ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 08, pp.37264-37271, August, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

RECURRENT APHTHOUS STOMATITIS MANAGEMENT – CURRENT TRENDS AND ALTERNATIVE MODALITIES

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ARTICLE INFO

Article History:
Received 22nd May, 2016
Received in revised form
15th June, 2016
Accepted 14th July, 2016
Published online 31st August, 2016

Key words:

RAS,
RAU,
Aphthous stomatitis,
Aphthous ulcers,
Management of RAS,
Treatment of RAS.

ABSTRACT

Recurrent Aphthous Stomatitis (RAS) is sometimes termed as recurrent oral ulceration, but it is important to note there are various causes of recurrent oral mucosal ulceration, hence the term RAS is considered more appropriate. RAS was first described in antiquity and since has been the subject of numerous clinical and laboratory investigations. However, the disease still remains poorly understood. It has been estimated that 20% of the general population will suffer from RAU at some time during their lives. While most aphthae are small and heal within seven to 14 days, larger ulcers can persist for weeks or months. It is the management of aphthous that poses a challenge. Treatment has largely been restricted to provide symptomatic relief to the patients and hardly any success has been achieved in preventing recurrence of the disease. Topical anti-inflammatory agents remain the cornerstone of treatment and myriad of drugs have been researched in curing this condition, rather with limited success. Dietary restrictions, topical steroids, topical antibiotics, topical immunomodulators, and coating agents are the mainstay to reduce pain and inflammation. Systemic drugs are used when the lesions are extensive, (major and herpetiform) and no relief is obtained with topical agents. Several alternative treatment have been tried including certain herbs, natural substances, chemical agents which have shown limited success in treating this self limiting but challenging condition. This review focuses on the various management modalities used in the treatment of RAS.

Citation: Dr. Abhishek Dubey, Dr. Manasa Anand Meundi, Dr. Ramnarayan, B. K., Dr. Chaya M David and Dr. Pankaj Gupta, 2016. "Recurrent Aphthous stomatitis management – current trends and alternative modalities", *International Journal of Current Research*, 8, (08), 37264-37271.

INTRODUCTION

Recurrent Aphthous Stomatitis (RAS) or recurrent oral ulcers (RAU) is an inflammatory condition of unknown etiology characterized by painful recurrent, single or multiple ulcerations of the oral mucosa. While recurrent aphthous stomatitis remains a common oral mucosal disorder in most communities of the world, its precise etiology remains unclear. Several etiologic factors have been suggested but no precise trigger has ever been demonstrated, and there is no conclusive evidence for a genetic predisposition to RAS in most patients. Lesions arise as a consequence of immunologically mediated cytotoxicity of epithelial cells. Recurrent aphthous ulcers are divided into three types, minor, major and herpetiform., according to the classification described by Stanley (1972). As the diagnosis of aphthous is relatively easier on the basis of its clinical picture, recurrence and self limitation of the condition, laboratory procedures are seldom required. Recurrent aphthous ulcers are treated using a variety of agents. These are directed at palliation of symptoms, shortening of healing time and prophylaxis against future episodes. Many of the treatments are used without research demonstrating therapeutic results specific to aphthous stomatitis.

Therapy for recurrent aphthous ulcers must be directed by the extent of the condition, as determined by the patient and the clinician. Patients often report great pain when clinical examination reveals only a minor ulcer of 1-2 mm in diameter. In addition, the frequency and the extent of involvement should direct therapy.

Management of recurrent Aphthous stomatitis

The treatment of RAS can be divided into a) dietary and general measures b) topical therapy c) systemic management.

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Dietary and general measures

