Review Article

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Etiology and Treatment of Oral Recurrent Aphthous Stomatitis

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ABSTRACT

BACKGROUND AND OBJECTIVE: Recurrent Aphthous Stomatitis (RAS) is one of the most common oral mucosal diseases. Nowadays, the majority of published systematic reviews is increasing, hence healthcare decision makers are meeting much evidence in order to solving their clinical problems. The aim of the present umbrella review was to report current knowledge on etiology, diagnosis and treatment of RAS.

METHODS: In the present umbrella review, we searched for systematic reviews using PubMed, ISI web of science, Scopus and the Cochrane Library from the beginning of 2000 up to end of 2018 using the following key words: "systematic review" "Meta-analysis" and "aphthous". Two investigators independently screened, extracted the data, and quality appraised the papers using Joanna Bridges Institute (JBI) protocol.

FINDINGS: Finally, 18 systematic reviews were included (8 on etiology and 10 on treatment). Out of these papers, findings of 6 meta-analysis suggested that hematologic deficiencies, interleukin polymorphism and helicobacter pylori seem to have association with RAS, however for treatment of RAS (including: topical, systemic and laser therapy) there were not conclusive findings.

CONCLUSION: According to results of this study, hematologic deficiencies, interleukin polymorphism and helicobacter pylori are among the novel etiologies of recurrent aphthous stomatitis, although there is no presented unique and conclusive treatment option for this common lesion yet.

KEY WORDS: *Umbrella Review, Systematic Review, Recurrent Aphthous Stomatitis, Oral Ulcer.*

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Introduction

Despite Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral mucosal conditions, which might be idiopathic or multifactorial in nature. Numerous studies revealed that many conditions such as stress, trauma, microorganisms, medications, nutritional deficiencies, immune disorders and genetic predisposition may contribute in the genesis of RAS (1-5). Various local and systemic therapeutic options have also been suggested; however, since no definitive etiology has been established for the condition, it is not possible to recommend a uniform treatment protocol for all the patients (6).

In a novel meta-analysis by Al-Maweri et. Al the results suggested a significant association between low levels of vitamin D and RAS (7). Recently Amorim Dos santos et. Al have stated that laser therapy is a safe alternative approach to treat RAS (8) and also in a recent systematic review by Alli et. Al the authors concluded that patients with RAS may benefit from SLS-free (Sodium Lauryl Sulfate) dentifrices (9). What was discussed above shows that evidence-based approaches are necessary to better understand the current status so that this clinical problem can be solved properly. A preliminary search in databases showed that several systematic reviews and meta-analyses have been published on RAS to date and it appears summing up and summarizing the results of these studies might be useful in this respect. Such evidence-based studies are referred to as umbrella reviews or overviews.

In umbrella reviews the aim is to find the most valid evidence and to summarize and synthesize systematic reviews and meta-analyses available on the subject in question. It was reported that 11 systematic reviews are published daily all over the world, which makes it difficult for researchers, clinicians, and policy-makers in the health field to refer to such a large volume of data to make clinical decisions (10, 11). Therefore, when there are large numbers of published systematic reviews and meta-analyses available, umbrella reviews might prove effective. Therefore, in the present study we reviewed the existing performed systematic reviews and meta-analyses about the etiology and treatment of RAS to evaluate the novel ideas about this common oral lesion.

Methods

The present umbrella review after approval by the Research Ethics Committee of Kerman University of Medical Sciences with the code IR.KMU.REC.1396.1946 was carried out based on Joanna Bridges Institute (JBI) protocol (11, 12). The PICO question was posed as follows: “In the systematic reviews published to date, which local and systemic treatments have been introduced as being effective (compared to each other) in improving the symptoms and signs of ulcers, in accelerating wound healing and in decreasing the recurrence rate in patients with RAS?”.

Only systematic reviews were included in the present study and simple review studies and the authors’ opinions were not evaluated. The inclusion criterion for systematic reviews in the present study was treatment for subjects with a clinical diagnosis of RAS. There was no age limitation; however, absence of systemic conditions or syndromes predisposing aphthous ulcers was a prerequisite; the present review did not include treatment options for conditions such as Crohn’s disease or Behcet’s syndrome. In addition, there were no cultural, geographical and ethnic limitations.

In the review of the collected articles, an attempt was made to translate non-English articles into English. However, the review did not include original studies such as clinical trials. All the systematic reviews were collected from the time they were available in their relevant databases up to the end of 2018. An attempt was also made to find possible reports in the “gray literature” (13, 14).

