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Review

Thioctic acid in oral submucous fibrosis (India's disease) – A better tomorrow

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ABSTRACT

Oral submucous fibrosis (OSMF), because of its common occurrence in Indian population is known as India's disease. Regardless of diagnostic and therapeutic developments, oral potentially malignant disorders (PMD) and cancers are disseminating at a distressing rate. There is this prerequisite for unrelenting determination to find out apt treatment options so that malignant transformation may be prevented and more so the prevailing morbidity and mortality. Considering the frequency with which oral submucous fibrosis undergoes malignant transformation with free radicals playing a major part, the role of antioxidants in general and thioctic acid also known as alpha lipoic acid (ALA) in particular need to be studied in these individuals. Previous few studies indicated the use of alpha lipoic acid in oral submucous fibrosis patients leading to improvement in signs and symptoms. So, it led us to set forth and propose probable role of thioctic acid in improving symptoms in these patients. As oral submucous fibrosis poses as a threat with its various signs and symptoms and as a potentially malignant disorder as well as considering the role of free radicals in malignant transformation, we proposed the possible mechanisms behind the commonest signs and symptoms in oral submucous fibrosis and role of alpha lipoic acid in managing these signs and symptoms.

1. Introduction

OSMF is "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although, occasionally preceded by and/or associated with vesicle formation, it is always associated with a juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat" [1].

All clinical appearances that carried a risk of cancer were termed "potentially malignant disorders" as it reflected their extensive anatomical dissemination and OSMF is one amongst them [2]. In India, 0.2% to 0.5% population are affected with OSMF (hence called as India's disease) [3].

Epidemiological studies revealed that chewing arecanut remains the foremost etiological factor for OSMF [4].

As OSMF is a potentially malignant disorder and free radicals act as initiators and promoters of oral carcinogenesis, this review embarks on to hypothesize the probable role of an antioxidant such as ALA in managing OSMF as well as preventing its malignant transformation.

2. Reactive oxygen species (ROS)

Arecanut has carcinogenic and clastogenic effects and is capable of generating free radicals [5]. These are compounds with one or more unpaired electrons [6]. As most of them are oxygen derived, they are called as the reactive oxygen species which initiates lipid peroxidation [7]. Free radicals produced are devastating enough to modify the cell membranes, proteins, lipids, lipoproteins, and deoxyribonucleic acid (DNA). A phenomenon called oxidative stress is created when excess of free radicals produced are not effectively destroyed by cells thus hampering normal cell growth and beginning carcinogenesis in the cell by instigating genetic mutations and modifying normal gene transcription [8].

3. Cellular antioxidant defense system (CADS)

The safety of cellular components from oxidative damage is brought about by antioxidants, indispensable for conserving

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optimum health and well-being, serving as the first line of defense against free radical injury [9]. The CADS comprises of two types:

- non-enzymatic- vitamin A, E and C;
- enzymatic-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) [10].

SOD present in aerobic cells is responsible for converting two toxic species: superoxide ($O_2\bullet -$) and hydrogen peroxide (H_2O_2) into water. GSH-Px, a selenocysteine-reliant enzyme plays a vital role in quenching H_2O_2 in cells [9].

4. ALA (Thioctic acid)

Antioxidant (B. Halliwell-1995)

"Any substance that, when present at low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate" [6].

ALA (1,2-dithiolane-3-pentanoic acid) [6] and it's reduced form dihydrolipoic acid (DHLA) are often called the "universal antioxidant" and are vital cofactors for various mitochondrial bioenergetic enzymes like pyruvate dehydrogenase and ketoglutarate dehydrogenase [11].

Atherosclerosis, lung, neurodegenerative disorders and chronic inflammation involves peroxynitrite production which are quenched by DHLA [12].

4.1. Mechanism of action

4.1.1. Metal chelation

Redox-active metals like free iron, copper, manganese and zinc are chelated by ALA and DHLA as direct ROS scavengers. This prevents oxidative damage from highly reactive free radicals generated by catalyzing reactions thus making ALA a useful tool in the treatment of chronic diseases [11].

