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Medical Management of Oral Submucous Fibrosis - A Narrative Review

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Abstract *Oral submucous fibrosis, an oral potentially malignant disorder is a prevalent condition especially in the Asian subcontinent. Medical management is an integral part in the treatment of OSF. Evidence based practice with efficient protocol and treatment plan to address the patients concern is the current strategy applied. Though several factors play a crucial role in choosing the appropriate drug, lifestyle change, and habit cessation are the preliminary steps towards the methodological and systematic approach in management of OSF. So far none of the reported studies have examined the beneficial role of therapies in preventing malignant transformation in OSF patients. Understanding the importance of medical management in OSF vital as it remains a dilemma for oral medicine practitioners. Literature is abundant with variety of Anti-inflammatory drugs, Immunomodulators, Proteolytic/fibrolytic drugs, Antioxidants, Vitamins and micronutrients, Novel therapies for treatment of OSF. Therefore, we provide a working classification of drugs in OSF along with their mechanism of action, formulation, administration, bioavailability, safety profile, treatment outcomes and adverse effects of the drugs.*

Keywords *Anti-inflammatory Drugs, Antioxidants, Fibrolytic Drugs, Immunomodulators, Medical Management, Oral Submucous Fibrosis.*

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Introduction

Oral Submucous Fibrosis (OSF), a predominant condition of approximately seven decades, remains a predicament for oral medicine experts. From the patient's viewpoint, the two main clinical symptoms that propels them to approach the practitioner are: 1. Reduced mouth opening/ trismus and 2. Burning sensation of the oral mucosa [1]. These symptoms, not only impede the patient from their daily routine, but also hampers their lifestyle at different levels: ranging from nutritional status, communication along with their physical, psychological and social well-being. However, in majority they recognize and report the former and appeal for symptom relief. From the practitioner's point of view, management of OSF is a perturbed subject. Apart from providing symptomatic relief, evaluating the habit history, addressing the etiological factors with emphasis on habit restriction and dietary counselling are equally important, thus directing towards a lifestyle change. From clinician's perspective, deterrence of progression of this chronic condition is their focus [2]. Further, being a potentially malignant disorder, it carries a jeopardy of developing cancer and hence beseeches a vigilant response from the practitioner.

Exploration of medical management of OSF remains an enigma. As appraised by Kerr et al at the 5th World Workshop in Oral Medicine, reinforced the time-honoured Caniff et al declaration that OSF management is both empirical and unsatisfactory [3], rationale being the extensive line up of therapeutics available. These medications not only differ in their mechanism of action, but also the route of administration ranging from oral to topical to intralesional and even in their derivation (natural/ synthetic), which may even form the basis of their classification. Though some medications are still in practice, however newer medications emergence cannot be deterred. Moreover, it has to be noted that some of them may be affiliated to more than one subcategory. For example, placental extract can be administered either topical or intralesional, similarly, corticosteroids are administered in the former two routes.

To date, scientists have not reached to a conclusive and widely accepted treatment protocol. Observations on compilation of scientific data over the geographies, demonstrated disparity in research design, sample size, grades of OSF, variation in areca nut habits, methodological differences in assessment and uncertain validity of limited data for the effectiveness of intervention of OSF. Further, the mechanism of action of each drug differs and even their combinations used. Variability in different forms of drug administration is also evident [4]. Moreover, development of various treatment schedules over the period of time with exploration of different routes of administration are noted. These wide range of approaches provide documentation of an absence of universal treatment protocol. Therefore, an evidence-based practice is the requisite to be followed in the management of OSF [3]. Thence, a comprehensive description of the available medical treatment regimens for OSF are discussed. Figure 1 provides a working classification based on the mechanism of action of the drugs in the medical management of OSF.

