“ORAL LESIONS: TOPICAL MEDICATIONS, A CLINICO-PHARMACOLOGICAL STUDY”

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Abstract - Clinical Practice & Hence Medical Education & Clinical Research, Witnessed Recent Considerable Increase, In Oro-Pharyngeal Diseases, With Substantial Statistically Increased Emergence Of Smoke, SmokeLess Tissue Reactions Clinical Entities E.g. Various Stomatitis, Oral Mucositis, Frictional Hyperkeratosis & Sub-Mucous Fibrosis Etc., Comprising Variety Of Clinico-Morpho-Pathological Combinations And Differing Pre-Malignant / Malignant Transformations.

Present Study Includes More Than (2) Decades Of, Thousands Of Patients Management, Manifesting Different Stages Of Distinctly Variables / Mixed Clinical Presentations, Of Oral Cavity Diseases, Due To Traditional Betel, Tobacco Chewing Habits & More Recently Available Preparations Like PanMasalas & Others. Conducted Mostly, In The Eastern Parts Of India, As One Of The Maximum Incidence In The World Or Elsewhere.


Keywords - 1. Smoke & Smokeless Tobacco Tissue Reactions  
2. Oral Reactive Lesions Variables, Oral Pre-Malignant Lesions (OPL I & II)  
3. Local Chemoprophylaxis: Clinical Efficacy & Drug Delivery System (DDS)  
4. Supportive Measures, Chemoprevention, Nicotine Dependence Treatments, Cancer Diagnostics,  
Surgical & Physiotherapy Interventions

1. INTRODUCTION Clinical Scenario  

WHO Classification Categorized Diseases, In 1970s & 1980s Onwards, Reactive Allergic Hypersensitivity Reactions, Exhibit Different Severity, Recurrence, Relapse And Chronicity Variants, Have Variable Premalignant (2) Malignant Transformation Potentials & Status Gradation As ‘Risk Factors’.

The Attributing Aetiological Factors Include Oral Hygiene, Tobacco Smoke & Smokeless Tissue Reactions, Different Methods Of Intra-Oral Tobacco Applications, Available By Different Names, Swedish Stuff etc. Used in United States, Scandinavia & South Asia Including India And Other Parts Of Globe. Presence Of Nonhomogeneous Group Of Compounds & Other Toxic Contents E.g. Aldehydes, Polycyclic Hydrocarbons, Nitrosamines, Heavy Metals & Other Chemicals Are Believed To Be Responsible Causative Factors.

In The Discussed Clinico-Pharmacological Study, The Aetio-Pathogenesis Based
Scientific Pharmacological Help To These Lesions Had Been Achieved By A Combination Of Different Groups Of Available Systemic Medications, Belonging To Different Pharmacological Category. The Various Different Ingredients Have Been Constantly Replaced By Recent More Efficacious, Gradually Available Drug Molecules, With Consideration Of ‘Drug Delivery Pharmaco-Therapeutics, To Achieve Maximal Available Medical Therapy Support, As Curative & Or Palliative Management Or As Adjunct To Latest Treatment Modalities.

Clinico-Pathological Oncology Aspects Of The Study, Comprised OverAll Control Of Severity, Chronicity & Transformations Of Oral Lesions, Because Of Constant Exposure To Aetiological Variants, By Management Of Initial Stages Of Oral Pathologies, Minimizing The OverAll Mortality & Morbidity Of Significantly Prevalent Disease Processes.

2.MATERIALS AND METHODS

The Study Includes More Than (2.2) Decades Of Management Of Thousands Of Patients, In Different Stages Of Distinctly Variable Diseases / Mixed Clinical Pictures Of Oral Cavity Manifestations Largely Conducted In The Eastern Parts Of India, As One Of The Maximum Incidence In The World Or Elsewhere, Due To Traditional Betel, Tobacco Chewing Habits & More Recently Available Preparations Like PanMasalas, Guthkas etc. Besides Other Conventional TobaccoUse Methods.

The Study Also Included Subjects Different Regions Of India, Europe, Africa, Middle East, South East Asia & Other Parts Of The World.

