Estimation of oral leukoplakia treatment records in the research of the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk

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Abstract

Introduction: Oral leukoplakia (OL) is the most common potentially malignant lesion of the oral cavity. The name derives from Greek, and is a combination of the words: λευχο (leuko – white) and πλακοσ (plakos – patch). It was first described by Erno Schwimmer in 1877 as a white colored lesion localized on the tongue which was probably connected to syphilis (glossitis syphilitica). Over 30 years ago World Health Organization (WHO) proposed the first OL definition: a white spot or shield which does not correspond clinically or histologically to any other diagnosis and is not caused by action of any physical or chemical agent except of tobacco [1]. During the last 30 years definitions of OL were modified, which complicated the exchange of information between clinicians, pathomorphologists and epidemiologists [2]. Finally, OL is defined as a white shield with an uncertain risk of malignant transformation by excluding other known diseases or disorders that are not connected with an increased risk of cancer [2]. Oral leukoplakia is a clinical diagnosis made by exclusion and it does not have a characteristic histopathological picture or reference to presence/absence of...

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dysplasia. The term ‘leukoplakia’ is used as a clinical one (initial and final diagnosis) or histopathological (initial and final diagnosis).

Aim

The aims of the research were to analyze the evaluation of OL treatment among patients diagnosed and treated in the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk, defining and comparing the effectiveness of OL treatment methods, assessing whether the stage of van der Waal classification of OL [3] and its location affect treatment results and define optimal treatment methods for OL.

Material and methods

The study was performed at the Department of Maxillofacial and Oral Surgery, Medical University of Gdansk (Head of the Department: Professor Adam Włodarczyk) between 1999 and 2009. Among 55 911 patients diagnosed and treated in the Department, 204 patients with OL were selected. The material includes 104 women and 100 men with an average age of 58.1 years. The study was constructed in a retrospective and prospective manner. In the retrospective segment, between the years 1999 and 2004, epidemiological and clinical evaluation of the treatment was performed. However, in this period of time patients with OL were treated solely with cryosurgery or surgery. Prospective studies were conducted in the years 2005–2009. At this time, besides the above-mentioned therapies, topical 0.05% tretinoin cream was applied. In each case of OL, the diagnosis was confirmed by histopathological examination. Each patient carried out sanitation procedures of the oral cavity in order to eliminate the factors sustaining the disease. The clinical diagnosis involved WHO criteria for potentially malignant disorders and the classification of leukoplakia by Axell and the four-stage classification of van der Waal. The moment of initial presentation of the lesions was noted, special attention was paid to risk factors and concomitant chronic diseases. Photographic documentation was performed using a digital camera (Kodak). A full course of therapy and 6-month follow-up period was completed by 178 patients (87.25%). In case of failure or relapse of OL after topical 0.05% tretinoin treatment, cryosurgery or surgery was performed. Regression was assumed when the changes were monitored 2, 4, 6 and 8 weeks and then every 6 months. Other changes were covered with granulation tissue. Patients were monitored 2, 4, 6 and 8 weeks and then every 6 months. No significant side effects or complications during the treatment which could interrupt the therapy were observed. Regression was assumed when the changes clinically subsided. Partial regression was assumed when at least 50% of the changes subsided. Other changes were classified as no improvement/relapse. The appearance of new lesions in an adjacent area was regarded as a relapse.

Statistical analysis

All calculations were performed using the statistical package Statistica 8.0 (StatSoft, Inc. in 2008) and Microsoft Excel 2003. To assess the statistical significance of differences in the results of tests, $\chi^2$ was employed (depending on the number of samples and on the expected sample size, an original method of Person, test with Yates’ correction or Fisher’s exact test were used). In all statistical tests the level of statistical significance was $p < 0.05$. 
Results

The percentage of fully recovered patients was 90.07% (127 patients). Despite treatment, relapses of OL were observed in 14 patients (9.93%). Results of treatment of 178 patients with OL are presented in Table 1. Statistically, improvement was higher after cryosurgical treatment (77.78% vs. 54.05%, \(p = 0.01\)) and surgical treatment (75.61% vs. 54.05%, \(p = 0.04\)) in comparison to tretinoin treatment. However, there were no statistically different differences noticed between surgical and cryosurgical treatment effectiveness.