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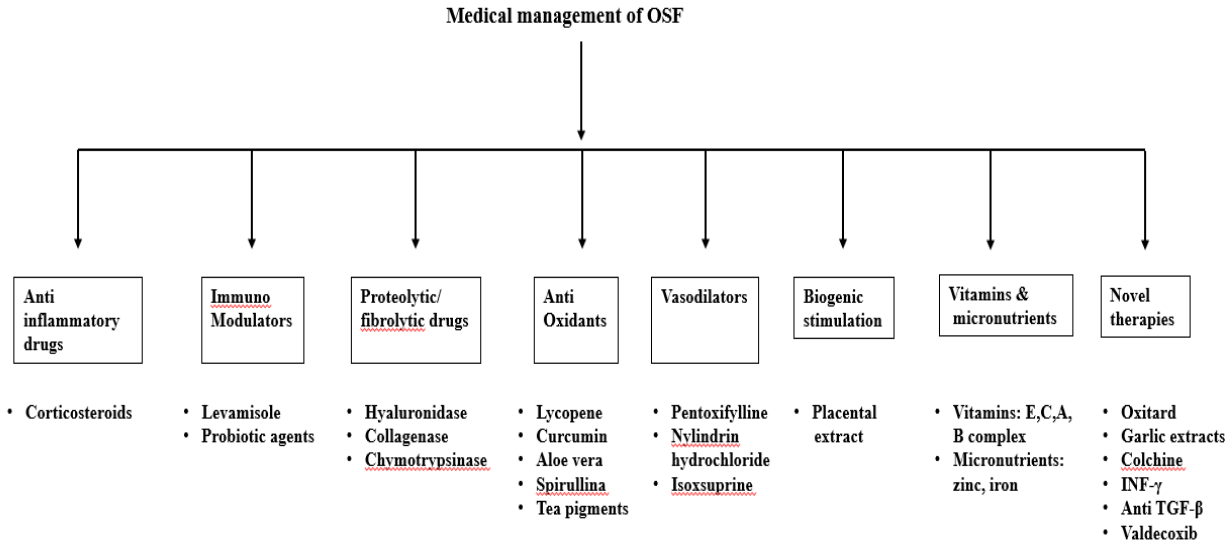

Figure 1. Classification based on the Mechanism of Action of Different OSF Drugs

Anti-Inflammatory Agents

Inflammation being a crucial part in the initiation and progression of OSF, anti-inflammatory drugs are the mainstream choice for its management. Though most of the drugs evaluated or are being evaluated, exhibit anti-inflammation component to an extent. Similarly, corticosteroids an effective anti-inflammatory drug is capable of inhibiting virtually all the different components of inflammation with instrumental immunosuppressive biological action.

Corticosteroids

Corticosteroids, are one of the extensively employed drugs almost in all areas of medicine. These natural steroid hormones secreted endogenously are produced by the adrenal cortex while their synthetic analogues are manufactured for therapeutic use. Corticosteroids application in OSF management is due to its inflammatory suppression action; fibrosis prevention by plummeting proliferation of fibroblasts and collagen deposition; and immunosuppressive by countering the action of soluble factors of sensitised lymphocytes. Reducing proinflammatory cytokines, chemokines, phospholipase A2, cell adhesion molecules, impairing release of arachidonic acid, decrease the COX and LOX expression, thereby the biosynthesis of PG and LTX, inhibition of NF-kappa-B pathway wherein the IL-6 and 8, MCP-1 expressions are targeted and many such biological molecules involved in the inflammatory response confers it the anti-inflammatory action [5].

Hydrocortisone, dexamethasone, triamcinolone and betamethasone are the commonly prescribed synthetic corticosteroids whose biological actions are on almost similar grounds. While betamethasone possesses a half-life of 36 to 54 hr, dexamethasone with 36-72 hrs, triamcinolone with 18-36 hrs, hydrocortisone is the least with 8-12 hrs.

Anti-inflammatory action of steroids is significant at doses 3–10 times of physiologic baseline dose i.e. 2.25–7.5 mg dose. The route of administration ranges from oral (tablets/ capsules), topical (creams/ ointment/ patches)

to intralesional injection. In OSF management, while betamethasone and triamcinolone acetonide are commonly used as topical agents; hydrocortisone, dexamethasone and triamcinolone diacetate are used as intra lesional injections. While few researchers preferred intralesional injections citing the bioavailability through the blanched and avascular oral mucosa will be less with topical compared to direct deposition with injections into the fibrotic tissue, on the other hand topical application is considered a better choice to address the drawbacks of intralesional injection like inflicting pain, scar formation due to needle prick and to avoid greater chances of relapse by others. Further, studies do advise topical formulation may be ineffective for prolonged use, hence, future trials using muco-adhesive patches are being considered [6].

The adverse effects range from initial itchiness, burning sensation, irritation, to headaches, dizziness and cardiovascular effects to hypothalamic-pituitary-adrenal (HPA) suppression, osteoporosis on prolonged use. Precaution needs to be taken when prescribed in known diabetes mellitus due to its hyperglycaemic adverse effects [7]. Further, need for repeated injections, prolonged half-life of the drugs raises safety concerns.

Immunomodulators

Immunomodulators are either biological or synthetic agents with the ability to stimulate, suppress or even modulate any aspect of the immune system comprising of both the adaptive and the innate arms of the immune system.