Other Indications For UseFull Applications, Included Different Stages Of Radiation ChemoTherapy Induced Mucositis, Oral Manifestations Of HIV/AIDS, KidneyTransplant Patients, Other Immunosuppressive Conditions And Therapies Etc.

The Local Application Ingredients Included, Local Antiseptics, Local Anaerobs, Antimicrobials, Local Antifungals, Local Steroids ± Chemoprophylaxis Agents In Suitable Soothing Emollient Base.

The Use Of ‘Oral Preparation’, As Definitive Curative Management, Symptomatic, Palliative Therapy, As An Adjunct To Latest Modalities Of PhysioTherapy; Oral Mouth Dilatation Devices Etc., Surgical Interventions; Submucosal Injections, CryoSurgery, Low Level Laser Therapy²⁰, Skin Grafting Etc. And Other Latest Modalities Of Oral Disease Manifestations Management Was Done Under Expert Supervision.

Referring The Needy Patients For Specific Specialized ManageMent, Depending Upon Available Resources Circumstances. OverAll Prognosis Explained Treatment Risk Consent Had Been Judiciously Retained With Proper AwareNess To Patients.

Supportive Measures: By Causative Factors Abstinence,Nicotine Dependence Treatments Etc., Along With Cancer Diagnostics (Oncosurgery Histopathology, Biomarkers & Imaging Etc.) For Premalignant And Malignant Transformations, Under Discrete Clinical Expertise Supervision, Were Incorporated As Available.
As Evident By Initial Phases Of Study, ‘Recorded Prescription During 1980s’

Ingredients Included Basic Essential Constituents In Those Forms, As Were Available About (25) Years Before, With An Inquest For More Sophisticated Effective Alternative Pharmacological Substances. Recently Availables Conveniently Effective Pharmacological Agents Were Replacedly Included To Maximize Patient Benefits.

Supplementary Treatment: Included Oral Hygiene Maintenance By Repeated Rinsing, & Or Use Of Available Mouth Washes, Fortified B. Complex Lactobacillus Preparations. & Other Available Minerals & Nutrients.

PHOTOGRAPH-1

The Comparative Therapeutic Assessment & Evaluation Of Various Ingredients Of Local Application; With Replacedly Better Available Alternatives, Having Comparable Mucosal Absorption, Minimal Side-Effects & Better Therapeutic Efficacy Results Had Been Timely Done.

VARIOUS INGREDIENTS
LOCAL ADMINISTRATION
AVAILABILITIES

- **Local Antiseptics**: Betadine, Povidone Iodine, cetrimide, chlorhexidine, benzydamines, glycols, thymols, menthols, KMNO₄ Etc.
- **Local Anaerobic Antiseptics**: Recent Availables; metronidazole Preparations Etc.
• **Local Antifungals:** Several Recent Preparations Including Antifungal Lozenges, nystatin, clotriamzole, Troches, fucanazole Preparations.

• **Local Steroids:** hydrocortisone, beclomethasone, triamcinolone Etc.

• **Local Anti-Allergic & Anaesthetic:** diphenhydramine and lidocaine Ointment Preparations

• **Spirulina Fusiformis** Therapy

• **Antimicrobials:** HSV – Antiviral Therapy,

calcium phosphate Rinse (Caphosol), fluoride Gel, magnesium hydroxide, aluminium Hydroxide, silver Nitrate Solution, chamomile Mouth Wash, Coating Agents (sucralfate), Effervescent mucomelt; n-acetyl cysteine (600 Mgm.), glutathione Replenishers Etc.

• **Traumeel S** (Homeopathy)


**ROLE OF OTHER MEDICATIONS**

• Vitamin ‘A’, Retinol Etc. Retinoids, β-Carotene, 13-Cis-Retinoids (Topical) 13,14, N-4-Hydroxy-Carbophenyl-Retinamide (4hcr), Fenretinide.

• Vitamin ‘E’: α-Tocopherol, Gelenium

• Lycopene

• Lactoferrin

• Cyproxanthin

• Transforming Growth Factor Beta 1

**As Primary/Adjuvant Chemo-Therapy Systemic & Chemoprevention Medications**

• Antioxidants, Anticholinergics & Coating Agents

• Antiinflammatory agents

• Aminoacids (Especially L-Glutamine with Enhanced Delivery Systems)

• Growth Factors: GM-CSF (Granulocyte Macrophage Colony Stimulating Factor), G-CSF (Granulocyte Colony Stimulating Factor), Topical & or Systemic Administrations. Most Effective Available e.g. Palifermin

• Protease Inhibitors, e.g. Bowman & Birk Inhibitor Concentrate (BBIC) etc.