According to some researchers, the exposition to some food ingredients, e.g., chocolate, gluten, cow milk, preservatives, nuts and food coloring agents may induce the pro-inflammatory cascade in RAS. In some patients, the clinical improvement has been observed after inducing the elimination diet. An elimination diet may help control outbreaks by revealing suspected allergic stimuli that initiate oral lesions. If food exposure is thought to be the culprit, a food diary can be helpful. A gluten-free diet helps patients with celiac disease control outbreaks of aphthae. Patients with oral lesions should avoid hard or sharp foods that may gouge existing ulcers or create new ones. Some patients report aphthae after exposure to nuts, pineapple, cinnamon, or other agents. In such cases, remission may be achieved by avoiding the inciting agent. Certain foods should be avoided as they appear to trigger the eruption of new aphthae and prolong the course of the lesions (e.g., foods that are hard, acidic, salty, or spicy, as well as nuts, chocolate, citrus fruits, and alcoholic or carbonated beverages). In addition, because surfactants and detergents can cause irritation, dental care products containing sodium lauryl sulphate should be avoided. (Zouboulis, 2003) Deficiencies of iron, vitamin B12, and folic acid predispose development of RAS. Wray *et al* reported hematinic deficiencies to affect up to 21% of adult patients with RAS, and when they replaced the deficient element, 59% of the patients showed resolution of RAS and 28% showed significant improvement. (Wray *et al*., 1978) Ozler suggested an association between zinc deficiency and recurrent aphthous stomatitis. (Ozler, 2014) The improvement of RAU with zinc sulphate supplementation were described in an open trial and in a case report of aphthous ulcers with zinc deficiency and immunodeficiency. (Merchant *et al*., 1977; Endre, 1991) Psychological stress as a triggering factor for RAS has been mentioned in the literature, and is typically observed during stressful situations. Huling *et al*. found that Stressful life events were significantly associated with the onset of RAS episodes. (Huling *et al*., 2012) Patient counselling and psychological intervention to reduce stress should be considered while managing a patient with RAS.

Topical agents used in the management of RAS

Topical regimens may include anti-inflammatory (eg, corticosteroids) and immunomodulatory agents (eg, retinoids, cyclosporin). These may include topical gels, creams, pastes, ointments, sprays, and rinses. Adjuvant rinses reduce bacterial load, which is thought to reduce inflammation and shorten healing. These may include chlorhexidinegluconate, dilute hydrogen peroxide, and topical lidocaine or benzocaine. An oral bioadherent (Gelclair) is a mucoadhesive that provides a protective coating to reduce pain.

i) Local Anesthetics

Drugs classified as local anesthetics reversibly block action potential propagation in axons by preventing the sodium entry that produces the potentials. (Hille, 2001) Both nociceptive and neuropathic pain are targeted by this group of drugs. Any part of the nervous system, from the periphery to the brain, may be where local anesthetics act to produce a desired anesthetic or analgesic effect. A variety of formulations of local anesthetics, routes of administration, and methods of administration are used. Procaine is the prototypic aminoester-linked local anesthetic, and lidocaine is the prototypic aminoamide-linked local anesthetic. Pain relief can be attained using topical lidocaine2% gel or lidocaine as 1% cream. Thus local anesthetics provide symptomatic relief and temporarily alleviate the pain from RAS.

ii) Antiseptic and Anti-Inflammatory Therapies

Research has shown that the use of chlorhexidine (CHX) mouth rinses on RAS may be particularly helpful. (Piccione, 1979) It is a bisbiguanide antiseptic and antimicrobial drug with bactericidal activity; at high concentrations of chlorhexidine the cytoplasmic contents of the bacterial cell precipitate and result in cell death. It is used primarily as its salts (e.g., the dihydrochloride, diacetate, and digluconate). Antiseptic mouthwashes containing Chlorhexidine are widely used for the symptomatic treatment of RAS and are considered helpful by many patients, particularly if oral hygiene is difficult to maintain because of oral ulceration. Chlorhexidine can reduce the number of ulcer days and increase ulcer-free days and the interval between bouts of ulceration, but cannot prevent the recurrence of ulcers. Chlorhexidine is generally used as a 0.2% w/w mouth rinse, but the 0.10% w/w mouthwash or 1% gel can also be beneficial (Porter and Scully, 1998).

Triclosanis a broad spectrum antibacterial agent that also exhibits antiseptic, anti-inflammatory and analgesic effects. Available formulations include toothpastes and mouthrinses. A randomized, double-blind study that explored the topical application of diclofenac 3% in hyaluronan 2.5% reported a significant reduction in pain. (Altenburg *et al*., 2014)