Levamisole

Levamisole, a broad spectrum anti-helminthic drug, was also discovered to increase cellular immunity, hence was permitted for its use in numerous autoimmune and anti-inflammatory diseases. Therefore, it is administered in the treatment of various oral lesions, namely recurrent aphthous stomatitis, oral lichen planus and herpes labialis [8].

This synthetic phenylimidothiazole salt, is a known immunomodulator as it functions as an immunosuppressant at prolonged doses and immunopotentiator on low and intermittent doses. Other biological actions other than anti helminthic are anti-inflammatory through TNFα and IL inhibition, antineoplastic by anti-angiogenesis and apoptosis [9].

Studies with levamisole as a treatment regime in OSF are a handful. Therefore, the dosage and safety profile are a limitation. Nevertheless, based on scientific documentation on other medical conditions, it was reported with adverse effects comprising of nausea, vomiting, fever, dizziness, headache, tiredness and skin rash. Agranulocytosis has been reported on long term therapy. Therefore, intermittent use with regular blood monitoring is recommended [10].

Probiotic Agents

Immunized cow's milk, milk from cows immunized with human intestinal bacteria (immune milk) was considered by Tai et al as treatment for OSF. The rationale for assessing it could be conferred to the anti-inflammatory component and modulation of cytokine production. 26 OSF patients in the study received 45 g of immune milk powder twice a day for 3 months along with oral habit intervention in contrast to 20 patients of control group with oral habit intervention alone. A significant improvement was recorded in the inter-incisor distance ≧3 mm of the baseline measurement in 18/ 26 cases while in control group none of the cases had an increase greater than 2 mm. Improvement in 16/20 patients with intolerance to spicy foods and 13/18 with xerostomia of experimental group were registered, thereby providing evidence of significant improvement when compared to control group. Hence, the authors concluded that immune milk did present with significant clinical improvement [11]. However, it is to be noted that no further studies are reported to

confirm reproducibility of the results reported of this one single study.

Proteolytic/Fibrolytic Enzymes

Though conventional therapeutics target the inflammatory stage of OSF, a school of thought have proposed addition of anti-fibrotic medications to the former. These fibrolytic or anti-fibrotic dugs are enzymes that have great scope in pharmaceuticals activities because of their highly selective nature and good efficacy at low concentrations, but remain largely unexplored owing to their expensive nature which in turn poses a hindrance to conduct trials in countries with high incidence of OSF cases, hence limiting its exploration [12].

Hyaluronidase

Hyaluronidase is an enzyme that breaks down hyaluronic acid has been in medical practice for long. This endoglycosidase is bestowed with the ability to hydrolyse the mucopolysaccharides aiding in tissue permeability and paving way to liquid diffusion through the microenvironment. This biological action lowers the viscosity of intercellular cement substance and allows better absorption of water- based medication. This feature of hyaluronidase is employed in the treatment of OSF. Steroids are commonly considered combinations with hyaluronidase for it facilitates better penetration. Significant improvement was documented with respect to trismus and fibrosis.

Dilution, diffusion and deactivation encountered on injection of hyaluronidase leads to a gradual activity decrease overtime. The short half- life is due to the presence of numerous hyaluronidase inhibitors and its metabolism in the kidneys and liver [13].

Chymotrypsinase

Chymotrypsinase, an endopeptidase, hydrolyses ester and peptide bonds, thus performs the role of proteolytic and anti-inflammatory agent. These actions are a requisite for the effective OSF management. Gupta et al subjected 200 OSF patients to biweekly submucosal injections and were divided into 8 different groups and evaluated for a period of 10 weeks. The groups were :1- Dexamethasone (4 mg) , 2- Hyaluronidase 1500 IU; 3- Chymotrypsin 5000 IU; 4- Placental Extract (2 mL); 5- Hyaluronidase+ Dexamethasone; 6- Chymotrypsin + Dexamethasone; 7- Hyaluronidase+ Dexamethasone+ Chymotrypsin; 8-placental extract +dexamethasone. They reported that Hyaluronidase+ Dexamethasone+ Chymotrypsin group provided with 100% relief in burning sensation and 94% improvement in mouth opening, while Chymotrypsin + Dexamethasone with 94% and 83% and Chymotrypsin with 84% and 76 % respectively. The authors concluded that the Hyaluronidase+ Dexamethasone+ Chymotrypsin provided the most satisfactory results when compared to other drugs either alone or in combination [14].

Collagenase

Collagenase, first identified in 1962, is an enzyme with known ability to break I, II, III, IV collagen and even cleave the triple helix domain of collagen. Since this enzyme abstain from causing harm to cell membrane, it is employed in cell dispersion, tissue separation and cell culture laboratories. Xiapex, comprising of collagenase enzyme, attained from Clostridium histolyticum bacterium, is promoted for Duputrene's contracture treatment and its efficiency was confirmed by Hurst et al. This enzyme is also considered in wound debridement and healing [15]. Gaps in data, limited evidence, economic feasibility though a major deterrent for their implementation, recent advancements of identification and characterization of other numerous collagenases of bacterial and mammalian origin may bridge this gap in the scientific literature.