There were statistically crucial differences (\(p = 0.002\)) while comparing the effectiveness of treatment (recovery vs. lack of improvement/relapse and partial regression) in three types of treatment methods. Higher effectiveness of cryosurgery and surgery in comparison to local treatment was observed. There were statistically important differences in effectiveness of local treatment methods depending on the lesion localization. In the case of lesions localized on the lower gingiva or buccal mucosae, remission occurred more often after cryosurgery and surgery in comparison to local tretinoin treatment (\(p = 0.05\) and \(p = 0.03\)). Lesions localized on the upper gingiva had better response to treatment by cryosurgery as opposed to tretinoin and surgery (\(p = 0.01\)). Analyzing effectiveness of a particular treatment method according to van der Waal classification and based on histopathological picture, statistically important differences were observed. Improvement occurred more often after cryosurgery and surgery in level I (\(p = 0.0007\)) in comparison to tretinoin. Comparing treatment results in smoking and non-smoking groups, statistically important differences were observed. In the smoking group, improvement was much more rare with tretinoin treatment (\(p = 0.003\)) in comparison to cryosurgery (44.23% vs. 65.52%) and surgery (4.23% vs. 68.18%) (Table 2).

Analyzing 0.05% tretinoin treatment effectiveness according to van der Waal classification based on the clinical and histological picture, no statistically important differences were observed (Tables 3, 4).

In over 77% of patients treated with tretinoin, total improvement was observed after 4 weeks of treatment time. In 22 patients (28.57%) who represented partial or total improvement, after interruption of treatment (on average after 3 months) relapses were observed (Figures 1–3). The results of cryosurgery are presented in Table 5.

Analyzing effectiveness of treatment according to van der Waal OL level based on the histological picture,
Table 4. Results of 0.05% local tretinoin treatment according to van der Waal OL level and histological picture

| Level | Cure      | Partial regression | No improvement/relapse | Total |
|-------|-----------|--------------------|------------------------|-------|
| I     | 47 (54.0) | 31 (35.6)          | 9 (10.3)               | 87    |
| II    | 27 (62.8) | 16 (37.2)          | 0 (0.0)                | 43    |
| III   | 13 (61.9) | 4 (19.0)           | 4 (19.0)               | 21    |
| IV    | 1 (50.0)  | 1 (50.0)           | 0 (0.0)                | 2     |
| Total | 88        | 52                 | 13                     | 153   |

Figure 1 A–B. Heterogenic OL of buccal mucosae. The patient treated with tretinoin for 3.5 months. Partial remission was observed after 1 week of treatment, total remission after 2 months of treatment

Figure 2 A–B. Homogenic OL of buccal mucosae. After 7 months of tretinoin treatment only partial regression of lesions was observed. The patient was treated by cryosurgery afterwards

Statistically significant differences were observed. Statistically, relapses were observed more rarely in level I in comparison to other levels ($p = 0.004$). In case of level III and IV – relapses were observed more often in comparison to other levels ($p = 0.05$ and $p = 0.02$) (Table 6).

Analyzing effectiveness of cryosurgery according to van der Waal classification based on the histological picture, no statistically significant differences were observed (Table 7). The results of surgical treatment are presented in Table 8.

Analyzing effectiveness of surgical treatment according to van der Waal classification based on the clinical picture there were no statistically significant differences observed (Table 9). Analyzing surgical treatment of OL classification and histological picture, statistically significant differences were observed ($p = 0.05$) (Table 10).
Discussion