The valid databases of Cochrane, Scopus, ISI Web of Science and Pubmed (Database of Systematic Reviews) were searched, using the following MESH Key words: meta-analysis, systematic, recurrent aphthous, aphthous stomatitis, canker sore, aphthae, aphthous ulcer, aphthous, stomatitis, using “AND” and “OR” logical operators; therefore, (aphthous AND “systematic review”) OR (aphthous AND “systematic review”) were the base of search in the fields of article title, abstract and key words.

Two reviewers searched and evaluated the articles independently. In the next stage, the articles were collected from the databases separately and then the duplicate titles were eliminated using the Endnote software program. In the next stage, the tittles, abstracts and the full texts of the articles were studied and the irrelevant articles were eliminated in 3 steps (15). In the next stage, the collected systemic reviews underwent a critical evaluation. To this end, the articles were scored using the valid PRISMA (Preferred Reporting Items for Systematic review and Meta-analysis) tool. The

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checklist used for this purpose consisted of 11 items and each item as scored using the following criterion: not applicable= 1, no= 0, and yes= 2. Articles that achieved >40% of the maximum score were included in the final stage of the study (13-15). It should be pointed out that items 8 and 9 were only considered for cases that had undergone meta-analysis. Therefore, the score of meta-analysis articles was calculated out of 22 and the score of systematic reviews was calculated out of 18.

To extract data from the articles included in the final stage, the standard checklist in this aspect, i.e. JBI data extraction form for review of systematic reviews and research, was used, which consists of 18 items in 4 sections (the details of the study, the details of the search, critique and analysis). This checklist was completed separately for each article (The fourth section was completed for articles that had also carried out meta-analysis).

Results

A total of 77 relevant systematic reviews were searched through electronic databases. Fifteen duplicate articles were excluded and 44 articles were further excluded based on assessing titles, abstracts and full texts (19 according to title, 22 for abstract and 3 for full text). Eight of the 18 finally selected articles reviewed about the etiology and 10 articles were about the treatment modalities for RAS (16-33) (Table 1 and 2). Evaluation of the quality of final articles at this stage showed that three studies by Chen, Wu and Yang had the highest methodological quality and three studies by Gomes, Vale and Afghari showed moderate methodological quality (16, 19, 29-31, 33).

In 6 of 18 included articles, meta-analyses had been carried out, all of which had evaluated the etiology of RAS and three etiologies (hematologic deficiencies, helicobacter pylori infection and interleukin polymorphism) were reported by these studies (Navabi, Chen, Li, Yang, Wu and Chen) (16, 17, 21, 23, 30 , 31). All of these performed meta-analyses presented statistically significant results for their mentioned outcomes which showed that the above etiologies contribute in RAS partly. Table 3 presents the results of these six meta-analyses with odds ratios and heterogeneity.

Table 1. Data Extraction of Systematic Reviews on Etiology of Recurrent Aphthous Stomatitis

Main result	Number of reviewed papers	Databases	Sample size	Etiology	Country	Year	Authors
(B12, Folic acid, Ferritin) deficiencies could be significant risk factors for RAS.	9 Case controls	Pubmed CNKI	710 RAS 602 Control	Hematologic deficiency	china	2015	Chen et al
(B12, Folic acid, Ferritin) deficiencies are significant in RAS	6 Cross sectionals Case controls 15 Interventional 3	Pubmed/cochrane Scopus/science Direct ovid	-	Hematologic deficiency	Iran	2013	Navabi et al
IL-1β(+3954C/T) Increases the risk of RAS.	10 Case controls	Pubmed Embase	884 RAS Control 1104	Interleukin polymorphism	China	2018	Wu et al
IL-10-1082 G/A IL-6-174 G/C May have a role in etiology of RAS	Case controls 10	Pubmed Embase ISI cochrane	779 RAS Control 1016	Interleukin polymorphism	China	2017	Yang et al
IL-1b+3954C/T Increases the risk and IL-1b-1082G/A Has protective role for RAS in Asian population.	11 RCTs	Pubmed Embase ISI	-	Interleukin polymorphism	China	2018	Chen et al
There is no correlation.	2 Cross sectionals 7 Case controls	Pubmed	-	Helicobacter pylori	Iran	2011	Afghari et al
There is no association.	15 Experimental 3 Reviews	Pubmed	339 Cases 271 Control	Helicobacter pylori	Brazil	2016	Gomes et al
Helicobacter pylori infection associates with RAS.	7 Case controls	Pubmed	649 RAS	Helicobacter pylori	China	2014	Li et al