Antioxidants in OSF

The role of oxidation process and its products such as free radicals, reactive oxygen

species (ROS), lipid peroxidation in OSF is well documented. Antioxidants are molecules that are known to prevent cell death or damage by preventing and intercepting these free radicals. They are antimutagenic, antimitogenic molecules and act by immune system stimulation or direct action on the target cells. Therefore, antioxidant supplementation would be an ideal choice to counteract it.

Lycopene

Lycopene, a fat-soluble red carotenoid, obtained from plants (tomatoes) and microorganisms, is a potent radical scavenger. This photochemical has gained interest due to its biological and physiochemical properties.

Being the most efficient singlet oxygen quenching carotenoid, enables it to protect the cellular components against ROS species. Encircling both physical and chemical antioxidant function, researchers have documented that lycopene reduces the lymphocyte DNA susceptibility to oxidative damage, inactivates the oxidative products, the free radicals, ROS, LPO, thereby preventing the membrane damage and cellular death. In addition, fibroblastic activity was inhibited by lycopene in hepatic fibrosis which was demonstrated by invitro studies [16].

Further, it decreases cellular cyclin D1 protein level, an oncogene, thereby inhibiting the progression from G0/G1 to S phase of the cell cycle curbing the progression and proliferation of tumor cells. It is also hypothesized similar action on P53 and Rb anti-oncogenes. Additionally, it also curbs the inflammatory process and modifies gene expression responsible for collagen deposition and its degradation.

Moreover, it also contributes in apoptosis induction, angiogenesis, regulation of gap junction communication, anti-inflammatory enzymes modulation to an extent. Various in-vitro an in-vivo studies have proved its effective antioxidant potential, hence its role in treating premalignant and malignant lesions, OSF being one among them [16].

Commonly dispensed as capsules or soft gels and oral route of administration is favoured. Though 0.5-27g / day is the dietary allowance of lycopene, its bioavailability is affected resultant of which only 10–30% of the total ingested lycopene is being absorbed by the human body. The dose range among the recorded studies varied from 16-32 mg / day [16].

Turmeric

Turmeric (Curcuma longa), also referred to as Indian Golden spice, a herbaceous medicinal plant native to South Asia, has been in traditional use for ages. Curcumin, its active ingredient, (accounts for about 2.9%, dry weight), a polyphenol compound is the main reason for its therapeutic action. Turmeric as a medicament for OSF dates back to the year 1998 by Hastak et al. However, it gained popularity owing to natural ingredient therapeutic revolution of recent times. Invitro and in-vivo investigations followed wherein turmeric extracts or active curcumin (mixture of three curcuminoids) were used [17].

Its actions range from anti-inflammatory, hepatoprotective, antimicrobial, antioxidant, antifibrotic to anticancer properties. Fibrinolytic activity of curcumin is well documented in literature. This particular mode of action is the resultant of its properties: 1. Lipid peroxidation, 2. Inspecting cellular proliferation, and 3. Impede collagen synthesis. Inhibition of NF-κB activation forms the crux of its anti-inflammatory action wherein it blocks its phosphorylation and degradation of the complex and hence it remains bound in the cytoplasm thereby active transcription is inhibited. Another important feature of curcumin is its scavenging effect on superoxide and hydroxyl radicals and nitric oxide from activated macrophages which decreases the burning sensation of the oral mucosa. Its anticancer properties are ability to modulate

molecular targets, inhibition of transcription factors, enzymes (COX-1 and 2, LOX) cytokines (TNF, IL-1 and 6,) and anti-apoptotic genes (BCL2, BCL2L1) [18].

It has low bioavailability, studies suggests use of curcumin in various forms: A) Oral forms include 1. Curcumin longa tablets (300mg +5mg pipperine tablets/ 400 mg tablets)., 2. Curcumin capsules (400mg+100mg black pepper capsules), 3. Curcumin caplets (1gram caplets), 4. Turmeric oil capsules, 5. turmeric oleoresin,6. turmeric extract, B) Topical forms include 1. losagens (2gram) 2. Mixture /paste (1 g tulsi powder +1g turmeric powder in glycerine), 3. Mouth wash (10 ml of turmeric, Triphala, and honey mouth wash). Variation in dosage administration is noted among studies. Overall, 2-3 times a day for a duration of 3- 6 months or even until cure has been reported [19].