iii) Topical Steroids

The most widely used drugs in immune-mediated oral mucosal diseases are the topical corticosteroids. The aim of such treatment is to eliminate the symptoms, thereby allowing the patient to eat, speak and perform normal oral hygiene, since topical corticosteroids reduce or even suppress the pain and shorten the aphthae healing time. In patients with RAS, the indicated drugs are triamcinolone acetonide, fluocinoloneacetonide or clobetasol propionate, in order of lesser to greater potency, according to the severity of the lesions. These three drugs can be administered as a pomade in orabase when the lesions are of a localized nature, or in rinse format when the lesions are diffuse or very numerous. Triamcinolone acetonide is used at concentrations ranging from 0.05-0.5%, applied 3-10 times a day for 3-5 minutes. It is indicated in patients with small and mild erosive lesions. Some authors consider the most effective concentration to be 0.1%. Fluocinolone acetonide at a concentration of 0.025-0.05%, applied 5-10 times a day for 3-5 minutes, affords medium to high potency, and is widely used in patients with more aggressive lesions. Lastly, 0.025% clobetasol propionate is the most potent topical corticosteroid, and is therefore reserved for moderate or severe disease presentations. In this context, it is regarded as an alternative prior to the prescription of systemic therapy. (Scully and Porter, 2008)

iv) Antibiotics

A more effective measure in the relief of symptoms caused by secondary infection is the application of topical antibiotics. Topical and systemic antibiotic treatments are empiric and are used because of a belief that some as-yet undiscovered infectious agent is causing the aphthous ulcer. Tetracycline and minocycline are the agents most commonly used. Tetracyclines are broad spectrum bacteriostatic antibiotics that inhibit protein synthesis. Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport. Susceptible organisms concentrate the drug intracellularly. A 250mg antibiotic capsule of tetracycline can be dissolved in 180 mL water and used as a "swish and swallow" or "swish and spit" treatment four times per day for several days in adult patients. Reduction of pain and duration of ulcerations may result. Tetracycline suspension, 250 mg per 5 mL, can also be used in a similar fashion, with 5 mL swished four times per day. Minocycline can also be used this way, with a 100-mg tablet dissolved in 180 mL water and swished twice per day. (Burgess *et al*., 1990)

v) Sucralfate

Sucralfate is a salt of sucrose complexed to sulfated aluminium hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours. Sucralfate has limited solubility, breaking down into sucrose sulfate (strongly negatively charged) and an aluminium salt. A variety of beneficial effects have been attributed to sucralfate, but the precise mechanism of action is unclear. It is believed that the negatively charged sucrose sulfate binds to positively charged proteins in the base of ulcers or erosion, forming a physical barrier that restricts further caustic damage and stimulates mucosal prostaglandin and bicarbonate secretion. Topical sucralfate is effective in treating RAS ulcerations when administered at 5mL, 4 times/day. Alpsoy *et al*. studiedtheuse of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease in a randomized, placebo-controlled, double-blind study and found significant reduction in frequency ($p = 0.003$) and duration ($p = 0.03$) of oral aphthous ulcers. (Alpsoy *et al*., 1999)

vi) Coating Agent

Carbenoxolone sodium

Carbenoxolone sodium has been effectively used for its anti-inflammatory and anti-allergic effects when applied externally and successfully used in viral-induced oral mucosal ulcers and aphthous ulcers. (Wattanakorn *et al*., 2010) Carbenoxolone reversibly inhibits the conversion of cortisol to the inactive metabolite cortisone by blocking 11β-hydroxysteroid dehydrogenase (11β-HSD). 11β-HSD also reversibly catalyzes the conversion of 7-ketocholesterol to 7-beta-hydroxycholesterol

Oral Bioadherent gel

Oral bioadherent adheres to the mucosal surface of mouth and forms a protective coating that shields exposed and overstimulated nerve endings. It is a mucoadherent which elicits mechanical action by adhering to the mucosal surface of the mouth. Ingredients include water, maltodextrin, propylene glycol, polyvinylpyrrolidone (PVP), sodium hyaluronate, potassium sorbate, sodium benzoate, hydroxyethylcellulose, polyethylene glycol (PEG)–40, hydrogenated castor oil, disodium edetate, benzalkonium chloride, flavoring, saccharin sodium, and glycyrrhetinic acid. (Buchsel, 2008)

vii) Topical Immunomodulators

These agents are inhibitors of the formation and/or release of inflammatory mediators Amlexanox 5% (Lexanox), a topical anti-inflammatory agent has recently been found to have significant role in management of minor aphthous ulcers. Amlexanoxis a topical anti-inflammatory, anti-allergic drug. Amlexanoxpotentialy inhibit the formation and release of histamine and luekotrines from mast cells, neutrophils, and mononuclear cells. Histamine and leukotrines are vasoactive inflammatory mediators which can only increase the permeability of vessels and therefore cause swelling of the involved tissues, but also contribute to inflammation by affecting the functions of other leukocytes in the involved area. (Liu *et al*., 2006) It is usually supplied in the form of an ointment at a concentration of 5%, and is applied 2-4 times a day. The drug has been shown to be effective in accelerating the healing of aphthae and in lessening the pain, erythema and size of the lesions.