Over 60 years have passed since the first attempts of using vitamin A and its derivatives in OL treatment were introduced [4]. Since then knowledge about these conjunctions has broadened, enabling the application of them in treatment of many other diseases. However, objective estimation of long-term oral use of retinoids in pre- and neoplastic treatment of lesions is difficult because of its disadvantageous side effects. Therefore, derivative substances of vitamin A – without these side effects are being searched for [5]. Local application of the substances mentioned above is far more accepted by patients. Until today, there have been only 5 studies which refer to effectiveness of locally used tretinoin in OL treatment [6–10]. US researchers [6] applied 13-cis-retinoid acid (isotretinoin) in 11 patients with histologically...
confirmed OL. After 6 months of treatment full regression was observed in 27% and partial regression in 54% of patients. Lesions relapsed in 90% of patients in 11 months’ observation follow-up. Epstein and Gorsky [7] applied 0.05% tretinoin gel in 26 patients with OL. Gel was used 4 times a day for 3.5 years. In comparison to the research mentioned above, percentages of full and partial lesion regression were identical, however, relapses of OL were undoubtedly lower – approximately 40% in 3 years’ time observation. Side effects which included mucosae irritation in the area of application were observed in 19% of patients. Even lower effectiveness of locally applied retinoids was observed by Italian researchers in two following reports [8, 9]. In both publications 0.1% isotretinoin was applied for 4 months. According to the authors, total regression was observed in 10–21.5%. In the rest of the patients the remission was only partial. Poveda-Roda et al. [10] estimated effectiveness of vitamin A derivatives in proliferative verrucous OL treatment. The effectiveness of locally applied 0.1% isotretinoin gel was approximately 30%. In our study, OL treatment with 0.05% tretinoin cream was performed in 74 patients (41.6% of all treated patients). The total number of treated OL was 153. The specimen was applied 2 times a day after rinsing and drying the oral mucosae (minimum 8 weeks). Total regression was observed in 54.05% of treated patients, partial regression of OL in 29.73%. Therapy occurred to be ineffective in 16.22% of patients. After unsuccessful retinoid treatment, cryosurgery was employed. In over 77.78% of patients with total regression, the tretinoin treatment effect was noticed on average after 4 weeks of therapy. In 22 patients (28.57%) with total or partial improvement, relapses were noticed after 3 months from discontinuation of the therapy.

Results of studies on locally applied retinoids in OL treatment are shown in Table 11.

In the presented studies, total regression of OL occurred in about 40%, while partial regression in 46% of patients. In the rest of patients (14%) therapy was ineffective. In our material, the majority of patients had homogenic OL without dysplasia. This fact may be responsible for lower relapse percentage after the treatment. In case of ineffectiveness of the above therapy we performed invasive procedures.

Cryosurgery is a method of treatment which involves controlled tissue damage caused by low temperatures. First reports concerning cryosurgery as a method of treatment date back to about 50 years ago [11]. Up to now there have been many studies published evaluating the effectiveness and safety of cryosurgery [12]. It appears that vascular lesions and potentially malignant lesions of the oral cavity epithelium are a reasonable indication for choosing this method of treatment [13, 14]. The choice of cryosurgical methods in the treatment of OL depends on the depth, area, and shape of the pathological lesion, as well as on access to cryosurgical equipment and operator’s experience [15].

Table 9. Results of surgical treatment according to van der Waal classification and clinical picture

| Level | Relapse | Cure |
|-------|---------|------|
| I     | 7 (22.6) | 24 (77.4) |
| II    | 4 (40.0)  | 6 (60.0)   |
| III   | 2 (22.2)  | 7 (77.8)   |
| IV    | –       | –           |
| Total | 13      | 37          |

Statistically relapse is more often in level III (p = 0.01)

Table 10. Results of surgical treatment according to van der Waal classification based on the histological picture

| Level | Relapse | Cure |
|-------|---------|------|
| I     | 7 (20.0)  | 28 (80.0)  |
| II    | 2 (22.2)   | 7 (77.8)    |
| III   | 4 (66.7)   | 2 (33.3)    |
| IV    | –         | –            |
| Total | 13        | 37           |