On evaluation of safety profile of the drug, human clinical trials have reported no toxicity on administration of 10g/day. However, reports of yellow coating on the tongue surface and teeth due to topical application which could be eliminated with oral prophylaxis and hygiene maintenance [17].

Aloe vera

Aloe vera (AV), a perennial green herb native to tropical and semi-tropical regions, archived for its intensive historic use in different ancient cultures in the eastern geography. Referred to as “medicinal plant for millennia” or “miraculous plant” by some, it is incorporated as an ingredient of food, cosmetics and various pharmacological preparations. Widely used as herbal treatment, adjuvant and even alternative treatment modality for various diseases and conditions, AV is a promising upcoming treatment [20]. However clinical trials published for oral diseases date to 2002 onwards.

Of the 360 species, Aloe barbadensis Miller and Aloe aborescens are of commercial importance. The mucilaginous gel secretion from parenchymatous cells of its leaves contain 98-99% water and 1-2% of active compounds. This small fraction in itself is a plethora of nearly 75 constituents ranging from simple minerals to complex compounds comprising of vitamins (A,C,E,B12), enzymes, minerals (Zn, Cu, Se, Ca), sugars, anthraquniones (Aloin, Aloe-emodin, Emodin, acemannan considered as the major active compounds), fatty acids, hormones ,essential and non-essential amino acids, others such as salicylic acid, arachidonic acid, saponins and many more [20].

World literature documents in-vitro, in-vivo and clinical trials elucidating the pharmacological activities of aloe vera, owing to its anti-inflammatory, immunomodulatory, antioxidant, wound healing, antimicrobial, anti-tumour, antiseptic exhibition of properties.

Administered either in systemic form: juice, syrup, capsules or even in topical form: gel (varied concentration available), cream, mouth wash. Easy availability and cost effective are two attractive attributes of aloe vera. It has also been reported to be safe and well tolerated without any side effects in general. However, allergic reaction on topical application due to anthraquinones compounds- diarrhoea, electrolyte imbalance on ingestion has been reported.Thereby, International Aloe Committee of Science Standards has determined that the maximum allowable Aloe vera juice content for oral medical use should be less than 10 ppm [21].

Positive results have increased its acceptance into various treatment protocols. In majority, clinical trials with aloe vera are documented rather than its isolated compounds. Hence the potential and efficacy can be better elucidated with further unravelling the complexity of action and its effects.

Spirulina

Arthrospira, commonly referred to as Spirulina, a ubiquitous blue-green filamentous unicellular microalgae, belongs to the class of cyanobacteria. Native to tropical – sub tropical

salt lakes with high pH, Arthrospira platensis is the predominant species among the family and most often commercially cultivated [22].

Known as a functional food, it is a rich source of proteins (60-70%), amino acids, vitamins (B complex, carotenoids, tocopherols) essential oils (stearidonic Acid, arachidonic acid, γ-linolenic acid), polysaccharides, cyanins (C-phycocyanin) and minerals (iron, calcium).

The bioactivity of these compounds includes cancer prevention due to antioxidant, anti-inflammatory and antimutagenic activity, mutagen trapping, xenobiotic metabolism modulation, apoptosis induction and ability to bind to heavy metals and radioisotopes [22].

These functions have been elicited and probable mechanism been put forward independently by many in vitro and in vivo studies. The antioxidant property has been attributed to its phytopigments, tocopherol, γ-linolenic acid and phenolic compounds, mainly the carotenoids and phycocyanin.

Commonly formulated as either a single ingredient or in a combination with other algae and its compounds. They are dispensed as tablets or powders commercially. This palatable alga is non-toxic with good bioavailability as reported by studies and even recognized as safe by the Food and Drug Association [23]. However, though well tolerated, headache, muscle pain, flushing of the face, sweating, and occasionally dermatological reaction as adverse effects are recorded. Along with additional clinical studies, research on development of local and nanoparticle-based delivery approaches are needed to reinforce Spirulina in OSF treatment [23].

Tea Pigments

Tea, (Camellia s6nensis), globally consumed beverage, is of different categories ranging from white, green, yellow, oolong, black, to dark teas. It is an ample reservoir of bioactive compounds: polyphenols, pigments, polysaccharides, alkaloids, free amino acids, saponins with a wide array of functions. Be it antioxidants, anti-inflammation, immunoregulation, anticancer function to hepato, neuro, reno, and cardiovascular protection, its benefits are many. Tea pigments, the oxidised products of polyphenols, mainly comprise of theaflavins (TFs), thearubigins (TRs), and theabrownin [24].

