and health journals and only 2 studies (about 4%) were published in dental journals (Figure 2).

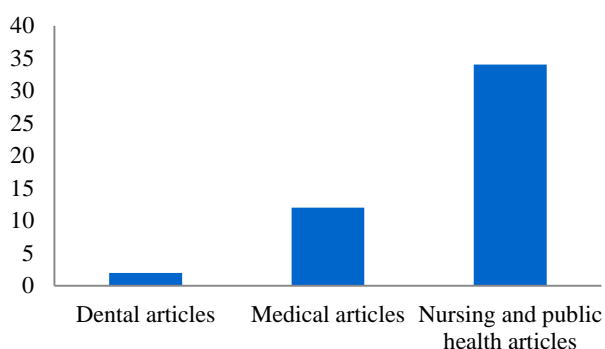


Figure 2. Frequency of qualitative papers in different subjects

Table 1 shows the frequency of papers that met each criterion of this qualitative checklist.

Aims of the research

In all 48 papers (100%) appraised in the

study, the goals of the research and the importance of these goals were clearly stated, as well as the qualitative approach was appropriate.

Study design

The study design was addressed in 38 (82%) papers. In these articles, the research question(s) clearly was defined and focused, and also the methods used were appropriate to the research question(s). While in rest of them study design items have not been addressed.

Recruitment and data collection

More than 62% have met recruitment and data collection items, for example, recruitment or sampling strategy was appropriate to the aims of the research. Methods of data collection were adequate to answer the research question and the roles of researcher were clearly described, but only in 14 (31%) articles ethical issues have been addressed adequately.

In large number of them, data analysis was sufficiently rigorous (93%) and problems were not apparent in analysis reports. In 7% of papers, there were problems with methodological rigor concerned a lack of detail in reporting that enables readers to see how the findings were derived, for example, some of them did not discuss items such as data saturation.

Findings/interpretation

Almost all qualitative researchers (98%) have reported the findings in a coherent and credible way and the findings were relevant and only 2% of them did not have enough discuss to judge about the relevance of the findings.

Implications of research

About 44 (93%) articles had clear reports about the implication of the study, for example the findings were placed in the local context (geographical, cultural, and socioeconomics). There discussed findings in wider context (in relation to other studies on the same topics) but only 12 (25%) had

adequate discussion on the study limitations because the weaknesses of the study design were discussed, and there was a discussion of new areas where research is needed.

According to the notes of the framework overall assessment showed that approximately half of papers (about 56%) of studies were well conducted and fewer than half of articles have not enough reports of the research.

Discussion

As we can see in the results of this appraisal of qualitative research in medical, health and dental studies in Iran, more than half of qualitative researches had met H Methodology checklist criteria.

Application of qualitative study is increasing in the field of medicine, public, and oral health; therefore, some problems may decrease the quality of this type of research. For example, some researchers may not have adequate grounding in theory or practice of qualitative study or they may not have enough experience and training, some of them are unwilling to request the assistance from whom that are expert in qualitative methodology. Moreover, the time and costs for doing a high-quality qualitative study is important.¹⁹ In addition, there is a lack of consensus between qualitative research approaches about how to assure quality of research. This reflects past and ongoing debates among qualitative researchers about how to define quality, and even the nature of qualitative research itself.²⁰ Consumers of research (researchers, administrators, educators, and clinicians) frequently use standard critical appraisal tools to evaluate the quality of published research reports. However, there is no consensus regarding the most appropriate critical appraisal tool for allied health research.¹⁷ However, there are frameworks and checklists equip reviewers to assess the quality of qualitative researches.¹⁵

Qualitative researchers often neglect a total description of their qualitative research

techniques and procedures. Providing detailed, clear and transparent accounts of the processes and steps used in the study method can enhance the integrity of the published qualitative studies. Transparency is essential if qualitative methodologies are to be developed further and to maintain methodological rigor.²

As we can see in the results of the study, only two articles (4%) were published in dental journals, so contribution of the qualitative study in dental journals was so low. Why the rate of qualitative study in the field of dentistry In Iran is too low? What is necessary to be done regarding this issue (low rate of qualitative methods in dental studies) in Iran. A hypothetical reason can be related to inadequate education of qualitative methods in graduate or postgraduate course of students. Of course, there may be more reasons that can be revealed with research.