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Table 2. Data Extraction of Systematic Reviews on Treatment of Recurrent Aphthous Stomatitis

Main result	Number of reviewed papers	Databases	Intervention	Country	Year	Authors
Laser therapy has the superiority in relieving pain and shortening healing time.	10 RCT	Pubmed-Embase sciencedirect cochrane- ISI	Laser therapy	China	2016	Han et al
The use of lasers (CO2, Nd:YAG & diode) to relieve symptoms and promote healing is a therapeutic option.	RCT 10 1 non randomized trial	Pubmed-Embase Cochrane	Laser therapy	Switzerland	2017	Suter et al
The results should be interpreted with caution.	RCT 2 Comparative 1 Prospective 1	Pubmed-Seience Direct Cochrane	Laser therapy	Bosnia	2015	Pavlic et al
CO2 lasers have the unique advantages.	RCT 7 Case report 2	Pubmed- ISI-Cochrane-Embase	Low level laser	Saudi Arabia	2016	Najeeb et al
Low level laser therapy can be suggested as an alternative for RAS treatment.	RCT 2	LILAC-Google scholar-Pubmed Cochrane	Low level laser	Brazil	2015	Vale et al
Chlorhexidine and topical corticosteroids are effective.	18 systematic reviews , RCTs and observational	Pubmed-Embase Cochrane	Topical treatments	England	2007	Porter et al
Chlorhexidine and topical corticosteroids are effective treatments with more evidences.	RCT 9	Pubmed-Embase Cochrane	Topical treatments	England	2013	Staines
The results of the studies are inconclusive.	RCT 8	Pubmed-LiLac-Scielo-Embase	Topical corticosteroids	Colombia	2008	Quijano et al
These medicines may be effective for treatment of RAS	RCT 11 Trial 1	Pubmed-Embase-Cochrane sciencecitation index	Chinese patent medicines	China	2017	Zhou et al
Results are inconclusive in regard to the best systemic intervention for RAS	Trials 25	Cochrane-pubmed-Embase-CINAHL AMED	Systemic treatments	Cochrane review	2012	Brocklehurst et al

Table 3. Main Results of Meta-Analysis Studies on RAS Treatment

Heterogeneity	Meta-analysis result	Association	Year	Authors
-	p<0.1 for (Vitamin B12, Folic acid and Serum Iron) deficiency and p<0.1 for effect of Iron supplement therapy	Hematologic deficiencies	2013	Navabi et al
-	Helicobacter infection was significantly greater in RAS patients than Non-RAS controls (OR=1.85)	Helicobacter pylori	2014	Li et al
-	The rate of hematinic deficiencies was significantly high in RAS group (Odds ratios: 3.75 for Vitamin B12, 7.55 for Folic acid and 2.62 for Ferritin)	Hematologic deficiencies	2015	Chen et al
Significant	IL-10- 1082 G1A (OR=1.49) IL-6-174G1C (OR=2.36/OR=7.0.5/OR=4.28/OR=2.59)	Interleukin polymorphism	2017	Yang et al
Significant	IL- 1beta(-511C1T) (OR=1.77) IL-1beta (t3954+CIT) (OR=1.52) C-gene (OR=1.46)	Interleukin polymorphism	2018	Wu et al
Significant	IL-10-1082 GIA was significant only in recessive model (OR=0.710) IL-10-592 C/A was significant in all models	Interleukin polymorphism	2018	Chen lei et al

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Discussion

Based on the results of the present umbrella review, hematologic deficiencies, interleukin polymorphism and helicobacter pylori are among the novel etiologies of recurrent aphthous stomatitis, although there is no presented unique and conclusive treatment option for this common lesion yet. Heterogeneity has been observed in all three studies to investigate the effect of interleukin polymorphism (17, 30, 31).

Both Yang and Chen evaluated IL (G/A-1082-10) and based on the resultant OR (odds ratio) and in the study by Yang et al the effect of IL on the incidence of RAS was significant (17, 31). The results of two meta-analyses in which the effects of hematologic defects on the etiology of RAS was evaluated showed that Chen et al have reported significant effects of serum deficiencies of folic acid, ferritin and B_{12} on the incidence of RAS; however, such an effect was not shown in the study by Navabi et al (16, 23). Gomes and Afghari evaluated the effect of H. pylori on RAS in their reviews and both reported no correlation between contamination with H. pylori and the incidence of RAS (19, 33). However, it should be noted that Li reported OR=1.05 in a meta-analysis (21). Therefore, it appears further studies are necessary in this field.