• Bleomycin 5 FU Based Chemotherapy (Edatrexate etc.)

• High Dose Melphalan

• Tea and Tea Components, Especially Green Tea (Polyphenolic Compounds Called AS Catechins Most Abundant Epigallocatechin, -3 Gallate (EGCG).

**Recent Available Include**:- Amlexanox Oral Paste, 100 Mgm Paste Contains (5) Mgm Amlexanox (Anti-Ulcer Agent) - Rebamipide, Anti-Ulcer Drug, (100) Mgm Tablet, TDS Orally

**SCAR MANAGEMENT MEDICATIONS**

• Centella Asiatica, Wheat Germ Oil, Lavandus, Aloe Vera, Tea Tree Oil & Honey Cream Etc.

• Other Herbal Preparations

• Chinese Medications

• Choline Salicylates, Tannic Acids, Tannins Etc.

• Recent Scarolytic Ointment; Contractubex Etc.
ACUTE(-) CHRONIC ORAL PATHOLOGIES

SUBMUCOSUS FIBROSIS

Schwartz (1952) Formulated the term, ‘Atrophica Idiopathica Mucosa Oris’ to describe an oral fibrosing disease, while Joshi (1953), used ‘Oral Sub-Mucous Fibrosis (OSF)’, to describe diseases characterized by:

- Fibrous tissue reaction beneath oral mucosa, due to variable aetiological variants attributing constant prolonged friction; irritation, chemical, repeated trauma, nutritional, recurrent infections & inflammations of different causes.
- Leading to allergic hypersensitivity reactions; increased fibrogenesis beneath oral mucosal layer. This hypersensitivity reaction may often result in a juxta-epithelial inflammation that leads to increased fibroblastic activity resulting in formation of collagen fibre lamina propria. These collagen fibers are non-degradable and the phagocytic activity is minimized.
- "Oral Submucous Fibrosis--A Chronic Disseminated Intravascular Coagulation Syndrome With Local Coagulopathy."

Reports are available in literature.

Prevalence & Aetiology: The clinical entity being well recognized for its malignant potential.

Statistical reports of prevalence, in (4/1,000) adults in rural India and as many as (5) million young Indians sufferers.

Known Causative Agents Include: Areca Nut, Betel Quid chewing, the ingredients and nomenclature of Betel Quid vary by region, all though basic constituents in different combinations are:

- **Areca Nut** (fruit of the Areca Catechu Palm Tree, erroneously termed Betel Nut): Arecoline, an alkaloid found in the Areca Nut, promotes salivation, stains saliva red, and is a stimulant.
- **Betel Leaf** (from the Piper Betel, a pepper shrub), Tobacco,
- **Slaked Lime** (Calcium Hydroxide): Maintains the active ingredients in its freebase or alkaline form, thus facilitating their entrance into the bloodstream via sublingual absorption.
- **Catechu** (extract of the Acacia Catechu Tree): Stains saliva red.

The habit practiced predominately in Southeast Asia and India, from thousands of years. Similar to tobacco chewing in Westernized societies.

The increased popularity of the habit of chewing Pan Masala (mixture of spices including, Betel Nuts, Catechu, Menthol, Cardamom, Lime and others), with mild stimulating effect, often eaten at the end of the meal to help digest food and as a mouth freshener.

