I. Administrative information:

1. Title:

Evaluation of the Chemo-preventive effect of Combined Topical and Systemic Metformin on Oral Leukoplakia: A Randomized Clinical Trial

2.Date of Submission to clinical trials:

12/9/2025

3.Date of Ethical Approval:

April 2021

4. Protocol Registration:

The protocol is being registered on clinicaltrial.gov

5. Protocol version:

This protocol has only one version (the one submitted)

6. Funding:

Self-Funded

7. Author contributions and responsibilities:

- G.A.Z: Conceptualization, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing
- M.G.A: Methodology, Investigation, Visualization , Resources, Writing - Original Draft, Writing - Review & Editing
- A.H.H: Methodology, Investigation, Visualization , Writing - Original Draft, Writing - Review & Editing
- T.H.S: Methodology, Investigation, Supervision ,Writing - Original Draft, Writing - Review & Editing
- N.A.A: Conceptualization, Formal analysis, Supervision, Writing - Original Draft, Writing - Review & Editing

I. Introduction

1. Background and rationale:

Research question:

In patients with oral mucositis, will MEBO result in clinical improvement as compared to Benzydamine Hydrochloride spray?

PICO:
Population [P]: patients with oral mucostis attending the National Cancer Institute clinic
Intervention [I]: MEBO
Comparison [C]: Benzydamine Hydrochloride spray
Outcome [o]: clinical improvement and quality of life

Outcome measure		Method of measurement	Unit of measurement
1ry Outcome	Clinical improvement	World Health Organization (WHO)scale.(1) Oral Mucositis Assessment Scale (OMAS).(2)	Ordinal
2ry Outcome	quality of life	Patient-Reported Oral Mucositis(PROMS scale).(3)	Continuous outcome (Score codes).

Statement of the problem:

Oral mucositis (OM) refers to mucosal damage secondary to cancer therapy occurring in the oral cavity. Mucositis can be caused by chemotherapy and/or radiation therapy. It occurs in approximately 20% to 40% of patients receiving conventional chemotherapy, 80% of patients receiving high dose chemotherapy as conditioning for hematopoietic stem cell transplantation, and nearly all patients receiving head and neck radiation therapy. OM can disturb speaking and eating, resulting in nutritional deficiency.(4)

The management of oral mucositis is a challenge, due to its complex biological nature. Over the last 10 years, different strategies have been developed for the management of oral mucositis.(5)

Rationale for conducting the research:

Oral mucositis consequences can range from pain, decreased oral intake, impaired speech and swallowing to adverse events as severe as septicemia, increased hospitalization, and G-tube feeding (6)

A wide variety of agents have been tested to prevent OM or reduce its severity.(7)This trial will assess the usefulness of MEBO versus Benzydamine Hydrochloride mouth wash in management of oral mucositis in patients receiving radiotherapy and/or chemotherapy.

Background:

The term "mucositis" was introduced to describe inflammation of the oral mucosa induced by radiotherapy, chemotherapy and bone marrow transplantation. At present, oral mucositis is considered to be the most serious non-hematological complication of cancer treatment.(8)

Numerous predisposing factors have been blamed for oral mucositis, including: the type of tumor involved, age of the patient, dental health, the nutritional condition of the patient, the maintenance of kidney and liver function and the type of cytostatic agent used.(9)

Clinically, oral Mucositis may appear as erythema, edema or ulceration that can be accompanied by alterations ranging from mild burning sensation to large and painful ulcers that worsen patient's quality of life and limit basic oral functions such as speech, swallowing of saliva or eating.(10)

According to Multinational Association for Supportive Care in cancer and the International Society of Oral Oncology (MASCC/ISOO) guidelines for the management of mucositis, Management of oral mucositis is divided into the following sections: nutritional support, pain control, oral decontamination, palliation of dry mouth, management of oral bleeding and therapeutic interventions for oral mucositis.(11)

Since the primary symptom of oral mucositis is pain which significantly affects nutritional intake, mouth care and quality of life, thus, management of mucositis pain is a primary component of any mucositis management strategy. Use of saline mouth rinses, ice chips and topical mouth rinses containing an anesthetic such as 2% viscous lidocaine can help in reducing pain (12)

Based on the pathogenesis of mucositis with complex biological inflammatory pathways, various therapeutic approach have been proposed to improve oral mucositis.(13)