viii) Aminosalicylic Acid

Drugs that contain 5-aminosalicylic acid (5-ASA) have been used successfully for decades in the treatment of inflammatory bowel diseases. 5-ASA differs from salicylic acid only by the addition of an amino group at the 5 (meta) position. Aminosalicylates are believed to work topically (not systemically) in areas of diseased gastrointestinal mucosa. Application of 5-aminosalicylic acid 5% cream (applying a small amount to cover the aphthae 3 times/day), or a toothpaste containing amyloglucosidase and glucose oxidase can reduce pain and lessen the duration of oral aphthae. (Collier *et al*., 1992)

ix) Hyaluronic Acid

Hyaluronic acid (HA) is an anionic, nonsulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is unique among glycosaminoglycans in that it is nonsulfated, forms in the plasma membrane instead of the Golgi, and can be very large, with its molecular weight often reaching the millions. (Fraser *et al*., 1997) HA is implicated in a range of activities including activation and moderation of the inflammatory responses, promoting cell proliferation, migration and angiogenesis, promoting re-epithelization via proliferation of basal keratinocytes and reducing collagen disposition and scarring. Nolan *et al* carried out randomized, placebo controlled investigation into the efficiency of a topical HA gel 0.2% (RF02 APH) in the relief of symptoms of RAU and concluded that topical HA (0.2%) may be of benefit in the management of RAU. (Nolan *et al*., 2006)

x) Use of Topical Ozone

Dr Richard M Logan demonstrated the beneficial use of topical application of ozone using the Healozone'appliance (Kavo) in a patient with long standing aphthous ulceration involving the lateral border of the tongue. The topical application of ozone provided an effective means of producing resolution of clinical symptoms related to aphthous ulceration for his patient. (Logan, 2005)

Systemic Management

The outbreaks of RAS are normally resolved with topical treatments, though in some cases these measures prove insufficient because of the severity of the lesions or for unknown reasons. This is when second line therapy with systemic drug substances is indicated.

Systemic drugs used for the treatment of RAS

i) Corticosteroids

Corticosteroids are the first choice systemic treatment. They are usually used as rescue therapy in patients with acute severe RAS outbreaks. Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids. There is decreased release of vasoactive and chemoattractive factors, diminished secretion of lipolytic and proteolytic enzymes, decreased extravasation of leukocytes to areas of injury, and ultimately, decreased fibrosis. Glucocorticoids can also reduce expression of proinflammatory enzymes, such as COX-2 and NOS. Oral prednisone has been used at a starting dose of 25 mg/day, followed by stepwise dose reduction, during two months, with disappearance of the pain and reepithelization of the lesions in the first month of therapy. The drug can produce long-term adverse effects; as a result, its efficacy has been compared with that of other drugs, in search of an alternative treatment.In this context, Femiano *et al*.compared the efficacy of prednisone prescribed at a dose of 25 mg/day via the oral route during 15 days, 12.5 mg/day during 15 days, 6.25 mg/day during 15 days, and then 6.25 mg on alternate days during 15 days, in comparison with montelukast (a leukotriene receptor antagonist used as an antiasthma drug) 10 mg via the oral route each night, followed by administration on alternate days during the second month. The authors found both treatment modalities to be effective in reducing the number of lesions, affording pain relief and accelerating healing of the ulcers. (Femiano *et al*., 2010)

ii) Antibiotics

Studies have been done with systemic antibiotics such as potassium penicillin G in 50 mg tablets administered four times a day during four days, which help reduce the size of the ulcers and lessen the pain. (Zhou *et al*., 2010) Diaminodiphenylsulphone (Dapsone) a widely used drug in the long-term treatment of leprosy and some dermatologic conditions have been tried with limited success in the management of major aphthae. Dapsone has both anti-inflammatory and antimicrobial properties. It inhibits folate synthesis. Dapsone is given 100mg orally in divided doses and may be increased at the rate of 50mg/day per week to a maximum of 300mg/ day. Dapsone, a potentially toxic drug, can precipitate hemolyticanemia, hence, the patients should be monitored for hemolysis, methemoglobinemia, anemia and agranulocytosis. (Lynde *et al*., 2009)

