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TOPICAL MANAGEMENT OF RECURRENT APHTHOUS STOMATITIS

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ABSTRACT

Recurrent aphthous stomatitis (RAS) is a common condition that is affecting young adults. The management of RAS aims at identifying and controlling the possible predisposing factors, exclude possible underlying systemic causes, control pain and to accelerate healing.

A wide variety of systemic and topical agents has been suggested for the treatment of RAS. Although there are several trials employing different systemic and/or topical agents in the treatment of RAS, there is no strong evidence on the superiority of any therapeutic or curative agent for this disorder.

Topical agents may be sufficient to lessen the pain in some patients; however systemic corticosteroids/immunosuppressant agents may be necessary to control pain in others. Therefore, the severity and frequency of ulcers may be used as guidance in the management of RAS patients. This paper reviews the available topical agents that have been used in the management of RAS.

INTRODUCTION

The management of recurrent aphthous stomatitis (RAS) aims to identify and control the possible predisposing factors, exclude possible underlying systemic causes, control pain, accelerate ulcer healing and prevent secondary infection (Jurge et al., 2006; Belenguer-Guallar et al., 2014). RAS lesions are self-limiting and tend to recur and heal without scarring. However, major lesions may heal with scar in some instances, and with time, a group of patients may adapt to compromised mild-moderate pain and necessitate no treatment.

A wide variety of systemic and topical drugs/herbal agents have been suggested for the treatment of RAS. Although there are numerous randomized-controlled trials (RCTs) employing different systemic and/or topical agents in the treatment of RAS, there is no strong evidence on the superiority of any therapeutic or curative agent for this disorder. Although there is a consensus on the diagnosis and management of RAS (Scully et al., 2003), in practice, there is wide variability in the management between different specialists and clinicians. There is great variability in the severity, frequency and duration of mouth ulcers. In addition, there are

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differences in response between RAS patients. Hence, where topical agents (antiseptic, analgesic or topical corticosteroids) may be sufficient to lessen the pain in some patients, systemic corticosteroids/ immunosuppressant agents may be necessary to control pain in others. Therefore, the severity and frequency of ulcers may be used as guidance in the management of RAS patients.

A review based on evidence levels 1 and 2 (metaanalyses, systematic reviews, phase I and II randomized clinical trials, cohort studies and case-control studies) suggests that therapy with either topical or systemic agents has to employ only in cases with continuous attacks. Treatment always initiated with topical agents and to reserve systemic therapies with patients with constant and aggressive outbreaks (Belenguer-Guallar et al., 2014).

Spectrum of topical agents in the management of RAS

Topical corticosteroids

Topical corticosteroids are considered the mainstay of treatment and have been reported to lessen pain and accelerate healing. A consensus approach suggests that topical corticosteroids with or without other immunomodulatory topical agents may control RAS symptoms in the majority of patients (Scully et al., 2003).

Different topical corticosteroid formulations and agents have been used in the management of RAS, including hydrocortisone mouthwash (Holbrook et al., 1998), clobetasol (Lozada-Nur et al., 1991; Lo Muzio et al., 2001), fluocinonide (Pimlott and Walker, 1983), mometasone furoate (Teixeira et al., 1999), topical dexamethasone and triamcinolone acetonide (Yel et al., 1994; Al-Na'mah et al., 2009; Keenan, 2012).

For example, 40 patients who had recurrent oral ulcers for a mean period of 11.1 years were prescribed topical triamcinolone acetonide (0.1% or 0.2% aqueous suspension) alone or in combination with prednisone (40- 60 mg). At the end of the follow-up period (mean of 22.9 months), most patients (34/40; 85%) had complete healing of their ulcers presented at initial consultation with fewer new ulcers, while 5 patients had partial response to this topical therapy. Candidiasis was evident in five patients as a complication of topical corticosteroids (Vincent and Lilly, 1992).