The current guidelines recommend the use of non-medicated oral rinses such as Benzydamine hydrochloride mouthwash and the use of short-term pain killers. Benzydamine hydrochloride - which is a non-steroidal anti-inflammatory drug - can be used in the form of mouth rinse to reduce the severity of oral mucositis. Other management strategies include cryotherapy before the start of chemotheraputic agent administration and application of low-level

laser therapy. Palifermin (Keratinocyte growth factor) is the only recommended preventive measure recommended by the ESMO Clinical Practice Guidelines.(14)

7. Objectives

Aim of the study:

To assess the effect of MEBO versus Benzydamine Hydrochloride spray regarding clinical improvement of oral mucositis and quality of life of patients receiving readiotherapy and/or chemotherapy

8.Study design:

Phase III Randomized clinical trial (parallel arms)

II. Materials and Methods

Participants:

9.Study settings:

The patients will be selected from the pool of the Out-Patient Clinic of National Cancer Institute

Population: A random sample of adult patients receiving radiotherapy and having sign and symptoms of oral mucositis

10.Eligibility criteria:

A- Inclusion criteria:

1) Patients having clinical signs of chemotherapy-induced or radiotherapy-induced OM (WHO oral mucositis grading scale: Grade II, III and IV)
2) Patients over the age of 18 years
3) Patients having no history of allergy, allergic rhinitis and asthma

B- Exclusion criteria:

1) Patients allergic to the used treatment
2) Patient receiving systemic steroids
3) Patients who don't approve to participating in the clinical trial.

11.Interventions:

Enrolment: Enrolment is expected to be done within a one-year period. The enrolled patients will be divided randomly into two groups, each consisting of 33 patients.

Intervention group: Patients will receive mixture of MEBO three times daily for 14 days

Control Group: Patients will receive Benzydamine Hydrochloride spray three times daily for 14 days.

Follow up: The patients will be recalled at one week interval for 14 days.

Criteria for discontinuing intervention:

Occurrence of any harmful side effects from either of the treatment modalities.

Strategies to improve adherence to intervention:

The patients will be recalled at one week interval and asked to bring the drug package.

12.Outcomes:

Outcome measure		Method of measurement	Unit of measurement
1ry Outcome	Clinical improvement	World Health Organization (WHO)scale.(1) Oral Mucositis Assessment Scale (OMAS).(2)	Numerical rating score
2ry Outcome	Quality of life	Patient-Reported Oral Mucositis (PROMS questionnaire).(3)	Continuous outcome (Score codes).

Clinical parameters:

Clinical improvement of the lesion:

The clinical data will be scored according to The World Health Organization (WHO)scale(1). It is graded from 0 to 4. If the patient has no signs and symptoms, it is graded as 0. If the patient has painless ulcers, edema, or mild soreness, it is graded as 1. If there is painful erythema, edema, or ulcers but able to eat, it is graded as 2. If there is painful erythema, edema, or ulcers but unable eat, it is graded as 3. If there a requirement for parenteral or enteral support, it is graded as 4