Table 11. Studies results of OL treatment with retinoids

| Authors (country) | Number of patients | Total regression of lesions (%) | Partial regression of lesions (%) | Relapse of lesions (%) | Observation period [months] |
|-------------------|--------------------|---------------------------------|----------------------------------|------------------------|---------------------------|
| Italy [63]        | 14                 | 3 (21.5)                        | 11 (78.5)                        | ?                      | 4                         |
| Italy [62]        | 10                 | 1 (10)                          | 9 (90)                           | ?                      | 4                         |
| Canada [61]       | 26                 | 7 (27)                          | 14 (54)                          | 40                     | 42                        |
| United States [60]| 11                 | 3 (27)                          | 6 (54)                           | 90                     | 11                        |
| Poland            | 74                 | 40 (54)                         | 22 (30)                          | ?                      | ?                         |
| Total             | 135                | 54 (40)                         | 62 (46)                          |                        |                           |
freezing with swabs (deep steak), open or closed spraying methods and cryoapplicators [16]. When dinitrogen dioxide (N₂O₂) is applied, open or closed spraying methods and cryoapplicators can be used. Deep steak method can be administered only in shallow or benign lesions [17]. Modification of the deep steak method might be by putting swabs on an open source of N₂O₂; what enable deep, however not precise freezing. Advantage of this method is ability of setting adequate intensity of N₂O₂ stream, what enables better control of the freezing area, increases precision of treatment and reduces damage to surrounding tissue. The spraying method involves liquid N and N₂O₂. Liquid N stream is placed 1.0–1.5 cm from the treatment area, N₂O₂ – 0.5 cm. This method is used in very superficial lesions, while a part of damaged area becomes defrosted during freezing time. To make this method more precise, a closed spraying method can be used which involves cone-shaped and cylinder-shaped covers. In our study cryosurgical treatment of OL was performed in 63 patients. Cryodestruction was applied by the spraying method using N₂O₂. Freezing exposition time was dependent on the size of the lesions (average 40 s). After defrosting time, N₂O₂ spraying was reapplied. Cryoapplicators allow the treatment of lesions ranging in size from 1 mm to a few cm. The freezing surface of the cryoaplicator is usually circle-shaped (it can be also cone- or needle-shaped). In this method, initial applicator coating of the cryoaplicator and applying pressure over the exposed tissues, can be considered. Adequate diameter should be chosen, estimation of the freezing area and defrosting time should be defined [14, 18]. When the largest lesion size is bigger than the tip of the cryoaplicator, methods of overlaying areas should be induced. Effectiveness of therapy depends on adequate freezing time and proper freezing depth. In the case of superficial lesions, clinical manual examination and measurement of freezing/defrosting time seems to be sufficient. In deeper lesions manual assessment does not ensure adequate precision. Assessment based on observation of temperature transmission in tissues appears to be helpful in such cases. The so-called ice front area is crucial. It is a margin of frozen tissue that surrounds the tip of the applicator. It is assumed that its width equals the depth of freezing and its ratio is close to 1:1.3. However, some authors pay attention to the fact that this dependence is not constant and depends on freezing technique, shape of the applicator, applied pressure as well as the tissue type. The proportion of freezing/defrosting tissue time should be equal and at least 1:2. Unfreezing time should not be shortened due to the fact that this is the moment when inside-cell damage is made. In the presented study 111 lesions were cryodestructed. More than half of them (53.2%) were localized on the buccal mucosa, Total regression was observed in 49 patients (77.8%), lack of improvement in 14 patients (21.2%). In analyzing relapses and total regression of OL lesions, the tongue occurred to be the place where the largest percentage of healing was observed (85.7%). In the gingiva it was 81.5% and in the buccal mucosa, it was 76.3%. Relapses of OL were observed most often on the floor of the mouth. Analyzing effectiveness of OL treatment according to van der Waal clinical scale, relapses of stage I statistically occurred more rarely than the others, however this dependence was observed according to the histological scale. The advantage of cryosurgery in comparison to local application of retinoids is the permanent destruction of OL lesions. Furthermore, newly rebuilt epithelium is less likely to become corneous again. Gwiazda-Chojak et al. [14] treated cryosurgically 30 patients with histopathologically confirmed OL. The freezing agent was liquid N, closed and adequately shaped cryoapplicators were used. The time of cryoapplication ranged from 5 to 30 s. One therapeutic session consisted of two or three freezing/unfreezing cycles (deep freezing was induced). Treatment effectiveness was 100%. Similar results are published by Romankiewicz [19] and Dawiec et al. [18]. In Waśkowska et al.’s study [20], the percentage of full remissions was about 90%. The authors mentioned above indicate that the reason for OL reoccurrence was probably continued smoking. Sako et al. [21] report cryosurgery effectiveness of about 80%. In conclusion, the estimation of cryosurgical effectiveness in the treatment of OL is quite problematic because of the use of different methods and different freezing agents by particular authors. Cryosurgical effectiveness is high and ranges from 80% to 100%.