Submucous fibrosis leading to restricted mouth opening ability, buccal mucosa has marbling appearance.
Submucous Fibrosis Tongue: Atrophy, Erosions


Aetiopathogenesis:
- Dose Dependence Between Areca Quid Chewing Habit & SMF
- Areca Nut: Alkaloids; Arecoline (Most Imp.)
- Modulation Metal Proteinases, Lysal Oxidases & Collagenases Effect Collagen Metabolism: Increased Fibrosis
- During ↑ Fibrosis: Water Retaining ProteoGlycans → Increased Collagen Type 1 Production → Genetic Predisposition: Aetiological Importance
- Gene Polymorphism: Coding For Tumor Necrosis Factor-α (TNF-α): Fibroblast Stimulation → Fibrosis
  - Other Cytokinsics Aberrations → Transforming Growth Factor-Beta & Interferon-γ → Collagen Production & ↓ Degradation
- Genetic Predisposition → Human Leukocyte Antigen Molecules: HLA-A10, B7 & DR-3

Clinical Manifestations:

Submucous Fibrosis Tongue With Squamous Cell Carcinoma Development

Wrinkles, White Leathery Lesion, Ulcer (±), Hyper Keratinization, Acanthosis, Epithelial Fibrosis + Atrophy & Hyper-Plasia, Overlying Epithelium, Epithelial Dysplasia, Epithelial Vacuolations, Gingival Reactions (±)

Including Progressive Difficulty In Opening Mouth Of Variable Extents, Diffuse, Localized Fibrous Bands, Adhesions Formation At Various Folds & Sulci Of Oral Cavity, With Differing PreMalignant & Or Malignant Transformations.

PINDORG J.J: (3) Clinical Stages
- Stage 1: Stomatitis
- Stage 2: Fibrosis
  - A- Early Lesions, Blanching Of The Oral Mucosa
  - B- Older Lesions, Vertical And Circular Palpable Fibrous Bands In And Around The Mouth Or Lips, Resulting In A Mottled, Marble-Like Appearance Of The Buccal Mucosa
- Stage 3: OSF Sequelae
  - A- Leukoplakia
  - B- Speech And Hearing Deficits

Treatment: Depends On The Degree Of Clinical Involvement.
- Early Disease Detection, Cessation Of The Habit Is Sufficient.
- Most Patients Present With Moderate-To-Severe Disease. Moderate-To-Severe OSF Is Irreversible.
- Medical Treatment: Symptomatic, Predominantly Preventive & Aimed At Mouth Movements Improvements.
Pentoxifylline (Trental), A Methylxanthine Derivative With Vasodilator Properties, Increases Mucosal Vascularity, Recommended As An Adjunct Therapy In The Routine Management

- **Submucosal injections:**
  - Hylase
  - Hydrocortisone
  - Human Chorionic Gonadotrophins (Placentrex)²,³,⁴
  2-3 ml per sitting twice or thrice in a week for three to four weeks.

  **Aim** To Achieve Similar Results By Using ‘Steroidal Constituent’ Of The ‘Oral Lotion’, Had Been Practiced For Years, With Differentially Successful Result Outcomes. The Latest Availability Of ‘Topical Steroid’ E.g. triamcinolone Etc., The Clinical Efficacy, Safety Profile, Local & Systemic Side Effects Are Comparatively Convincingly Acceptable.

- **Surgical Treatment:** Indicated In Progressive Fibrosis, When Inter-Incisor Distance Becomes Less Than 2 Centimetres (0.79 In).

  Multiple Release Incisions Deep To Mucosa, Submucosa And Fibrotic Tissue And Suturing The Gap Or Dehiscence By Mucosal Graft Obtained From Tongue And Z-Plasty. Multiple Deep Z-Shaped Incisions Are Made And Then Sutured In A Straighter Fashion To Gain Length.

  **Excision Of Bands & Adhesions Etc.**

  **Stem Cell Therapy:** Autologous BoneMarrow Stem Cells Intrallesional Injection, Is A Safe And Effective Treatment Modality. Induces Angiogenesis In The Area Of Lesion Decreasing The Disease Extent (Fibrosis), Leading To Significant Increase In Mouth Opening.

**MUCOSITIS (MUCOSAL INFLAMMATION)**

- **Aetio-Pathogenesis:** Besides Various Etiological Variants Of Vivid Clinical Disease Entities Including Metabolic, Nutritional, ImmunoCompromised States, Transplant Patients Chemotherapy (Standard & Or Marrow Ablative), Radiation Therapy, Drugs, Chemicals Induced Are Important.

- **Clinical Manifestations:** Beside Other Presentations, ‘Dysgeusia’ Or An Alteration In Taste Perception Or "Taste Blindness,” Temporary Condition, Because Of Effects On Taste Buds.