iii) Levamisole

Levamisolewas synthesized originally as an antihelminthic but appears to "restore" depressed immune function of B lymphocytes, T lymphocytes, monocytes, and macrophages. It is believed to reduce pain, number, durarion and the frequency of ulceration in major RAS. An increase in T-helper cells (CD4+ cells) and a decrease in T suppressor cells (CD8+ cells) may accompany RAU during periods of disease exacerbation and normalize during remission. Levamisole is an immunopotentiating agent that has demonstrated the ability to normalize the CD4+ cell/CD8+ cell ratio and improve symptoms in RAU patients. (Sun *et al*., 1994) Correction of T-suppressor cell deficiency may reduce the inflammatory response resulting from cellular immunity and promote resolution of aphthae. Levamisole in the dosage of 150mg/day for 3 days in every 2 weeks is found to have reduced the frequency and duration of aphthae in most of the studies. However, the reductions in pain often did not parallel the reductions in frequency and duration. Most of the trials neglected to exclude concurrent medications used in managing aphthae, which may have contributed to the disparity between subjective and objective findings.

iv) Colchicine

It is a toxic natural product and secondary metabolite, originally extracted from plants of the genus Colchicum. Colchicine renders cell membranes more rigid and decreases the secretion of chemotactic factors by activated neutrophils. Colchicine inhibits the release of histamine-containing granules from mast cells. Colchicine has been shown to reduce the number and duration of lesions in up to 63% of patients with RAS. (Fontes *et al*., 2002) Treatment over 6 weeks, followed by long-term (years) therapy (1-2mg/day) is recommended. However, relapse following treatment discontinuation is common.

v) Thalidomide

Thalidomide is a sedative drug that was withdrawn from the market in the 1960s because of its disastrous teratogenic effects when used during pregnancy. It has significant immunomodulatory actions and is currently in active use or in clinical trials for over 40 different illnesses. Thalidomide inhibits angiogenesis and has anti-inflammatory and immunomodulatory effects. It inhibits tumor necrosis factor-alpha (TNF-á), reduces phagocytosis by neutrophils, increases production of IL-10, alters adhesion molecule expression, and enhances cell-mediated immunity via interactions with T cells. The complex actions of thalidomide continue to be studied as its clinical use evolves. Owing to thalidomide's serious toxicity profile, considerable effort has been expanded in the development of analogs. Immunomodulatory derivatives of thalidomide are termed IMiDs. Some IMiDs are much more

potent than thalidomide in regulating cytokines and affecting T-cell proliferation. Thalidomide has pronounced efficacy in healing oral aphthae. In two trials involving difficult cases, thalidomide completely healed 48–55% of patients, compared with 7–9% of patients receiving placebo. However, the effect of thalidomide was temporary, with most patients having recurrent ulcers an average of 20 days after stopping therapy. Thalidomide also significantly increased subjective improvement. (Revuz *et al*., 1990) Under standard (100-300mg/day) or low (50mg/day) dosing levels of thalidomide, a dose-dependent effect against orogenital ulcerations emerges within 7-10 weeks following treatment. Due to teratogenicity and other potentially severe side-effects, therapy should be reserved for exceptional cases.

vi) Antimetabolites (Azathioprine and Methotrexate)

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase (and are, therefore, cell-cycle specific). Azathioprine, an imidazoyl derivative of mercaptopurine isoften used for immunosuppression in humans. It is started at 50mg/day and escalated up to 150mg/ day. The toxic effects of azathioprine include bone marrow depression, hepatic dysfunction, gastrointestinal disturbances and nephrotoxicity. Hence, complete blood count examination before and during azathioprine treatment is mandatory. It is contraindicated for women who are pregnant or breastfeeding, and it is not recommended for use in pediatric patients. In a randomised, double- blind and placebo controlled study of 73 patients of behcet's disease, azathioprine (2.5 mg/kg body weight/day) have been found to be effective choice in ulcerations in behcet syndrome patients. (Yazici *et al*., 1990) Methotrexate (7.5-20mg/week) has been proven to be effective in severe aphthosis. While on therapy, folic acid should be administered intermittently. (Vivek and Bindu J Nair, 2011)

vii) Cyclosporine A

Cyclosporine is a lipophilic cyclic polypeptide composed of 11 amino acids (several of the amino acids are methylatedon the peptidyl nitrogen). The drug is extracted from the soil fungus Beauverianivea. Cyclosporine is used to prevent rejection of kidney, liver and cardiac allogeneic transplants. Cyclosporine preferentially suppresses cell mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, cyclosporine binds to a cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin. The latter is responsible for dephosphorylating NFATc (cytosolic Nuclear Factor of Activated T cells). Because the cyclosporine-calcineurin complex cannot perform this reaction, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a numberof cytokines, including IL-2. The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes. Cyclosporine A, at a dosage of 3-6mg/kg, was shown to be effective in about 50% of Behcet Disease patients with respect to aphthosis. (Zouboulis, 2003) However, abrupt withdrawal of therapy may lead to a rebound phenomenon.