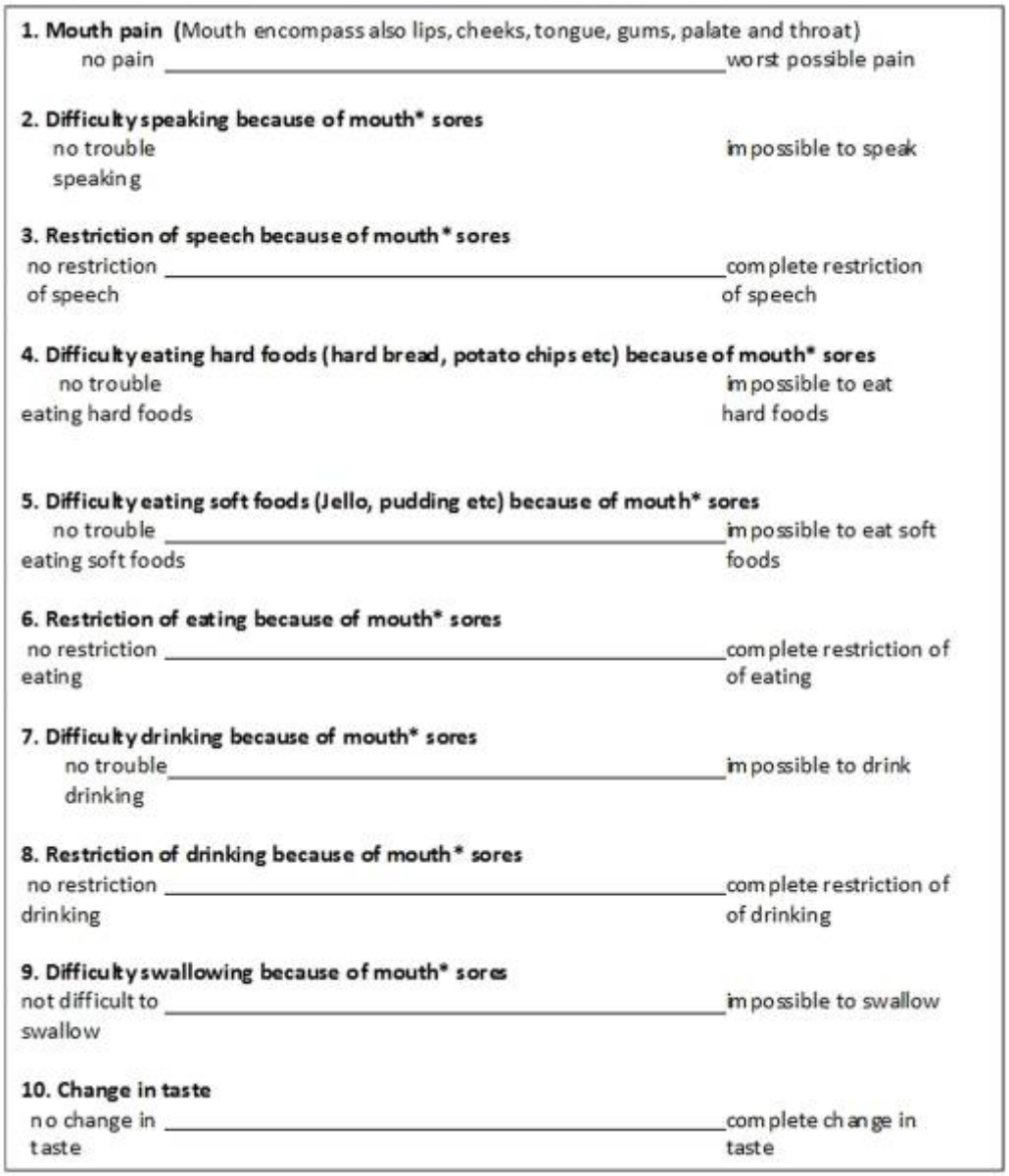
Adverse Events

Any adverse events and safety issues related to the administered drugs will be reported.

Quality of life

The secondary outcomes will be quality of life assessed by PROMS scale.(2)
The PROMS scale consists of 10, 100-mm horizontal visual analogue scales addressing oral functions affected by oral mucositis. Participants will be asked to mark a point on the line that best represents their present intra-oral condition. During the baseline examination and prior to their completion of the actual PROMS scale questionnaire, participants were subjected to a few training test-visual analogue scale questions focused on simple everyday topics to familiarize them with the concept of visual analogue scale assisted measurements(19). The participants will

complete the PROMS questionnaire thrice; baseline, after the first week, and at the end of the study after the second week.



1. Mouth pain (Mouth encompass also lips, cheeks, tongue, gums, palate and throat)
no pain _____ worst possible pain

2. Difficulty speaking because of mouth* sores
no trouble speaking — impossible to speak

3. Restriction of speech because of mouth* sores
no restriction of speech _____ complete restriction of speech

4. Difficulty eating hard foods (hard bread, potato chips etc) because of mouth* sores
no trouble eating hard foods — impossible to eat hard foods

5. Difficulty eating soft foods (Jello, pudding etc) because of mouth* sores
no trouble eating soft foods _____ impossible to eat soft foods

6. Restriction of eating because of mouth* sores
no restriction eating _____ complete restriction of of eating

7. Difficulty drinking because of mouth* sores
no trouble drinking _____ impossible to drink

8. Restriction of drinking because of mouth* sores
no restriction drinking _____ complete restriction of of drinking

9. Difficulty swallowing because of mouth* sores
not difficult to swallow _____ impossible to swallow

10. Change in taste
no change in taste _____ complete change in taste

13. Participant timeline

Enrolled patients will be divided randomly into two groups, each consists of 33patients.