**Aspirin Burn**

**Antibiotic Induced Stomatitis**
Agricultural Compounds
Contact Stomatitis, Erosions

MUCOSAL INJURY PATHOPHYSIOLOGY

Mucosal Injury & Subsequent Healing Process Involves All Mucosal Layers Including Extracellular Matrix Besides Epithelium Only.

(5) Stages Process Involve Complex Molecular, Cellular & Histopathological Events

(1) Initiation Phase: Oxidative Stress Due To Different Mechanisms Being Basic Causative Factor.

(2) Upregulation Of Transcription Factors & Messenger Signals Generation Phase:
- NK-κ beta (Central vital role)
- Subsequent Upregulation Of Cycloxygenase-2
- Upregulation Of Matrix Metalloproteinase System
- Multiple Proinflammatory Cytokines, e.g., TNF-α, IL-1β, IL-b

In Addition Sphyringomyelinase & Ceramide Pathways, Fibronectin Break-Up And Macrophagic Activities (Complex Events) Lead To, Further Mucosal Injury & Apoptosis.

(3) Additional Signaling & Amplification Phase: Enhancement Synergism Of Previous Pathways Leading To Generation Of Additional Proinflammatory Cytokines. Upto This Stage Mucosal Anatomy Being Intact.

(4) Symptomatic, Ulceration Phase: Clinical Manifestations Including Ulcerations, Pain, Bleeding, Complicated By Microbial SuperInfections & Decreased Salivary Function Leads To Enhance Mucosal Injury


All (5) Phases Does Not Necessarily Follow Linear Progression, But May Occur Simultaneously At Different Locations.

Mucositis Assessment Evaluators: Scales Commonly Used, Combined Information From Both Patient’s Signs And Symptom Scores, With Patient’s Functional Status & Ability To Eat.

NICOTINE DEPENDENCE TREATMENTS
(A) **Non-Pharmacologic Treatments**

1) **Self Help, Intervention & Counseling**

   By Print, Live & Various Electronics Media Aids Including Telephone Based Cessation Counseling & Others.


(B) **Pharmacologic Treatments**

1) **FDA (Food & Drug Administration)- Approved Nicotine-Replacement Therapies:**

   US-FDA Approved (5) Nicotine Replacement Therapies (NRTs):


   NRTs Are Tolerable, Safe With Results Achieved By:

   (i) **Ameliorating Withdrawal Symptoms**

      Due To Initial Physical & Psychological Reactions To Cessation, E.g. Irritability, Restlessness, Depressed Mood & Poor Concentrations

   (ii) **Reducing Nicotine Craving Experience** & Limiting Possible Weight Gain (For Gum & Patch)

   (iii) Providing Safer Way To Experience Neurobiological&Psychophysiologic Effects Of Nicotine.

   For Quit Rates Relapse Intervals, Rapid Release Formulations Have Better Efficacy For Post Cessation Cravings.

   **Overall NRT Efficacy** In Various Subgroups Including Different Smoking Characteristics Varying Mild, Moderate, High Dependence Levels, Body Weights, Ethnic, Racial Groups & Genders, By Various NRT Preparations, Studies Are Available & In Process.

2) **FDA-Approved Non-Nicotine Pharmacologic Treatments:**

   (i) **Bupropion SR (Zyban)** – An Anti-Depressant, Exact Action Mechanism Not Fully Known, Efficacy Mediated By Reduction Dopamine & Norepinephrine Uptake & Or Nicotine Receptor Antagonist Effects. The Second Mechanism May Involve Drug Ability To Prevent / Diminish Post Cessation Negative Effects & Weight Gain, Cited As Causes Of Relapse Among Smokers.

   (ii) **Varenicline (Chantix)** – Is An $\alpha_4\beta_2$ Neuronal Nicotinic Acetylcholine Receptor (nAchR) Partial Agonist, By Activation Of These Receptors Widely Expressed On Dopamine & GABA Neurons In The Ventral Tegmental Area, Varenicline Has Attenuation Effect On Dopamine Release While Maintaining Dopaminergic Tone, Thus Minimizing Nicotine Craving & Withdrawal By Agonist Function, While Antagonist Properties May Attenuate Reinforcing Nicotine Effects, Leading To Reduced Smoking Satisfaction And Relapse Likelihood.