About 25% of these qualitative studies were related to different topics of medicine and health that were published in medical journals, whereas it is worth mentioning that the majority of papers (70%) were published in nursing and health journals. As well as the majority of authors were graduates of nursing and health, therefore these professionals are dealing with qualitative study more than other professionals of medicine and health, as some articles addressed this issue.²¹

According to the idea of both researchers in this study (if there was no consensus between them we request the opinion of the third researcher) in 100% of articles the objectives of the research were addressed and qualitative approach was appropriate for the objectives. It means that based on the hints of the checklist; in all of articles, the goals of the research were stated clearly and the researcher mentioned why these goals are important. Appropriateness of qualitative approach of all studies was acceptable because the research methodology sought to understand or illuminate the subjective experiences or views of research participant

and what is happening and the reasons why observed situation or outcomes occurred.

The research approach influences its design and the research design helps reader about the implementation of the research approach. In 82% of studies, the research design was appropriate to address the aims of the study as the question(s) was relevant to the aim of the study and structured in a way that sought to answer all the objectives of the study. Some of researchers had not justified the research design (for example they did not discuss how they decided to use which methods).

Despite enough funding and resources for a project, the process of a study may be compromised. For example, the sample size in a study may be insufficient in relation to the aims of the study, a situation observed in some of the papers appraised in this study. By a too small size sample, findings cannot adequately represent all the dimensions of a problem or the full range of views held by members of the target population, limiting conceptual generalization.²²

In any research project, recruitment forms are an important part of the research. In qualitative researches the researcher often wants to collect the thoughts or opinions of a specific group of people who have experienced a specific phenomenon. Therefore for qualitative researchers, it is more important to ensure that participants have experienced the phenomenon so randomly selecting people who may not be able to answer the questions may not be a correct approach.²³ There should be an explanation of the selection of the sampling strategy (e.g., purposive sampling, theoretical sampling, extreme case sampling, snowball sampling) and how it is appropriate to the aims of the research and methodology selected (e.g., grounded theory, ethnography, phenomenology).

The researcher should illustrate with justification about sampling methodology, why the selected participants were the most appropriate to access to the type of knowledge sought, why some people were

not selected to take part.² The most common methods of data collection within qualitative research are interview, questionnaire or observation. These different methods have been designed to obtain slightly different data. Therefore, the method of data collection should address the research issue/question.²³ In our study, more than 87% of articles have met recruitment and data collection items and sampling strategy was appropriate to the aims of the research.

Only in 14 articles (31%) ethical issues have been addressed adequately, whereas Ethical issues are important and should be considered at every step of the research process. This is not just about obtaining "ethical approval" for a study but also ensuring the rights of participants are not violated. When reporting qualitative research, participants' anonymity and confidentiality must not be breached ethically.²³ According to our results, ethical issues were not considered adequately in Iran or maybe reporting of them is not appropriate, because there were not sufficient details of how the research was explained to the participants. Consent procedure used and how consent was obtained were not explained as well as there were not clear notes about confidentiality and privacy assurance in the study. Some of them did not report seeking approval from the ethics committee.

Reporting of data analysis was clear in more than 90% of articles and the findings clearly displayed. Most of researchers organized qualitative data into common groups/topics (themes) and reported with examples (quotes) from each them. Some of researchers have critically examined their own role, potential bias and influence during analysis and selection of data for presentation.

Through almost all qualitative studies appraised in this study the findings were derived from analysis of collected data, and there was adequate discussion of the findings, the findings were relevant to the study aims/objectives/questions, but these items had not been met in one article.

Because some limitation in a study process may affect the quality of the research and consequently the results of that, reports of limitations are necessary for any qualitative study. However, this issue was neglected in the most of the qualitative researches in Iran.

There were only few studies in the field of dentistry in the literature to compare their results to other studies.⁵ Because oral health has an important subjective aspect, therefore qualitative research adjacent to clinical surveys is recommended.

Conclusion

The qualitative methods are underutilized on dentistry topics in Iran and the most

frequency of qualitative methods were presented in nursing and health journals. The quality of more than half of qualitative research in dental, medical and health journals of Iran is good but less than half of them had not met some important items of Appendix H Methodology checklist for the qualitative study.

Conflict of Interests

Authors have no conflict of interest.

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The use of re-surgery in the treatment of teeth with severe sensitivity in the buccal mucous membrane: A case report with 75 months follow-up

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Case Report

Abstract

BACKGROUND AND AIM: A periapical endodontic surgery is an alternative treatment when teeth are not responding to conventional treatment and endodontic re-treatment.