viii) Cimetidine

Cimetidine has been advocated for a number of dermatological diseases. The cutaneous uses and immunological effects of cimetidine have been actively studied over the past few years. Cimetidine has a valuable role in treating of PFAPA syndrome (Periodic fever, apthous stomatitis, pharyngitis, adenitis). In one study, it was as an effective first-line therapy for PFAPA at 20 mg/kg/day, curing 49 of 83 patients. (Lee *et al*., 1999; Pillet *et al*., 2000)

ix) Biologics

Biologics or biological agents like Infliximab (a monoclonal antibody) which acts against TNF alpha (an inflammatory cytokine), at 5mg/kg IV can be administered at different time intervals. As early as several days following the first dose, rapid healing can occur. It is possible that relapses may not occur within the first 6 weeks of starting therapy. Etanercept (tumor necrosis factor inhibitor) at 25mg, twice weekly, given subcutaneously, appears to be effective on oral aphthae. (Sfikakis *et al*., 2007)

Use of lasers

Laser therapy has been reported to provide pain relief and lesion resolution for isolated lesions, but it does not affect episodic recurrence. Nd:YAG laser has been found to afford immediate pain relief and faster healing, and is well tolerated by patients with RAS, since it is a brief form of treatment, results in lesser pain after application, and has few side effects. (Tezel *et al*., 2009) Pulsed neodymium: yattrium-aluminum-garnet lasers (Nd-YAG) have been used to treat all three types of recurrent aphthous ulcers successfully. The lasers vaporize the lesions and leave a healthy bed of tissue. It ablates the lesion in 30 to 45 seconds. The treatment is painless and patients report immediate relief of symptoms. Laser treatment compares favourably with other treatment modalities owing to lack of side effects and contraindications, and immediate palliation of lesions. (Convissar and Massoumisoure, 1992) A prospective clinical study was performed to compare immediate pain relief, healing time between minor recurrent aphthous ulcers treated with a single session of carbon dioxide (CO_2) laser and a placebo on 25 patients with minor recurrent aphthous Stomatitis. It was concluded that CO_2 laser therapy in recurrent aphthous stomatitis (RAS) provide immediate pain relief sustained over 24 h, along with accelerated healing time. (Prasad and Pai, 2013)

Alternative treatment modalities

Sage and Chamomile mouthwash, created by infusing equal amounts of the two herbs in water, may be helpful when used four to six times a day. Salvia officinalis (sage, also called garden sage, or common sage) is a perennial, evergreen subshrub, with woody stems, grayish leaves, and blue to purplish flowers. Popular uses of chamomile preparations include treating hay fever, inflammation, muscle spasm,

menstrual disorders, insomnia, ulcers, gastrointestinal disorder, and haemorrhoids. Echinacea is reported to speed healing, perhaps through its immune modulatory effect.

Rosa Damascena, more commonly known as the Damask rose, is a rose hybrid, derived from two rose variants, Rosa gallica and Rosa moschata. A randomized, double-blind, placebo-controlled study reported anti-inflammatory and antinociceptive properties, in the treatment of recurrent aphthous stomatitis. Rosa damascena mouthwash was found more effective than the placebo in the treatment of recurrent aphthousStomatitin on days 4 and 7. (Hoseinpour *et al*., 2011)

Shark Liver Oil has been used for centuries as a folk remedy to promote the healing of wounds and as a remedy for respiratory tract and digestive system problems.Shark liver oil contains compounds that have a positive immunomodulation action and alleviate the course of disease. (Gurañska *et al*., 2001)