Intervention group: Patients will receive mixture of Mebo and pumpkin seed oil spray three times daily

Control Group: Patients will receive Benzydamine Hydrochloride spray three times daily

Follow up: The patients will be recalled at one week interval for 14 days.

14. Sample size:

According to the study by Ahmed et al. [7] , the effect size reported for the mean mucositis score was 1.011. We used a power of 80%, alpha of 5% and an allocation ratio of 1:1 to calculate a sample size of 17 subjects per group.

15. Recruitment:

A random selection of adult patients complaining from signs and symptoms of oral mucositis attending at the clinic of National Cancer Institute will be enrolled by the investigator in the study in a consecutive order starting from January 2022 without any financial incentives.

16. Allocation:

16a. Randomization:

Method of random sequence generation: computerized random number generator
Type of randomization: Simple
Allocation ratio: 1:1.

16b. Allocation concealment mechanism:

All randomization numbers will be concealed in separate, sealed, opaque, serially numbered envelopes.

16c. Implementation:

NAA will generate the random sequence and perform the allocation concealment while the investigator will enroll and assign participants to interventions.

17. Masking/blinding:

This will not be possible as treatments are given in different forms

C) Data collection, management, and analysis:

18. Data collection methods

Outcome data will be collected as printed questionnaires, clinical pictures, and written grading. Outcome data will be entered into excel sheets and clinical photos will be downloaded as a soft copy. Data will be backed up with the supervisors.

19. Data management:

Patient data will be stored on safe computers with antivirus software accessed only by the investigators.

20. Statistical methods:

Data will be analyzed using IBM SPSS advanced statistics (Statistical Package for Social Sciences), version 21 (SPSS Inc., Chicago, IL). Descriptive statistics in case of normal distribution will be presented as mean and standard deviation, while if non-normal; median and 25^{th} and 75^{th} percentile will be used. Intergroup comparison will be done using t-test or Mann-Whitney test while Intra-group comparison will be done using student's t- test.

D) Data monitoring:

21. Monitoring

The collected data will be monitored by the main supervisor and co-supervisor. The entire study will be monitored by the Faculty of Dentistry's Ethical committee.

22. Harms

Any adverse effect from the treatment will be recorded and documented in details.

23. Audit

Auditing will be done by the Faculty of Dentistry's Ethical committee.

III. Ethics and dissemination

21. Research ethics approval

After proper study design revision, the study protocol will be presented to the ethical committee for approval.

22. Protocol amendments

The protocol will be registered on clinicaltrials.gov in its current form, further amendments will be updated on the system.

23. Informed consent

informed consent will be obtained by the investigator from all study participants.

24. Confidentiality

The candidate will be responsible for data collection and storage. Patient's personal information will be available to the candidate and the research team only.

25. Declaration of interest

If there will be any conflict of interest it will be declared by the investigators.

26. Access to data

The Data (Demographic, Clinical and Analytical) will be available only to the supervisors

30. post-trial care

Any harm from the study, the participants will be managed completely.

V. Appendices:

32. Informed consent

Informed consent form is as follows in Arabic and English

Faculty of oral & dental medicine

Cairo University

Research Ethics Committee

Application Form

Human Subjects

Kindly fulfill the following:

Research title:

Clinical Evaluation of MEBO Versus Benzydamine Hydrochloride In Management of Patients with radiotherapy induced Oral Mucositis: Randomized Clinical Trial

Research objective:

To assess the effect of MEBO versus Benzydamine Hydrochloride spray regarding clinical improvement of oral mucositis and quality of life of patients receiving readiotherapy

- ***Research Procedure in brief:***

A random sample of adult patients receiving radiotherapy or chemotherapy and having sign and symptoms of oral mucostis and this Enrolled patients will be divided randomly into two groups, each consists of 21patients.

Intervention group: Patients will receive MEBO three times daily for two week

Control Group: Patients will receive Benzydamine Hydrochloride spray three times daily

Follow up: The patients will be recalled at one week interval for two week

as there is no treatment of oral mucositis available in Egyptian market

We will offer palliative treatment that will alleviate the pain of oral mucositis

value and social benefits:

treatment of chemotherapy and radiotherapy induced oral mucositis

Expected risk to the human subjects:

No risk is expected because we use a natural product however patient may experience mild burning sensation and any patient report a problem from the treatment we will stop it

Signature: ***Noha Adel Azab***

Approval Number

VII.References:

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