In a RCT, topical clobetasol propionate (3 different preparations, 2-3 times/day) was effective in the management of 30 patients. Clobetasol in an adhesive denture paste, in comparison to other preparations, induced quick pain relief (Lo Muzio et al., 2001). Acute pseudomembranous candidiasis was evident in 18.5% of the patients in this study, which was effectively managed by miconazole and chlorhexidine (Lo Muzio et al., 2001). In another study, clobetasol propionate (0.05%) was found to be as effective as amlexanox (5%) in lessening the painful symptoms of RAS as well as healing of ulcers (Rodríguez et al., 2007). In a study by Abbasi et al. adcortyl (Triamcinalone) was effective as amlexanox in relieving pain and reducing the ulcer size (Abbasi et al., 2016).

In a study in which dexamethasone ointment was assessed among 810 RAS patients in a randomized, double-blinded, multicenter clinical trial to compare the efficacy and safety of dexamethasone ointment with placebo (3 times a day for 5 days), dexamethasone ointment was found to be efficient and safe with no severe adverse effect and with no serum dexamethasone detection (Liu et al., 2012). In another study, dexamethasone ointment was efficient and safe in reducing ulcer size and lessening symptoms in RAS patients (Keenan, 2012).

A systematic review showed that studies concerning the effect of topical corticosteroids in the management of RAS are inconsistent and not conclusive (Quijano and Rodríguez, 2008). However, these agents result in reduced time of ulcer healing in RAS patients (Quijano and Rodríguez, 2008).

Antimicrobial

Topical antiseptic agents (e.g., chlorhexidine and triclosan) can be used for symptomatic relief of RAS pain. Several open and RCTs investigated the effect of chlorhexidine in patients with RAS (Addy and Hunter, 1987; Edres et al., 1997). It has been reported to lessen ulcer pain (Edres et al., 1997). In addition, chlorhexidine mouthwash was as effective as triamcinolone acetonide (0.025%) in a cohort of RAS patients (Miles et al., 1993). Triclosan, in a double-blind cross-over clinical trial, employing 30 subjects, resulted in a reduction in ulcer number (Skaare et al., 1996).

Tetracycline, Minocycline, Doxycycline

Tetracyclines inhibit matrix metalloproteinases (degradative enzymes of the extracellular matrix), which play a role in tissue inflammation and contribute to ulcer formation (Vidal et al., 2007; Skulason et al., 2009).

In a double-blind trial, tetracycline, as a suspension, lessened the symptoms of a cohort of RAS patients; however, as with most other agents, it failed to stop ulcer recurrences (Graykowski and Kingman, 1978). However, tetracycline mouthwash (0.25%) was less effective than minocycline mouthwash (0.2%) in the control of pain and duration of ulcers in 17 patients in a randomized cross-over study (Gorsky et al., 2007).

Topical minocycline (0.2%) was reportedly more effective than placebo mouthwash in reducing the pain severity and ulcer duration in a randomized trial of 33 patients (Gorsky et al., 2008). However, more recently, it was found that 0.5 % minocycline - mouthwash is more effective than 0.2% minocycline (Yarom et al., 2017).

It has also been reported that a single application of doxycycline hyclate decreases pain and improves the healing of RAS lesions (Vijayabala et al., 2013). Skulason and co-workers (2009) conducted a randomized, double-blind, placebo-controlled trial with low-dose doxycycline in an adhesive gel that resulted in healing of mucosal ulcers in 68% of patients within 3 days of commencing treatment, while just quarter of the patients on placebo had resolution of oral ulceration.

Amlexanox

Amlexanox is an anti-allergic and anti-inflammatory topical agent that has been suggested for the management of RAS (Greer et al., 1993; Khandwala et al., 1997; Bell, 2005; Murray et al., 2005; Murray et al., 2006; Liu et al., 2006; Rodríguez et al., 2007; Meng et al., 2009). Amlexanox, at the onset of the prodromal stage, reportedly prevents the development of ulcers and significantly reduces symptoms if ulcers develop (Murray et al., 2005). Greer and colleagues (1993) in a double-blind placebo controlled clinical trial concluded that amlexanox is an effective and tolerable agent in the treatment of RAS patients.

In a large multicenter randomized, double-blind clinical trial employing 1335 RAS sufferers, 5% amlexanox paste was found to accelerate the healing and resolution of pain of ulcers within 48 hours of development (Khandwala et al., 1997).