CASE REPORT: The following case report presents a clinical case of maxillary right and left central incisors with unsatisfying endodontic surgery and severe sensitivity in the buccal mucous membrane. Radiographic examination revealed several fragments of amalgam as root-end filling material, surrounded by a periapical radiolucent area. The chosen treatment plan was to perform endodontic retreatment. Symptoms persisted in spite of the gutta-percha removal and calcium hydroxide intracanal medication. Hence, periradicular re-surgery was performed. However, deep tissue penetrated amalgam particles were difficult to explore and could not be removed completely. The root-end filling was done with mineral trioxide aggregate (MTA), and the lesion was subjected to histologic analyses. The treatment was successful due to the absence of painful symptoms and due to periapical bone repair after 75 months follow-up.

CONCLUSION: MTA can be used successfully in the situations with failed previous periradicular surgery with amalgam.

KEYWORDS: Amalgam; Apicectomy; Mineral Trioxide Aggregate; Periapical Re-surgery; Root End Filling Material

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The goal of endodontic treatments is to remove bacteria and their products from root canal system and to seal the apical foramen.¹ Periradicular surgery is a treatment for teeth with previous unsuccessful endodontic therapy, when non-surgical re-treatment is not practical.¹⁻³ Successful outcomes of periapical surgeries vary from 25.0 to 99.0%.⁴ Among the many factors contributing to the success of endodontic surgery, the obturation

material plays a critical role. The ideal root-end filling material should possess properties such as biocompatibility, ability to set in a wet environment, adequate sealing ability, antimicrobial activity, and ability to induce bone repair. Several root-end filling materials are available including amalgam, zinc oxide-eugenol based cement, glass ionomer, mineral trioxide aggregate (MTA), and biodentine.^{5,6}

MTA has shown many favorable

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properties including a good sealing ability and biocompatibility.^{7,8} However, there are several drawbacks to its use such as its difficult handling properties and its long setting time which explains why many clinicians favor amalgam.^{3,9} Many clinicians have encountered the problem of incomplete healing of the periapical tissues around some of the teeth that have been treated with amalgam as a root-end filling material. Healing is often retarded by persistent leakage from the root canal.¹⁰

In a study using alternative root-end filling materials, the success rate with intermediate restorative material was 74% compared with 57% when amalgam was used.¹¹ In a systematic review, Peterson and Gutmann¹² reported that healing associated with a surgical retreatment was approximately 36%. In the study by Gagliani et al.,¹³ root-end re-surgery had a worse radiological outcome compared with primary root surgery. However, most of the literature available on repeated surgical procedures is old and includes data from procedures using materials and techniques that are no longer suggested today. The aim of this study is to report a clinical case of surgical retreatment of teeth with failed previous apicoectomy as an alternative to extraction.

Case Report

A 35-year-old female in good health (American Society of Anaesthesiologists' Classification 1) admitted to an endodontic office complaining of severe sensitivity in the buccal mucous associated with the maxillary central incisors. The teeth were also tender on percussion. No periodontal pocket was identified, and the pattern of mobility was normal. Radiographic examination revealed a slightly porous root canal obturation. Several fragments of the root-end filling material, surrounded by a periapical radiolucent area were visible (Figure 1).

Based on the patient's reports, the first endodontic treatment had been performed nearly 21 years before her admission. About 2

years later, a sinus tract appeared on the buccal mucosa and apical surgery was performed by a general dental practitioner. After 13 years, strong pain and tenderness were associated with these teeth.



Figure 1. Periapical view before re-surgery

The clinician explained different treatment options such as implants and other dental prosthetics to the patient. However, the patient preferred to try to save her natural teeth. Hence, the recommendation was to perform a second endodontic re-treatment aimed at improving the quality of the biomechanical preparation, followed by complementary antiseptics with calcium hydroxide root canal dressing and obturation. If the periapical lesion persisted, a further periapical surgery would be performed. The patient agreed with the treatment plan and signed an informed consent form.

During retreatment, Hedstrom files #30 and 35 (Mani, Japan) and chloroform (Kimia Co., Tehran, Iran) were used to remove the gutta-percha until the root-end filling material had been reached. Root canals were irrigated with 5.2% sodium hypochlorite solution. The smear layer was removed by irrigation with a 17.0% ethylenediaminetetraacetic acid (Asia Chimi-Teb, Tehran, Iran) solution, followed by further irrigation with sodium hypochlorite. Calcium hydroxide (Golchai, Iran) and saline solution were put in place for

10 days, during which no healing of the symptoms occurred. The obturation of the root canal was, therefore, performed, and the periapical re-surgery was scheduled for the next dentist's visit. Gutta-percha (Ariadent, Iran) and AH26 sealer (Dentsply, Konstanz, Germany) were used with the lateral condensation technique, and the teeth were restored with composite resin.