This polyphenol component is considered as the main antioxidant component of tea. It functions both as a direct and indirect ROS scavenger. Its antioxidant activity involves the NF-κB signalling pathway. They improve microcirculation, increase the activity of superoxide dismutase [25].

Tea and tea pigments have an exceptional set of benefits. Global availability, popular beverage, economic, safe and well tolerated, they also surpass the antioxidant capacity of vitamins and offsets the latter disadvantages of photosensitivity of natural vitamin and adverse effects of synthetic vitamin [25].

However, many challenges are met for its clinical applications, be its form, usage, dosage, regulation of bioavailability of tea and its compounds. Further studies on tea and its compounds as a treatment modality are required to establish its role in treatment of OSF.

Vasodilators

The basis for prescribing vasodilators in OSF is capillary dilation which help to restore the nutrients and therapeutic supply to the area of interest.

Pentoxifylline

Pentoxifylline, a methylxanthine derivative, is used to treat peripheral vascular diseases owing to its vasodilating property. It is a non-specific type IV phosphodiesterase inhibitor, with multiple biological functions. Reduction in collagen production (fibrinolytic response), IL-6, IL-2 and TGF α and β1 expression (anti-inflammatory response); upregulation of VEGF mRNA through mRNA stabilization and its half-life prolongation (vasodilation); increase in leukocyte chemotaxis, anti-thrombin, anti-

plasmin activities, red cell deformability; increase in PGE2 and PGI2 by vascular endothelium(cellular integrity and homeostasis) ;decrease in aggregation of red cells and platelets, granulocyte adhesion and fibrinogen levels are few functions documented [26].

The fibrinolytic activity by PTX is credited to increased collagenase activity and decreased collagen, glycosaminoglycans, and fibronectins production by the fibroblasts. Studies have also reported PTX inhibitory activity on IL-1 induced fibroblast proliferation and TNF-α induced fibroblast collagen and glycosaminoglycans synthesis. The drug is prescribed as capsules or sustained release tablet for oral consumption initially through lesser dose followed by recommended dose which is 400 mg three times a day after food [27].

Dose related side effects such on gastro intestinal and central nervous system on PTX administration comprising of dizziness, headache, tremor, anxiety, confusion, dyspepsia, nausea and/or vomiting, bloating and flatus. In addition, SRT may lead to minimal gastric intolerance. As contrasting results were observed with PTX in OSF, Lui et al conducted a meta-analysis and authors observed that PTX effectively improved the burning sensation and its therapeutic efficacy also increased with time [27].

Nylidrin Hydrochloride

Nylidrin hydrochloride is a peripheral vasodilator which is chemically associated to the epinephrine-ephedrine series. In diffuse fibrosis, it is believed to act by relieving the local ischemic effect, leading to blood vessels dilation hence warranting nutritional and therapeutic measures reach site of interest. This action is considered beneficial in OSF wherein local ischemic effects secondary to local fibrous conditions; hyperkeratosis are its features. it is orally administered commonly in combination with other conventional OSF therapies. It is noted to be more effective in early onset cases and in younger age group [28].

Isoxsuprine

Isoxsuprine, a phenylalanine derivative of epinephrine, is a β-adrenoreceptor agonist. It causes an increase in cytosolic calcium concentration level, thereby stimulating the production and release of various endothelium-derived vasodilators. Further, it also inhibits platelet aggregation and reduces blood viscosity. It is reported to cause facial flushing on low dose and tachycardia and hypotension on high dose administration. Studies have reported no adverse effects for the dosage administered. Among all the vasodilators studied, isoxsuprine was reported to be effective and well tolerated with the used dosage [29].

Biogenic Stimulation

Biogenic stimulators are substances with capability to stimulate the biochemical and regenerative process when placed in contact with diseased tissue. Various sources considered for tissue therapy are placenta, placental extract, cod-liver oil, to name a few, are administered either as auto-transplants, homologous and heterologous transplants and injections. The readily available homologous substance, the human placenta, is on the path to revolutionise the modern medicine.

Placental Extract

Placental extract, an immunologically privileged organ, is known to stimulate recovery of diseased tissues through biogenic stimulation. It is an assembly of assorted bioactive molecules ranging from peptides, amino acids, growth factors, glycosaminoglycans, nucleic acids, polydeoxyribonucleotides, hormones and proteins whose actions on various sites and conditions have been studied and recorded [30].

Immunotropic effect exerted on both humoral and cell mediated immunity; restoration of T and B lymphocytes dysfunction

to normal depicting immunomodulatory effect; suppression of prostaglandin synthesis and perotonin release aiding anti-inflammatory action; vascularization flow promoting wound healing, metabolism stimulation, analgesic function, enhancement of recovery and regeneration of tissue owing to the growth factors present are some on the biological functions reported. These assorted actions are considered favourable in OSF management [30].