Murray and colleagues (2006), in a randomized controlled trial, used amlexanox (4 times/day for 3 days) in the management of RAS. They employed thermographic imaging to identify ulcers in the prodromal stage in 52 patients. The number of patients who developed an ulcer by the fourth day in the amlexanox group was lower than those who received only vehicle treatment (50% and 69%, respectively). In another large randomized, double-blind, vehicle-controlled trial (Liu et al., 2006), 104 patients used amlexanox oral adhesive tablets (4 times a day for 5 days) and 108 used vehicle. Liu and coworkers (2006) found amlexanox to be effective and safe in lessening patients' symptoms and signs.

Additionally, in a multicenter, double-blind randomized trial of 95 RAS patients, 5% amlexanox (5%) was found to be effective and as potent as topical corticosteroids (0.05% clobetasol propionate) in

reducing pain and ulcer size (Rodríguez et al., 2007). In a randomized, blinded, placebo-controlled, multicenter trial with 216 subjects, amlexanox pellicles (4 times a day for 5 days) were found to be effective and safe in reducing pain and ulcer size (Meng et al., 2009). In another randomized, double-blind, vehicle-controlled, unparallel multicenter clinical trial, amlexanox oral adhesive tablets were found to be effective and safe in the management of RAS (Liu et al., 2006).

In a few other studies, 5% amlexanox oral paste was clinically effective in the management of RAS (Bhat and Sujatha., 2013; Darshan et al., 2014) and was reported to reduce the frequency, duration and symptoms with no adverse side effects (Greer et al., 1993; Darshan et al., 2014). Likewise, in another study, amlexanox, as an oral adhesive pellicle, was found to be as effective and safe as amlexanox oral adhesive tablets and more comfortable (Meng et al., 2009).

In a study by Rodríguez et al., 5% amlexanox or a 0.05% clobetasol propionate both relieved pain and reduced the ulcer size, with no significant differences between patients employing them (Rodríguez et al., 2007). In studies conducted by Murray et al, OraDisc (2 mg amlexanox) (Murray et al., 2006) and Aphtheal (5% amlexanox paste) (Murray et al., 2005) found that preventing the progression of RAS in the prodromal phase into the ulcer phase in comparison with no treatment or vehicle alone and amlexanox significantly reduced symptoms if ulcers develop (Murray et al., 2006).

Hyaluronic acid

In a large randomized, controlled, double-blind trial, topical hyaluronic acid was used in the management of 120 RAS patients. Hyaluronic acid resulted in the reduction of ulcers more than observed with those on placebo (Nolan et al., 2006). However, hyaluronic acid and placebo resulted in a significant lessening of pain after commencing treatment (Nolan et al., 2006). In a cohort of 33 RAS or Behçet's disease patients, topical hyaluronic acid (0.2%; twice/daily for 14 days) resulted in lessening the symptoms in most patients (75.8%), as reported with a VAS, as well as a reduction in the number of ulcers and the healing period. Specifically, the authors reported a reduction in ulcer numbers in 57.6% of the patients, and most ulcers (78.8%) showed a decrease in size, and the treatment was without any adverse side effects (Lee et al., 2008).

In a systematic review on the effects of hyaluronic acid on painful oral lesions, including recurrent aphthous stomatitis, both subjective and objective parameters were significantly improved (Casale et al., 2017).

Chemical cautery

Coagulation, employing chemical cautery, has been suggested to be effective in the management of RAS.

Debacterol

Debacterol (a liquid, topical, debriding agent composed of sulfonated phenolics-50% and sulfuric acid-30%) was found to be more effective than triamcinolone acetonide in lessening RAS pain in a cohort of 60 patients (Rhodus and Bereuter, 1998). More than 70% and less than 20% of patients had lessening of their symptoms by day 3 of commencing debacterol and triamcinolone acetonide, respectively. However, there was no difference in ulcer size between the two therapeutic agents (Rhodus and Bereuter, 1998).