After endodontic re-treatment, the patient still suffered from sensitivity in the buccal mucous. She then was referred to Endodontic Department of Kerman Dental School (Iran) for periradicular surgery. Immediately before surgery, the teeth and mucosa were washed with 0.2% chlorhexidine gluconate followed by a local anesthetic injection of 2% lidocaine with 1:100000 epinephrine (Darou Pakhsh Pharmaceutical Co., Iran). After reflecting a triangular flap, it was possible to view the buccal plate destruction of the affected tooth; this allowed easy location of the apex. An osteotomy was performed (Figure 2). Periapical curettage was then conducted to remove granulation tissue as well as amalgam particles. However, deep tissue penetrated particles were difficult to explore and could not be removed completely. Resection of approximately 3 mm of the apical part of the root was performed perpendicular to the root axis with magnification and illumination using an operating microscope, $\times 4$ (Carl Zeiss, Germany). The retro preparation was performed ultrasonically (NSK Varios 750, Nakanishi, Tochigi, Japan) to a depth of 3-4 mm and the root-end filling was done with White Pro Root MTA (Dentsply Tulsa Dental). A radiograph was taken to check the root-end filling level, its adaptation to the root canal walls, and its density. Finally, the flap was repositioned and the wound was sutured with 5.0 black silk.

The patient was given post-operative instruction, and antibiotics and analgesics were prescribed. A review appointment was scheduled after 1 week for suture removal and soft tissue healing assessment. The

patient was told to return for the first follow-up visit after 6 months, but she did not, because of distance from the medical center.



Figure 2. Destruction of buccal plate

The specimen with a total size of $0.5 \text{ cm}^2 \times 0.5 \text{ cm}^2 \times 0.5 \text{ cm}^2$ was sent to the Department of Oral Pathology in formalin solution. Paraffin-embedded blocks of tissue were prepared. Sections were cut, stained with hematoxylin and eosin and were examined with light microscopy. Amalgam was found in two forms in microscopic examination, as numerous fine black granules scattered within the connective tissue associated with a mixture of lymphocytes and plasma cells (Figure 3).

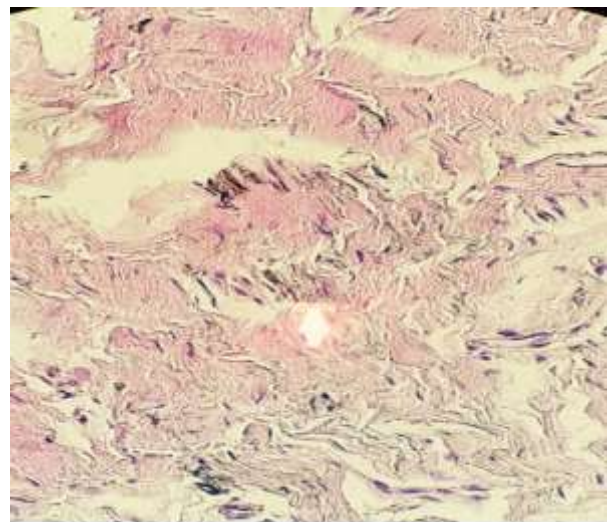


Figure 3. Microscopic examination; white arrow shows numerous fine black granules scattered within the connective tissue (hematoxylin-eosin, original magnification $\times 400$)

The amalgam particles tend to stain encircling vascular channels (white arrows in Figure 4). Large dark solid fragments of amalgam were also found in a space which was surrounded by dense fibrous connective tissue (Figure 5-white arrows).