4.1.2. ROS scavenger

As ALA is both hydrophilic and lipophilic, it acts in the cytosol, lipoproteins, serum and plasma membrane. ALA scavenges oxygen singlets, hypochlorous acid and hydroxyl radicals and DHLA scavenges peroxyl and superoxide radicals leading to inhibition of free radical-mediated peroxidation of proteins without becoming involved in the process [11].

4.1.3. Regeneration of endogenous antioxidants

Free radicals are scavenged by an antioxidant: to scavenge additional ROS, it must first be reduced as it is already oxidized. Essential antioxidants including vitamin C, vitamin E and glutathione are reduced and regenerated from their oxidized forms by DHLA which is a powerful reducing agent [11].

4.1.4. Oxidative damage repair

Nicotinamide adenine dinucleotide (NADH) is made available as a source for reductive reactions by ALA.

In addition, DHLA improves the action of peptide methionine sulfoxide reductase (PMSR) thereby mending oxidative damage to proteins [6].

4.2. Dosage

Orally, ALA can be given in the range of 600–1800 mg daily. IV doses are given in the range of 300–600 mg [13].

ALA should be taken 30 minutes before or 2 hours after food because of reduced bioavailability.

5. OSMF – signs and symptoms

OSMF presents with various findings of which the most relevant are:

5.1. GSH depletion

The mechanism underlying arecoline-induced cytotoxicity is possibly due to GSH depletion playing a key role in the pathogenesis of fibrosis. GSH depleted buccal mucosa fibroblasts in OSMF were found to be more susceptible to other reactive agents within the areca quid. Thus, areca chewers agonized from OSMF at a high risk ratio for oral cancer. Arecoline-induced cyclooxygenase (COX-2) is critically reliant on intracellular GSH concentration [14].

5.2. Burning sensation

It is the most common presenting complaint of the patient which precludes him from consuming regular food comfortably resulting in various deficiency states.

Various hypotheses:

- coarse fibers of arecanut results in micro trauma [15] of the buccal mucosa which probably leads to erosions;
- 4-hydroxylproline found solely in collagen requires iron and ascorbic acid for the reaction. As OSMF is principally a collagen disorder, iron is used up resulting in decreased iron levels leading to improper vascular channel formation and attendant reduction in vascularity. Iron containing enzyme cytochrome oxidase is required for normal epithelial maturation. As a result of reduced iron levels, low levels of this enzyme causes subsequent atrophy of epithelium, leading to burning sensation and ulcerations of the oral cavity in areca chewers. Thus ingestion of regular diet may be unpleasant for the patient further leading to anemia [16];
- increased fibrosis of minor salivary gland (MSG) was reported to be associated with increased burning sensation of the oral cavity [17].

In OSMF, there is decrease in the salivary secretion as a result of fibrosis and hyalinization in and around MSG resulting in reduced secretion of mucins (insulators) [18] at the tips of microplicae (oral mucosal barrier complex) of superficial cells of the oral epithelium [19].

This results in decreased salivary mucus gel (SMG) production leading to SMG barrie\r loss producing the following consequences [17]:

In OSMF, normal physiologic friction results in rapid exfoliation of superficial cells of the oral epithelium owing to less protection leading to epithelial atrophy. The surface is further sensitive to burning sensation as a result of decrease in the distance of intra-epithelial nerve endings from the surface. Furthermore, burning sensation is also because of spicy food elements diffusing easily towards intra-epithelial nerve endings as a result of diminished defensive diffusion membrane (DDM) function of SMG [17]:

- lesional keratinocytes showed nuclear positivity for phosphorylated SMAD2, suggesting the role of transforming growth factor beta (TGF-β1) in inhibiting the epithelial growth and thereby causing pronounced epithelial atrophy in OSMF [20];

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