Review Article

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COMBINATION SYNDROME: A SYSTEMATIC REVIEW

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ABSTRACT:

The group of complications which representing as a syndrome are interlinked to one another progressing in a sequential manner is known as 'combination syndrome' by Ellsworth Kelly in 1972. Combination syndrome progresses in a sequential manner.

The various features includes loss of bone from the anterior portion of the maxillary ridge, overgrowth of the tuberosities, papillary hyperplasia of the hard palatal mucosa, extrusion of mandibular anterior teeth, and loss of alveolar bone and ridge height beneath the mandibular removable partial denture bases, also called anterior hyperfunction syndrome.This is an attempt to provide an overview of combination syndrome.

Key Words: Syndrome; TuberoSity; Papillary hyperplasia; Epulis fissuratum

INTRODUCTION

Oral sub mucous Fibrosis is a well known clinical entity since the time of sushruta when it was known as Vidari [1]. It has been a subject of controversy ever since Schwartz [2] described an arcaine and inexplicable Fibrotic condition affecting the oral cavity in 5 Indian women of East Africa in 1952.

Pindborg and Sirsat [3] described oral sub mucous fibrosis as an insidious Chronic disease affecting any part of the oral cavity and sometimes the Pharynx although occasionally preceded by 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 oral mucosa and causing trismus and inability to eat.

The management of oral Sub Mucous Fibrosis falls under two broad categories medical and surgical. The medical management includes intralesional injections of hyalouronidase, hydrocortisone [4] placental extract [5], interferon [6] gamma and topical application of triamcinolone acetonide with systemic intake of vitamins, antioxidants and iron supplements [3]. The recent medical treatment includes oral administration of milk from cows [5] immunized with human intestinal bacteria.

MANAGEMENT- NON SURGICAL (MEDICINAL) THERAPY

As the exact causative factor for OSMF is a matter of conflict, the failure to achieve a proper or specific treatment

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for it may be the reason for its incomplete regression or abolition [7]

Restriction of Habit behavioral therapy

The exact role of pan chewing, betel nut, chilies and spices in Indian food in the causation of this disease is not clear. Yet, the incidence of this condition is higher amongst individuals with these habits.

So, regardless of treatment modality opted, discontinuation of any deleterious habit has been emphasized by almost every pioneer in the field.

Various treatment modalities have been described from time to time owing to the obscure etiology of the disease which can be grouped as:

- Non surgical therapy
- Surgical therapy
- Supportive therapy

NON SURGICAL (MEDICINAL) THERAPY

❖ **Iodine and B-complex preparation [8]**

It is a combination of iodine preparation with systemic B-complex factors.

Each 2ml ampoule consists of

- ❖ Methyl trioxyethyl iodomine in 10,25,50,75 and 125 mg active iodine doses.
- ❖ VitBl 1.0 mg
- ❖ VitB2 0.6 ml
- ❖ VitB6 0.3 m
- ❖ Nicotinamide 5.0 mg
- ❖ Ca Pantothenate 1.0-mg

Dose: I.M. injection starting with smaller doses and continuing with larger doses (10 25, 0, 75 and 125 mg). 2 ml ampoule daily. The course of five injections repeated after every day.

The combination of Iodine compound with Vit. B complex is responsible for stimulation of metabolic processes and enzymatic processes within the body (oxygen reduction, transamination, etc.) Moreover, association with Vit B complex potentates the Iodine action and makes its use non toxic and hepatoprotective which is therapeutically extremely valuable.

A vitamin rich diet along with iron preparations helpful to some extent but have little therapeutic value when trismus, is to be relieved.

Use of Steroids

i). Systemic Steroids

In 1954, Rao and Raju [9] first used Cortisone in cases with submucous fibrosis. Also **Desai in 1957 [10]** treated patients with 5mg cortisone tablets in doses of 100 mg per day and observed some relief from burning sensation without untoward effects.

ii). Local Steroids

Desai treated 35 patients with Hydrocortisone locally 6.25 mg.+ 1% of Procaine HC1 in areas of fibrosis and found the following results [10]:-

1. Relief from burning sensation of mouth
2. Return of normal coloration of mucous membrane
3. Relief of trismus with improved mobility of palate.

iii) Combination of oral and local injection therapy

Desai recommended 200mg of cortisone for first two days following by 100 mg daily till 1000 mg was given along with local injection of hydrocortisone 0.25 ml i.e. 6.2 5 mg + 0.25 ml of Procaine HC1 and reported: favourable results [10].

Rao and Raju recommended 7 week treatment with Triamcinolone acetonide and Dexamethasone in gradually decreasing doses. A total of 600 mg of triamcinolone or 90mg of Dexamethasone being given which was supplemented with 25 mg of Hydrocortisone biweekly interval on affected side [9].

- **Dexamethasone:** It was used by many pioneers in the field later on as the local injection therapy [11].

Dose: Dexamethasone 4mg in divided doses of weekly interval for a period of 20 weeks. The total dose which can be given is 90 mg [12].

- **Traimcinolone Acetonide**: It can be used in local injection form, systemically and for topical application [13].

Systemic doses: Triamcinolone used by some workers in the total doses of 600mg.

Local injection therapy: Triamcinolone acetonide 40mg can be injected. On an average of 150 - 200 mg of submucosal injection can be given in divided doses [14].