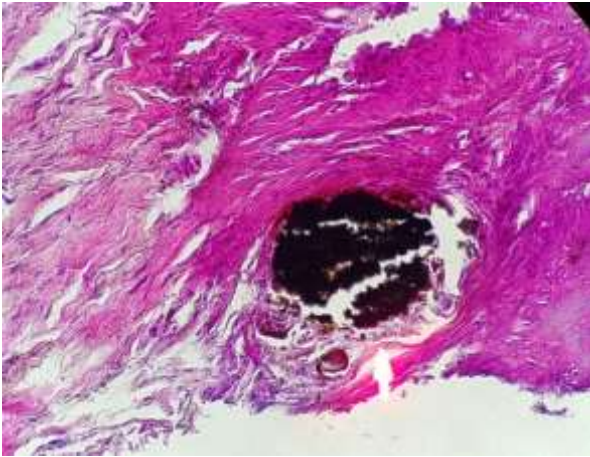


Figure 5. Microscopic examination; white arrow shows large solid fragments of amalgam in a space surrounded by dense fibrous connective tissue (hematoxylin-eosin, original magnification $\times 400$)



Figure 6. Periapical radiograph 75 months after treatment

After 75 months from the surgery, the patient returned to Endodontic Department of Kerman Dental School for the treatment of another tooth. A clinical examination of central incisors (including percussion and palpation) showed no pain, no periodontal defect, and no gingival discoloration. The restoration was intact with no signs of compromise in integrity or marginal adaptation. Radiographic examination

showed complete healing of the previous periapical radiolucency (Figure 6). The case was then considered to be completely healed. However, the patient was advised to attend for future follow-ups.

Discussion

Successful outcomes of periapical surgeries vary from 25 to 99%.⁴ This percentage can be affected by several variables such as marginal microleakage and biocompatibility of the material.^{4,14,15} However, there is little information available regarding the outcome of surgical operations performed on teeth that had previously undergone periapical surgery.

Amalgam has been and still is to some extent a widely used material.⁹ The studies have shown that the outcome of apicectomy with amalgam on the efficacy of the procedure on anterior and premolar teeth is only 50-70%.¹⁶⁻¹⁸ It seems that disadvantages of amalgam, including creep or electrochemical corrosion, should also be considered as reasons for failures. Gaps of up to 150 μm between the root-end cavity margin and amalgam are reported in the literature.¹⁹ Moreover, marginal adaptation and biocompatibility of amalgam have been shown to be considerable negative points.²⁰ In cases of poor endodontic re-treatment associated with periapical surgery, root-end filling with amalgam may influence the success of endodontic re-treatment.²¹

More recently, MTA has been suggested as having many of the properties of the ideal root-end filling material such as being capable of hermetically seal the apical portion of the root canal and promotes periapical tissue healing due to its low toxicity.^{22,23} MTA is able to induce cementum formation and make a biologic seal. It has been suggested that MTA stimulates osteo- and odontogenic cell proliferation via intra- and extra-cellular Ca²⁺- and Erk-dependent pathways and that MTA promotes cell survival via the PI3K/Akt signaling pathway.²² In addition, the sealing properties of MTA are not affected by moisture during treatment.²⁴

In this case, we were not able to remove all amalgam particles, despite our use of illumination and magnification. However, complete healing could be seen. We believe that in the present case, poor endodontic treatment associated with microleakage of the root-end filling material contributed to bacterial colonization of this segment. Orthograde endodontic retreatment along with the application of calcium hydroxide, making a good apical seal via periapical repeated surgery and proper coronal filling and restoration were the most important factors of successful treatment. Molven et al.²⁵ also found that the efficacy of the apical seal was the most important factor for a successful apicoectomy.

From the endodontic perspective, retreatment should always be considered before surgical treatment since there is evidence of greater healing rate in cases where re-treatment was performed before apical surgery.²⁶ Hence, we managed the root canal system non-surgically before the surgery.

Long-term follow-up of endodontic treatment is important. Healing tends to occur more quickly with surgical compared with non-surgical retreatment.²⁷ The literature has implied 4 years is a suitable follow-up period.²⁸ Therefore, the results after more than 6 years were a good predictor

of the successful treatment. However, a classic study by Frank et al.²⁹ reported that 42.3% of the cases, that had been documented successful initially, failed after 11-15 years.

Conclusions

Radiographs taken 75 months after surgery showed complete healing of the previous periapical radiolucency. In clinical examination, both of the maxillary central incisors were asymptomatic and also the soft tissue was healthy. These findings suggest that the use of amalgam as the reverse-filling material of choices should be re-evaluated. MTA can be used successfully in the situations with failed previous periradicular surgery with amalgam. It is important to remember from this case report that high success rate for endodontic treatment can be achieved when both the intraradicular, and the extraradicular causes of failure of endodontic treatment are well managed.

Conflict of Interests

Authors have no conflict of interest.

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