Both topical and intra lesional injection are advocated, however clinicians did report difficulty while administering intralesionally in severe grade OSF cases. On its efficacy assessment, it was observed that though mouth opening was partially relieved, however, improvement in burning sensation was substandard.[30] On the contrary, its post operative use in OSF patients treated with fibrotomy with buccal fat pad coverage and coronoidectomy, mouth opening presented with superior results.

Vitamins and Micronutrients

Vitamins and micronutrients are essential for the overall well-being and maintenance of health.

Vitamins

Vitamin E also known as tocopherol, functions as a chain breaking antioxidant which inhibits propagation of free radical reaction. It is believed to harbour a preventive role in oral carcinogenesis owing to its ability to inhibit tobacco specific nitrosamine reactions. The diverse actions interpreted by vitamin E in literature are experimental carcinogenesis retardment, adequate Langerhans cells sustainment, effective humoral immune response stimulant, anti-inflammatory action and even stimulation of potent immune response to eradicate microscopic carcinoma foci [31]. Vitamin C, also known as L-ascorbic acid, is a potent anti-oxidant and immune modulating agent. It exerts multitude beneficial effects ranging from stimulation of neutrophil migration, enhancement of phagocytosis, killing of microbes, limits vitamin E degradation, constrains formation of nitrosamine, supports in absorption of iron and so on. Vitamin A, also known as retinol, possess both promotion and regulation role on the innate and adaptive immunity [32]. Vitamin B complex plays an essential role to maintain optimal health status. It is though to alleviate the clinical presentation of OSF like glossitis and cheilosis. Further, it exerts a positive influence towards wound healing [33].

Micronutrients

Zinc, an essential micronutrient for the maintenance of good health possess anti-inflammatory, anti-oxidant function through activation of superoxide dismutase and production of metallothionein protects the cells and the DNA from damage. Additionally, it is also important for activation of numerous enzymes and proteins. It is also vital in the absorption of vitamin A, E, and folate [34]. Iron, another crucial element, participates in diverse metabolic processes , including oxygen transport particularly haemoglobin and myoglobin, deoxyribonucleic acid (DNA) synthesis, respiratory and oxidative metabolism, electron transport and an essential component for various enzymes [35]. Commonly dispensed as oral supplements in the form of tablets, capsule, chewable tablets or even as injections either as an individual vitamin or multivitamins with or without the micronutrient supplement are available commercially.

Novel Therapies

Oxitard

Oxitard, a phytopharmaceutical formulation, with a protective action. The capsules of oxitard are a combination of 1. Extracts: Mangifera indica (antibiotic, anti-asthamatic, antiseptic, antiviral, hypotensive, anti-emetic), Withania somnifera (anti-stress, anti-anxiety, anti-

inflammatory, anti-convulsive and anti-arthritic properties), Daucus carota (antiseptic), Glycyrrhiza glabra (immunomodulatory and anti-inflammatory, normalizes the hoarseness in voice), Vitis vinifera (anti-inflammatory, astringent and an effect to curb the burning sensation); 2. Powders: Emblica officinalis (vitamin C and is a potent antibiotic) and Yashada bhasma (protein synthesis, cell division and wound healing); 3. Oils: Triticum sativum (minerals and has an antioxidant property) [36].

It is an antioxidant, gastro and cardio protective with adaptogenic and immunomodulatory in function. Its ability to neutralises oxidation reaction and its products provides cellular protection.

The formulation is dispensed in capsules, advised oral administration of 2 capsules twice daily. Though oxitard was well tolerated, studies have reported mild gastrointestinal discomfort for a short duration in patients. Further studies are required to evaluate the mechanism of action and its efficacy in the treatment of OSF

Garlic

Garlic (Allium sativum), traditionally used allium vegetable, known for its nutritional and medicinal values, is consumed worldwide. Allicin, an organosulphur functional compound in garlic is one among the most investigated component. It is known to be associated with anticancer, anti-inflammatory, antimicrobial, immune modulatory, antifibrotic, cardio-protective functions and even modulate cholesterol levels to name a few.

Studies have reported its anti-cancer role by its ability to target cells in G0/G1 phase and induce G2/M phase arrest in Oesophageal Squamous cell carcinoma cases. Reports also suggest that allicin treatment was able to reinstate cell surface glycoconjugates as observed in DMBA altered plasma glycoconjugates and tumours of buccal mucosa [37].