Surgical treatment still remains one of the most common treatment methods in OL and should be the method of choice in OL with histologically diagnosed epithelial dysplasia [22, 23]. The hypothesis stating that surgical removal of a potentially malignant lesion decreases the chances of occurrence of oral squamous cell carcinoma (OSCC) remains still unconfirmed [12]. While speaking of invasive treatment of OL, it should be indicated that most of excisions were made by lasers (especially CO₂ and Nd:YAG) [24–30]. In the mentioned publications, total laser vaporization of tissues was performed. In other studies, laser excision with consecutive histological examination was described. Studies with classic surgical excision were carried out more seldom. Total laser vaporization makes histological examination of lesions impossible, this is crucial in the case of dysplasia. Chande and Smith [24] presented a study of 69 treated OL lesions. Relapses were observed in approximately half of the cases. An even higher risk of relapses, of about 57.1%, is reported by Flynn et al. [28]. According to the authors, laser vaporization can be considered as a good treatment method in OL without dysplasia.

This method can be applied in treating multifocal OL as well as larger areas of OL. This makes it superior to the classic surgical excision. In the case of laser therapy the risk of relapses is also much lower. Chiesa et al. [25] observed the lowest rate of relapses – 3.7%. The other...
authors report 10–17.8% [26, 31, 32]. In the treatment of OL with dysplasia this method is appropriate.

The classic OL excision has been estimated in some studies [33, 34]. Holmstrup et al. described 89 patients who had surgical excision of their lesions performed. In 6.8 years of observation, relapses were observed in 13.5%. The author treated 53 patients. In 12 months of observation, relapses were noticed in 17% of patients. In our study, surgical treatment was performed in 41 patients (23% of all treated patients). Fifty lesions of OL were totally removed. Relapses were observed in 24.4% of patients. Statistically relapses were observed more often in lesions located on the upper gingiva.

Concluding, the risk of relapse of lesions in the case of classic surgical treatment is approximately 20%, making it comparable to cryosurgery. Taking into consideration that all lesions qualified for traditional surgical treatment had features of epithelial dysplasia and were nonhomogenous. This automatically placed them in the highest risk of relapse rate irrespective of the applied method. Traditional surgery should be considered a more effective treatment method than cryosurgery. It is worth mentioning that every patient treated because of OL should undergo control examinations because up to now there has been no method that can prevent invasive OSCC in all cases.

Analyzing results of OL treatment with described three methods, local tretinoin treatment can be considered as a good choice in homogenic OL without dysplasia or as an initial treatment in other cases of OL. In case of no improvement, treatment should become more invasive. Cryosurgery and surgery can be applied as a substitution therapy in every case of OL with dysplasia. Relapses or no improvement after any form of treatment is associated with tobacco use. These relapses are situated in the areas neighboring the treated places. This observation supports the concept of multifocal carcinogenesis in the flat epithelium of the oral cavity.

Conclusions

Effectiveness of locally applied tretinoin is smaller than surgery and cryosurgery in OL treatment. However, tretinoin enables reduction in size and number of lesions, which reduces the number of ablative procedures. Results of OL treatment depend on lesion localization and its clinical stage. Tobacco smoking is the most important patient-dependent factor which influences treatment effectiveness. Combination treatment of OL is an interesting therapeutic option.

Conflict of interest

The authors declare no conflict of interest.

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