Eupatorium Laevigatum: Lam is a plant common to the central region of Brazil, where it is a widely used remedy for lesions such as buccalaphthae. A study was conducted to evaluate the toxicologic safety of *E.laevigatum* extracted orabase paste in 20 healthy volunteers and then to conduct randomized, double-blind comparison of efficacy with triamcinolone 0.1% orabase in 60 patients. The healthy volunteers tolerated the phytotherapeutic paste well, and no adverse effects could be attributed to its use. In the clinical comparison, after 5 days of treatment, 40% of the patients who used the paste and 26.7% of those who used triamcinolone obtained complete cure of the ulcers. Pain was alleviated in 70% of the phytotherapeutic group and in 33.3% of the triamcinolone group. The phytotherapeutic paste of *E. laevigatum*was a found to be a safe and effective treatment of buccal aphthae. (Filho *et al*., 2000)

Propolis is a bee product used in some cultures as treatment for mouth ulcers. In a randomized, double-blind, placebo-controlled study by Nachum Samet *et al*. patients were assigned to take 500 mg of propolis or a placebo capsule daily. Subjects reported a baseline ulcer frequency and were contacted biweekly to record recurrences. The data indicated a statistically significant reduction of outbreaks in the propolis group. Patients in the propolis group also self-reported a significant improvement in their quality of life. (Samet *et al*., 2007)

Alum: Astringent alum are protein precipitants, which have low cell penetrability and the action is essentially limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced but cells remain viable. The alum action is accompanied by contraction and wrinkling of the tissue and by blanching. The cement substance of the capillary endothelium is hardened, so that pathological trans-capillary movement of plasma protein is inhibited and local edema, inflammation, exudation are thereby reduced and promote healing. Also have the ability to interact with fatty acids liberated or produced by action of bacteria on lipids and by an action suppressing bacterial growth, partly because of a decrease in pH. (ALtaei *et al*., 2005)

Aloe vera (A.V.) is a tropical plant with anti-inflammatory and immunostimulant effects, which could be of benefit in a diversity of wound healing conditions. A.V. 2% oral gel is not only effective in decreasing the recurrent aphthous stomatitis patients' pain score and wound size but also decreases the aphthous wound healing period**.** Babaee N evaluated the effect of topically administered A.V. gel on oral cavity minor aphthous healing. The healing time (days after gel application), patient's pain score; the lesion and its surrounding inflammation diameters were recorded for 2 weeks. The duration of complete wound healing, pain score, wound size and inflammation zone diameter in the A.V.-treated group were significantly lower than the control group on specific time points after treatment. (Babaee *et al*., 2012)

Honey is a sweet food made by bees using nectar from flowers. The variety produced by honey bees (the genus Apis) is the one most commonly referred to, as it is the type of honey collected by most beekeepers and consumed by people. Honeywas found to be effective and safe in reducing minor aphthous ulcer pain, size, and erythema in a Saudi cohort study carried out by El-Haddad *et al*. The agents were commercial honey (34 patients with 67 RAU in group 1) triamcinolone acetonide 0.1% (30 patients with 57 RAU in group and 2) Orabase adhesive paste (30 patients with 56 RAU in group 3). It was found that Topical honey was associated with more dramatic reduction in ulcer size compared with triamcinolone, which was associated with larger reductions than Orabase. (El-Haddad *et al*., 2014)

Camel Thorn is a common name for Vachelliaerioloba, a southern African legume. A single trial of camel thorn randomised 93 participants to the plant distillate (n = 49) or placebo (n = 44) for the aphthous ulcer episode duration (Pourahmad 2010). The authors report a shorter mean time to complete resolution for camel thorn (mean 4.02 days; range from 3 to 7 days) compared to placebo (mean 8.9 days; range 7 to 14 days). Outcomes of lesion diameter and intensity of pain were analysed at multiple time intervals until 14 days frominitial referral. The authors reported lower pain and smaller lesions in the camel thorn groups up to 10 days after referral. (Pourahmad *et al*., 2010)

Conclusion

Management of aphthous ulcers has largely been restricted to provide symptomatic relief to the patients and hardly any success has been achieved in preventing recurrence of the disease.

Topical anti-inflammatory agents remain the cornerstone of treatment and myriad of drugs have been researched in curing this condition, rather with limited success. Dietary restrictions, topical steroids, topical antibiotics, topical immunomodulators, and coating agents are the mainstay to reduce pain and inflammation. Systemic drugs are used when the lesions are extensive, (major and herpetiform) and no relief is obtained with topical agents. Several Alternative treatment have been tried including certain herbs, natural substances, chemical agents which have shown limited success in treating this self limiting but challenging condition.

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