Topical application: Triamcinolone acetonide 0.1 % used for topical application 3-4 times a day.

Action of corticosteroids in oral submucous fibrosis is fibrinolytic, anti allergic and anti inflammatory. One of the therapies in the etiopathogenesis of submucous fibrosis is that of autoimmune factor related to sensitized lymphocyte following action of specific antigen, steroids act as non supportive agents **.**Steroids also prevent and suppress inflammatory reaction thereby prevent fibrosis by decreasing fibroblastic production and deposition of collagen [15].

If steroids are used continuously in large doses, its withdrawal will lead to toxic effect like adrenocortical insufficiency.

Hyaluronidase

Hyaluronidase, by breaking down hyaluronic acid (the ground substance of connective tissue) lowers the viscosity of the intracellular cement substance that is hyaluronidase is known to decrease cell formation by virtue of its specific action by hyaluronic acid which plays an

important role in formation of collagen. Thus, it decreases collagen formation.[16]

Dose: 1500mg i.v. (0.5ml injected intralesionally twice a week or ten weeks,

Contraindication: It should not be injected into an area where there is local infection as it may enhance the spread.

Collagenase

In vitro studies have revealed that altered collagen is attacked by collagenase and elastase, more slowly, by trypsin and very slowly by hyluronidase. It was used first by **Kumar et al in 1980** for the treatment of oral submucous fibrosis.Significant improvement is noted in the burning sensation of mouth, vascularity of mucosa and presence of fibrous bands. Also, improvement in mouth opening was noted [17].

Dose: 2mg of collagenase materials dissolved in 1ml of distilled water for injection purposes.

Adverse reactions: Adverse reactions like pain swelling and trismus may be seen after injections of collagenase which is considered to be allergic reaction of this agent.

Placental extract

Rainanjaneyulu and Prabhakar Rao (1980) studied 10 cases of oral submucous fibrosis and treated them with a new drug, Placentrix [18].

Placentrix is an essential biogenic stimulator". It is suggested that it stimulates pituitary, adrenal cortex and regulates metabolism of tissue. It is also proven to increase vascularity of tissue. Its use is based on a new method of tissue therapy' This theory was that animal and vegetable tissue when severed from the parent body and exposed to conditions unfavourable, but not mortal to their existence undergo biological readjustment leading to development of substance in state of their survival to ensure their vitality biogenic stimulators. Such a tissue extract when implanted into body offer resistance to pathogenic factors, stimulate metabolic or regenerative process therapy favouring recovery [19,20].

Placental extract can be separated into four different factors:-

1. Aqueous extract
2. Lipid extract
3. Immune gamma globulin.
4. Tissue coagulants.

Only the aqueous extract of placenta acts as biogenic stimulator, It has following actions on the body: -

1. It stimulates pituitary and adrenal cortex and regulates metabolism of tissues.
2. It increases vascularity of tissues.
3. Stimulates regenerative process.
4. It possesses notable anti-inflammatory effect.

Placental extract contains

- Nucleotides- Ribonucleic acid (RNA)
  -Adenosine triphosphate (ATP)
- Enzyme- Alkaline and acid phosphatase.
  - Glutamic oxalo-acetic acid transaminase.
  - Glutamic acid pyruvic acid transaminase.
- Vitamins- Vit E, Vit B, Vit 86, Vit B12, pantothenic, Acid, nicotinic acid, biotin. PABA, folic acid.
- Amino acids- Alanine. glycine, threonine. serine, valine.
- Steroids- 17 ketosteroids. Cholesterol
- Fatty Acids - Linoleic acid and linolenic acid,palmitic acid.
- Trace element- Sodium, potassium, calcium,magnesium,Copper,iron, phosphorus and silicon.

Doses: 2ml of solution deposited locally at the interval of three days for 15 days. 2ml solution deposited weekly over a period of 10 weeks [21].

INF gamma

IFN gamma is known antifibrotic cytokine and through its effect of altering collagen synthesis appears to be a key factor to the treatment of patients with oral submucous fibrosis. Intralesional injection of the cytokines may have a significant therapeutic effect on OSMF [22]

Pentoxyphylline [23]

It decreases production of TNF ALPHA, which is a mediator of inflammation.Suppresses leucocyte function.Stimulates fibrinolysis.

Dose: Trental 400mg TDS

Turmeric oil [24]

Curcuminoids isolated from turmeric - have an antioxidant effect, DNA protectant and anti mutagen action.

Dose: 600mg of turmeric oil+3g of alcoholic extracts of turmeric for 3 months. (topical)

Lycopene [25]

Lycopene is a powerful antioxidant obtained from tomatoes. lycopene either singly or in combination with intralesional steroids is, indeed, efficacious in improving the mouth opening in patients with submucous fibrosis and in reducing associated symptoms. It upregulates lymphocyte resistance to stress and suppresses the inflammatory response. It offers a noninvasive option that yields significant improvements in the symptoms as well as objective signs of the condition. It should therefore be used as a first-line drug that would further the motivation and compliance of patients with this debilitatingcondition.

Dose: 16 mg in 2 equally divided doses for 2 months.

CONCLUSION

Management of OSMF should include counseling of patient along with lycopene/spirulina/multivitamin/minerals in the initial stages. Moderate stages of OSMF should be treated with intralesional steroids or pentoxifylline,

where as advanced stages should be treated surgically.

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