In 10 articles in the field of treatment of RAS, 5 reviews evaluated the effect of laser therapy; 3 reviews evaluated the effects of local treatments; one review evaluated the effect of Chinese traditional medicine and one review evaluated the effects of systemic treatments (18, 20, 22, 24, 29, 32). Han, Suter, and Pavlic evaluated the effect of laser therapy in general for RAS (20, 24, 28), and Najeeb and Vale specifically discussed the effect of low-power lasers in this field (22, 29). Use of laser resulted in two clinical effects (pain relief and a decrease in the duration of ulceration) in patients with RAS. However, Han believes that the relatively high heterogeneity between studies in this field has made it difficult to carry out meta-analyses in this field (20).

Furthermore, Vale, reported that the wavelength factor had a significant role in such studies; in addition, factors such as duration of exposure, the number of treatment sessions and the type of laser should be taken into account. Therefore, it is not still possible to suggest a specific protocol for the laser therapy of aphthous ulcers (29). Najeeb et al reported that CO_2 laser had specifically a unique advantage in this respect due to its short irradiation time (5-10 seconds) (22). However, Pavlic et al believe that the effects of low-level lasers on RAS should be interpreted with caution and consistent with Han and Vale emphasized that various effective parameters on one hand and the limited number of studies on different lasers on the other hand should caution us against definite conclusions in this respect (20, 24, 29). One of the noticeable facts about such studies is the control group. As pointed out by Pavlic, in studies evaluated by them, placebo or local corticosteroids have frequently been used in the control group in contrast to the group undergoing laser treatment; this makes it difficult to compare the results of studies (24).

In the field of local treatments, Porter and Staines reported in their reviews that the majority of evidence available in relation to effective local treatments for RAS was related to chlorhexidine mouthwash and local corticosteroids. Porter et al reported that use of CHX mouthwash decreases the severity of pain and relieves pain resulting from aphthous ulcers, which is probably due to the antiseptic effect of this mouthwash and elimination of the members of the oral microbial flora that secondarily infect the aphthous ulcers. Staines et al reported the side effects of this mouthwash, including tooth staining, and emphasized that CHX should not be used without prescription by a physician. Porter and Staines reported that local treatment agents such as CHX cannot prevent the incidence of new ulcers; however, local corticosteroids might prevent such new ulcerations in addition to their pain relief effect and acceleration of wound healing. These two researchers emphasized in their reviews that sufficient evidence is not available on the effects of local analgesic agents, tetracycline mouthwashes and benzydamine mouthwash, with Staines reporting that 44% of the subjects preferred benzydamine mouthwash, which is due to the local anesthetic effect of this medicine (25, 27).

Quijano et al in their review only evaluated the effect of local corticosteroids on RAS and reported an important consideration, which might appear to be the etiologic factor for the heterogeneity in such studies; this factor might be the large number of tools used to determine the outcomes. For example, some researchers have used an objective numeric sale to determine relief of pain resulting from ulcerations, and some others have used other scales such as the mean time of wound healing, the decrease in erythema after treatment, the decrease in ulcer size and the decrease in the recurrence rate (from a week to one month). Staines believes that the diversity of local corticosteroids used by different researchers, too, is another factor in this field; in this context, triamcinolone, betamethasone, etc. have been

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used as local treatment options in different studies. Quijano et al, similar to Porter and Staines, have reported local corticosteroids, as one of the most effective local treatment options for RAS (25-27). A review by Brocklehurst is the only review on the effect of systemic treatments on RAS (a Cochrane review). They reported that no single systemic treatment has been reported as the most effective and definitive therapeutic intervention for RAS and it appears specific medications are effective in some specific groups of patients (18). In addition, administration of systemic treatments (such as systemic corticosteroids and immune system medications) is always associated with side effect challenges and the general advice is that these treatment options should be used in complex cases of RAS and when no noticeable effects are achieved from the use of local treatments (18, 34). One of the limitations of such studies was the overlapping of the initial studies evaluated in the review. In relation to the etiologies reported for RAS, such as H. pylori, hematologic defects and IL polymorphism, and effective treatments (especially in relation to systemic treatment), further randomized clinical trials are necessary in order to collect valid evidence for some treatment options (especially laser therapy) to be able to introduce standard clinical protocols.

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