Silver nitrate cautery

Silver nitrate cautery may be an effective option for symptomatic pain relief in RAS patients (Alidaee et al., 2005; Soylu Özler, 2014),

In a randomized, single-blinded controlled study, silver nitrate cautery resulted in 70% lessening of oral pain after 24 hours of the treatment procedure (Alidaee et al., 2005), while just 11% of patients receiving placebo reported a reduction in symptoms. However, within a week, there was no

difference between the two groups regarding re-epithelialization. The authors concluded that silver nitrate reduced ulcer pain but did not shorten the healing time. Additionally, the authors note that it is a rapid, simple and cost-effective means of treatment in patients with sporadic RAS (Alidaee et al., 2005).

Silver nitrate cautery produced a more statistically significant reduction in pain in comparison with people who were treated with placebo sticks on the first to the seventh day. RAS lesions were completely reepithelialized on the seventh day in 60% of patients managed by Silver nitrate and in 32% of patients in the placebo group (mean healing time of ulcers, reported by the Silver nitrate group, was 2.7 days (range 2-4) and in the placebo group, 5.5 days (range 4-7)) with no adverse side effects in both groups (Soylu Özler, 2014).

Laser therapy

Many studies have evaluated the use of different types and regimens of laser therapy in the management of patients with RAS (Tezel et al., 2009; Prasad and Pai, 2013; Albrektson et al., 2014, Nasry et al., 2016, Pentapati et al., 2016, Zeini Jahromi et al., 2017, Suter et al., 2017). A single application with a non-thermal, non-ablative CO2 laser therapy may accelerate healing without any adverse effect (Zand et al., 2012). CO2 laser therapy has been reported to give immediate pain relief (Prasad and Pai, 2013).

Low-level laser therapy can accelerate healing, decrease the pain, size, and recurrence of RAS lesions (Anand et al, 2013; Albrektson et al., 2014). low-level laser therapy (wavelength, 809 nm; power, 60 mW; frequency, 1800 Hz; duration, 80 seconds; dose, 6.3 J/cm(2)) in a randomized controlled trial found to be effective in reducing the pain and the inconvenience of eating, drinking, and brushing for patients with RAS (Albrektson et al., 2014).

In a study where laser therapy is used as an alternative method in the treatment of RAS. Er,Cr:YSGG (0.25 W without water) and a 940 nm diode laser may be appropriate to reduce pain, burn sensation and accelerate the healing of RAS (Misra et al., 2013; Yilmaz et al., 2017).

In a randomized clinical trial, diode laser treatment was found to be better with a statistically significant reduction in pain and ulcer size than treatment with adhesive pastes of A. nilotica and Glycyrrhiza glabra, adhesive oral tablets of 2 mg Amlexanox or patients just received a placebo adhesive tablet (Nasry et al., 2016).

Low-level laser therapy was as effective as amlexanox in relieving RAS pain, and both were effective, subjectively and objectively in the management of RAS (Jijin et al., 2016).

In a systematic review on the effect of laser on recurrent aphthous stomatitis (CO2 laser, Nd:YAG laser and diode laser), laser was found to be effective in the management of oral lesions (Suter et al., 2017), and in another systematic review on the low-level lasers, Najeeb and coworker (2016) concluded that various types of lasers are providing immediate pain relief and that carbon dioxide (CO2) lasers require a short application time.

The laser therapy has superiority in relieving ulcer pain and shortening healing time when compared with other treatment modalities (e.g., 0.1% triamcinolone acetonide, Granofurin and solcoseryl, amlexanox oral paste, inactive laser therapy, etc.). Although laser therapy is a promising effective treatment for RAS, high-quality clinical studies with large sample sizes must be performed to confirm the effectiveness of this therapy (Han et al., 2016).

Because there is a large variation in the different regimens in various publications in this field, it has been recommended to standardize the laser type, wavelength, power output and applied energy in the management of RAS to improve patient management (Suter et al., 2017).

Table. Example of effective topical agents evaluated in the management of RAS.