The pharmaceutical forms available are tablets, capsules, powder, aged extract, injections while to date intralesional injection of allicin is reported for OSF. The significant adverse effect reported is its characteristic breath odour.

Though scientific evidence exists about the beneficial aspects of garlic and its derivates, yet limited studies are documented irrespective of it being reported safe with few side effects and high tolerance. Lack of studies on bioavailability, pharmacokinetics and toxicology on garlic and its compounds are evident. Further, emphasis on clinical trials with these functional compounds to evaluate their efficacy and interconnection with the disease of interest are required [37].

Colchine

Colchine, an alkaloid, is an established antifibrotic agent, used for reducing fibrosis in liver and kidney diseases. It ensues inhibition of collagen synthesis by inhibiting procollagen secretion and its conversion to collagen. It further disrupts microtubule formation and its polymerisation. Additionally, by destabilizing microtubules, diminishing number of TNF-α receptors on macrophages and endothelial cells, inhibiting ROS production, affect chemotaxis and adhesiveness of leukocytes, affect PGE secretion and hinders inflammatory mediators release by preventing mast cell degranulation thereby exerting anti-inflammatory function. However, limited studies have been reported its use in OSF.

On oral administration of 0.5 mg colchine, no adverse effects were reported. Studies also suggest combination therapy with other drugs would be more effective, leads to reduced dosage with better outcomes [38].

Interferon Gamma

Interferon gamma, a cytokine is known to inhibit collagen synthesis. It basically inhibits transcription for type I and II collagen synthesis by fibroblast and myofibroblasts. This

biological action may have a significant therapeutic effect on OSF. Haque et al demonstrated in vitro inhibition of arecoline induced collagen synthesis by INF-γ in a dose related manner. They also observed in vivo improvement in the mouth opening of OSF patients with post treatment of 30±8 mm 6 months reading in comparison to 21±7 mm pre-treatment values. Further, comparatively decreased amount of inflammatory cell infiltrate was noted post intervention lesional tissue. As INF-γ were able to inhibit collagen synthesis in vivo, further studies are required to evaluate its applications and therapeutic potential in the treatment of OSF [39].

Valdecoxib

Valdecoxib, a novel selective cyclooxygenase-2 inhibitor has shown to be beneficial in treating premalignant disease. Averineni et al developed a sustained release mucoadhesive buccal film of valdecoxib made of chitosan and hydroxypropyl methylcellulose for local action. They concluded that they were able to produce comfortable, non-irritant, self-administrable films that delivered the required therapeutic dose at the area of interest. These films overcame the short residence time of oral gels, flexibility and comfort of adhesive tablets [40].

Many other drugs such as the anti-TGF β agents, copper chelators, borneol, Danuxan Koukunga, Saliva miltiorrhiza are studied and proposed for the treatment of OSF. However, further exploration of studies on their mechanism of action, bioavailability, dosage, safety profile through larger clinical trials is required.

Combination Therapy and Adjuvant Therapy of OSF

This comprehensive data on the different drugs available, the number of clinical trials conducted, the combination of drugs explored are extensive for the medical management of OSF. However, a striking feature to be noted is that studies did consider two principal drugs that differed in their primary mechanism of action, were administered thereby a combination therapy was followed. For example: steroids + hyaluronidase. On the other hand, some studies considered adjuvant therapy wherein treatment in addition to the primary protocol was also considered. For example: antioxidants, vitamins and micronutrients in combination with steroids. The added advantage noted of such therapy are

1. Better efficacy
2. Reduced dosage required
3. Reduced visits
4. Persistent treatment with adjuvants when compared to the weekly dosage of principal drug
5. Economic feasibility

Future Directions

Prevention of progression, thwarting malignancy development and avoidance of recurrence are the prime principles in the management of OSF. Future directions should aim for a better cognizance of the contemporary dugs and development of targeted drug delivery system which are patient friendly and economically feasible. Moreover, the scientific research community is on a constant exploration for newer effective drugs for the treatment of OSF analysing at the different levels in the pathogenesis of OSF.

Conclusion

Various surgical modalities though proposed, medical management forms an inseparable part of OSF management. Irrespective of numerous limitations among the different treatment regimens that are evaluated, vigorous clinical research is a prerequisite to address those shortcomings. Clinicians' treatment plan should be governed by numerous factors comprising the subjective symptoms to objective signs; to choose from the evidence-based interventions. Additionally, education intervention with reference to the habit

cessation and dietary counselling are indispensable aspects for which the patients are required to be counselled.

Conflict of Interest

None.

Ethical Approval

Not applicable.

Data Availability

Not applicable.

Authors Contribution

Dr Vidya Gurram Shankar - writing - original draft, editing and review.

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