   Tobacco Dependence Treatment & Clinical Oncology, Have Different Versatile Aspects.

**If Tobacco Is The Choice, Chewing May Be Preferred Over Smoking, With Assured Oral Hygiene Maintainence.**

**Overall Assessment And Management Of Generalized Body Affections Of Tobacco**

4Including Atherosclerosis, Peripheral Vascular Diseases Etc,

Being Important Constituent Of Nicotine Dependence Management.

**DIAGNOSTIC AIDS**

Include:

(A) **Surgical Pathology**
• FNAC, Histopathology: Excisional, Incisional Biopsy, Exfoliated Cell Sampling\textsuperscript{25,26,27}
  \begin{enumerate}
  \item Global Obtained by Mouth Rinse, Swabs Etc.,
  \item Specific, e.g. Scrapes of Leucoplakia Or Other Lesions.
  \end{enumerate}
• Immuno-Histochemistry (IHC)
• For Deciding Type, Nature Of Lesions, Tissue Of Origin, (±) Metastasis, Including Dysplasia Presence With Severity Degree, Loss Of Heterozygosity (LOH), Allelic Imbalance (AI), CIS Being Important Predictive Parameters.
• For Confirming Various Benign Lesions, Premalignant (OPL I & II), Malignant Lesions & Course Of Disease Process.

(B) Molecular Diagnostics \textsuperscript{19,20}
Circulating Tumor Markers Detection\textsuperscript{26,27,28}, Tumor NDA, Circulating Tumor Related Antibodies, Mutant P53 Gene Sequences, Viral DNA - ELISA Test For Serum IgA Response To EBV-related diseases, Anti-TK (Thymidine kinase) Antibodies, Fluorescence Spectroscopy, Mid-InfraRed Fibreoptic Spectroscopy, Attenuated Total Reflectance Spectroscopy, Being Important Tool For Differentiating Between Benign & Malignant Oral Mucosa\textsuperscript{21,22,23,24}

(C) Imaging
For Size And Other Details Of Lesion, Stage Migration By Plain X-Ray Films, CT, Angiography, USG, MRI & MR Spectroscopy Nuclear Medicine And Positron Emission Tomography (PET) Especially FDG (Radiolabelling)-PET.

HEAD & NECK CARCINOMA\textsuperscript{28}
RISK FACTORS:
• Alcohol, Tobacco, Areca Nut /Quids /Pan Masalas, Various Other Chewing Tobacco Preparations, Snuffs Etc. Alone Or Concurrent Use. Precipitated By Poor Dento-Oral Hygiene, Sumps, Sore Teeth, Susceptibility, Leucoplakia Etc.
• Human Papilloma Virus & Other Viral Infections Human Simplex Virus-1 (HSV-1), EBV, IG-18, E6 PRO, p3Tumor Suppressor Gene P53, Leading to P53 Degradation Tumorigenesis, P53 Tumor Suppressants, Plummer-Vinson & Paterson Kelly Syndrome
• Poor Nutrition, Carcinogen Exposure, Genetics.

Sanguinaria-Associated Oral Leukoplakia

Homogenous Leukoplakia Buccal Mucosa

MALIGNANT TRANSFORMATIONS \textsuperscript{29,30}

(A) High Risk Lesions
• Speckled Erythroplakia
• Erythroplakia

(B) Medium Risk Lesions
• Syphilitic Glossitis
• Oral Submucous Fibrosis

(C) Low Risk/ Equivocal Risk Lesions
• Discoid Lupus Erythematosus
POTENT

POTENTIALS FOR MALIGNANT CHANGE

- ↑ With ↑ Age Of Pt.
- ↑ With ↑ Age Of Lesion
- ↑ In Smokers
- ↑ In Alcohol Consumption

- Anatomical Site Dependence
  - Floor Of The Mouth
    - ↑ With Leukoplakia¹²
  - Ventral Surface Of Tongue
    - Esp. Younger ♂
    - Even Without Associated Risk Factors

LOCAL MEDICATIONS:
OTHER INDICATIONS

With The Use Of Discussed Preparation:
Reasonably Good Results Achieved, In Following Conditions:

(1) HIV AIDS Oral Manifestations
(2) Other Immunosuppressive Conditions
(3) Immunosuppressive Therapies
(4) KIDNEY TRANSPLANT PATIENTS

Leuko-Erythematous Lesions
Ulcerative Lesion
Uremic Stomatitis,

Gray-Pseudomembranous Lesion

Hyperkeratotic (White) Lesion

Necrotic Pseudomembrane

Covered Ulceration

UREMIC MANIFESTATIONS

(5) Radiation Mucositis Of Different Aetiopathogenesis, Chemotherapy Induced

(6) Drug Reaction Manifestations, Metal Poisonings Etc.

(7) Dentition And Denture Related Lesions

(8) Difficult Endo-Tracheal Intubation Conditions, ? (Decreased Mouth Opening) Oral SMF Extending To Oro-Naso-Pharyngeal Regions Re-Assessment during Pre-Anaesthetic Checkup Or Otherwise Important Cause

“RESULTS”

• The Discussed Clinico-Pharmacological Study Involves, Successful Overall Management Of Thousands Of Patients (>2500) Cases Comprising Large Variety Of ‘Oral Lesions’ Variables, Clinical Distinct & Or Mixed Clinical Manifestations, Differing In Regards To Cure, Definitive, Symptomatic Management, Of Varying Disease Severity & Chronicity, Recurrence, Relapse & Or Progression To Pre-Malignant & Or Malignant Lesions.

• Gradually Better Available Pharmacological Substance Alternatives, For The Basic Constituents Of The ‘Oral Preparation’, Were Replacedly Administered, During >2 Decades (20-25 Years) Continuing Study Duration.

• Augmentation Support By; Newer Efficacious Systemic & Or Local Medications, Chemoprevention Measures, Abstinence Control Management Regulations Of Various Causative Factors, E.g Nicotine Dependence /Replacement Treatments Etc. Gradually Available In Due Course Of These Many Years, Were Appropriately Incorporated.
• Retaining Discrete Expert Clinical Assessment
  As The Basic Diagnostic And Therapeutic Tool
  In Regards To Treatment Efficacy End Points,
  Various Surgical, Histopathologies, Molecular Diagnostics (Different Biomarkers) & Imaging Techniques, Assessments\textsuperscript{2,33} Were Collaborated, In The Disease Management Plan As And Where So-Ever Needed And Practically Available In Consideration Of Resources.


“DISCUSSION”

Retaining The Very Basic Aim Of The Study, Initiated More Than (25) Years Ago, To Definitively Treat & Or Provide Maximal Relief In The Usually Mixed Combinations Of ‘Oral Lesions’ & Or Solitary Variables, Under Closed Obsevation Clinical Expertise Supervision, With The Then Available Constituent Ingredients & Supplementary Therapy. Witnessed Gradually Available Efficacious Medication Alternatives, Supportive Chemo-Preventive Therapies, Surgical & Physiotherapy Procedural Supports, While The Sucessful Use Applicabilities Also Increased Several Folds For Oral Lesions Accompanying Recently More Prevalent Infective, Inflammatory Conditions, Immuno-Compromised Situations, Renal Transplant Patients, & Several Others Clinical Entities.

The Fundamental Need To Have All The Necessary Basic Ingredients (Anti-Septic, Anti-Microbial Specially For Anaerobs Flora, Anti-Fungal & Tropical Steroid In A Suitable Welcoming Use Flavour Base), Constituted For Efficient Delivery Convenient Preparation Module, Demands Intensive Pharmaco-Therapeutics Research To Provide Safe, Efficient Medications Effective By Local/Tropical /Regional Route Of Administration, With Maximally Effective Mucosal Barrier Absorption & Minimal Local & Or Systemic Side-Effects.


ACUTE (±) CHRONIC ORAL LESIONS
As Discussed The Study, Being One Of The Most Needed, Important, Clinical Research, Of Present Times, With An Aim To Control (Minimize), Considerably Prevalent Oral Disease Entities, More Disabling Due To Non-AwareNess, ‘No’ & Or Unproper Treatment, ManageMent GuideLines, Recurrence, Relapse, Chronicity, With Or Without Pre-Malignant & Or Malignant Transformations.


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