Agent	Study type	Efficacy	Vehicle	Reference
Allicin	Randomized double-blind placebo-controlled trial	Effective and safe	Oral adhesive tablets	Jiang et al 2012
Allicin	Review	Effective	---	Jiang et al 2008
Alchemilla vulgaris in glycerine	Open-label study	Effective and safe	Gel (Glycerine)	Shrivastava and John, 2006
Aloe vera- and myrrh natural gels, containing aloe vera and myrrh	Randomized double-blind placebo-controlled trial	Effective	Mucoadhesive gel	Mansour et al., 2014
AphtoFix®	In vitro and In vivo trial	Effective and safe	Cream	Sakly et al., 2016
Botulinum toxin A	A single blinded placebo controlled trial	Effective and safe	Injection	Yang and Jang, 2009
Chamomilla recutita	Clinical trial	Effective and safe	Fluid Extract	Ramos-e-Silva et al., 2006
Citrus oil and magnesium salts	Randomized controlled trial	Effective and safe	Muco-adhesive patch	Shemer et al., 2008
Dentifrice	A multicenter, double-blind, randomized, placebo-controlled trial	Effective and safe	Dentifrice	Coli et al., 2004
Dentifrice (sodium lauryl sulfate)	Randomized double-blind placebo-controlled trial	Effective	Dentifrice	Shim et al., 2012
Diosmectite and Basic Fibroblast Growth Factor paste	Randomized double-blind placebo-controlled trial	Effective and safe	Paste	Jiang et al., 2013a
Ginger Officinale	Randomized double-blind placebo-controlled trial	Effective	Bioadhesive patch	Haghpanah et al., 2015
Gelatin containing berberine (5 mg/g)	Randomized double-blind placebo-controlled trial	Effective and safe	Topical gelatin	Jiang et al., 2013b
Glycyrrhiza (licorice) herbal extract dissolving oral patch	Randomized double-blind trial	Effective	Oral patch	Martin et al. 2008
Homeopathic treatment	Randomized, single blind, placebo-controlled clinical trial	Effect and save	Oral liquid	Mousavi et al., 2009
Honey	Randomized double-blind placebo-controlled trial	Effective and safe	Topical	El-Haddad et al., 2014

Table (cont.). Example of effective topical agents evaluated in the management of RAS.

Agent	Study type	Efficacy	Vehicle	Reference
Human granulocyte-macrophage colony-stimulating factor	Clinical trial	Effective and safe	Solution	Herranz et al., 2000
Hyaluronic acid gel	Clinical Trial	Effective and Safe	Gel	Lee et al., 2008
HybenX	Randomized controlled trial	Effective and Safe	Topical	Porter et al., 2009
Intralesional Corticosteroids and Levamisole	Case report	Effective and safe	Interlesionsl Injections	Picciani et al., 2010
Iralvex	Randomized double-blind placebo-controlled trial	Effective and safe	Gel	Khademi et al., 2014
Licorice	Randomized clinical trial	Effective	Adhesive	Nasry et al 2016
Licorice bioadhesive hydrogel	Placebo controlled clinical trial	Effective and safe	Hydrogel patch	Moghadamnia et al 2009
Lactic acid	Single-blind controlled trial	Effective and safe	Mouthwash	Sharquie et al., 2006
Myrtus	Randomized controlled trial	Effective and improving the quality life	Paste	Babaee et al., 2010
Myrtus	Clinical Trial	Effective	Topical oil and decoctions	Mahboubi, 2016
Nicotine lozenges	Case report	Effective	Lozenges	Deen et al., 2015
Ozone	Non-randomized double blind, controlled observational study	Effective	Ozone in air	Al-Omiri et al., 2016
Penicillin G potassium	Randomized double-blind placebo-controlled trial	Effective with few adverse effects	Troches	Zhou et al., 2010
Topical prednisolone	---	Effective	Mucoadhesive films	Farid and Wen, 2017
Quercetin	Randomized controlled trial	Effective and safe	Dabs of quercetin (topical)	Hamdy and Ibrahem, 2010
Rhizophora mangle aqueous bark extract	Randomized, single-blinded, placebo control trial	Effective and safe	Topical (Extract)	de Armas et al., 2005

Others

Many other agents have also been used in the management of RAS. Few additional agents that are effective in the management of RAS have been summarized in the table below.

CONCLUSION

In conclusion, there is no single widely accepted treatment protocol for RAS. Most treatment modalities reduced pain and ulcer size. Topical corticosteroids are still considered to be the best mode of treatment of RAS, and they are effective in controlling symptomatic oral ulceration. These agents are easy to use with few adverse sides. Multicenter randomized controlled studies are needed to measure the real effect.

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