# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

08 Nov 2026

## A comparison of silymarin vs benzydamine rinse in the prevention of radiation-induced oropharyngeal mucositis in head and neck cancers: A randomized controlled trial

### Protocol summary

**Study aim**
Comparison of the effect of silymarin mouthwash with benzydamine mouthwash in the prevention of grade 3 radiation-induced acute mucositis with doses above 50 Gy in head and neck squamous cell carcinoma until the end of treatment

**Design**
A randomized, parallel group, double-blind phase 3 controlled trial of 98 patients. Randomization was carried using Sealed Envelope website (sealedenvelope.com).

**Settings and conduct**
The study population are head and neck squamous cell carcinoma patients of Shahid Rajaei hospital in Babolsar, who will be treated with head and neck radiotherapy for the first time. The researchers, treating physicians, and the patients are blinded

**Participants/Inclusion and exclusion criteria**
Inclusion Criteria: patients with head and neck squamous cell carcinoma, receiving at least 50 Gy radiation to 2 of the 4 areas of the head and neck including the oral cavity, oropharynx, hypopharynx and larynx Exclusion Criteria: History of severe allergy to silymarin, benzydamine or other NSAIDs, Narcotic use in the last month (even once), History of radiation therapy to the same target areas, Presence of mucositis on admission, History of dry mouth, Proven dementia or history of uncontrolled psychiatric disease, Pregnancy, Malnutrition

**Intervention groups**
Arm A receives Silymarin mouthwash, Arm B receives Benzydamine mouthwash

**Main outcome variables**
Grade 3 mucositis (according to Common Terminology Criteria for Adverse Events (CTCAE) v.5

### General information

**Reason for update**

**Acronym**
SIBERIA

**IRCT registration information**
IRCT registration number: **IRCT20211202053252N2**
Registration date: **2024-08-18, 1403/05/28**
Registration timing: **prospective**

Last update: **2024-08-18, 1403/05/28**
Update count: **0**

**Registration date**
2024-08-18, 1403/05/28

**Registrant information**

**Name**
Davoud Jahansouz

**Name of organization / entity**

**Country**
Iran (Islamic Republic of)

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**Email address**
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**Recruitment status**
**Recruitment complete**

**Funding source**

**Expected recruitment start date**
2024-08-31, 1403/06/10

**Expected recruitment end date**
2025-02-28, 1403/12/10

**Actual recruitment start date**
empty

**Actual recruitment end date**
empty

**Trial completion date**
empty

**Scientific title**

A comparison of silymarin vs benzydamine rinse in the prevention of radiation-induced oropharyngeal mucositis in head and neck cancers: A randomized controlled trial

**Public title**
SIlymarin vs BEnzydamine in Radiation-Induced orophAryngeal mucositis
**Purpose**
Supportive
**Inclusion/Exclusion criteria**
**Inclusion criteria:**
Age over 18 years old Any ECOG performance status Head and neck cancer patient Any setting of radiation (i.e. definitive, neoadjuvant, adjuvant) Receiving at least 50 Gy radiation to 2 out of 4 subsite of the head and neck, including oral cavity, Oropharynx, hypopharynx, and the larynx More than 2 cm of irradiated mucosal surface in any head and neck subsite
**Exclusion criteria:**
History of severe allergy to silymarin, benzydamine or other NSAIDs Narcotic use in the last month (even once) History of radiation therapy to the same target areas Presence of mucositis on admission History of dry mouth Proven dementia or history of uncontrolled psychiatric disease Pregnancy Malnutrition
**Age**
From **18 years** old
**Gender**
Both

**Phase**
3
**Groups that have been masked**

- Participant
- Care provider
- Investigator
- Outcome assessor

**Sample size**
Target sample size: **98**
**Randomization (investigator's opinion)**
Randomized
**Randomization description**
Permuted block randomization with a block size of 4 individual was carried out on Sealed Envelope website (www.sealedenvelope.com) and its Excel output file with three letter codes is only available to the study pharmacist who is based outside the hospital and is completely separate from the study process. Patients are stratified in terms of receiving/not receiving concurrent chemotherapy. The pharmacist of the study prepares the silymarin and benzydamine mouthwashes, which are completely similar in terms of color, smell, taste and consistency, and packs them into completely similar colorless 250 cc graduated bottles and sticks the three-letter codes on the bottles of treatment arms: A (silymarin ) and B (benzidamine). Next, the codes assigned to the strata (chemotherapy and no-chemotherapy) are printed with consecutive numbers (from 1 to 49 for each strata) and provided to the principal investigator. After determining the treatment plan by the treating physician, eligible patients are referred to the principal investigator. Following acceptance of the study conditions and signing the informed consent form, they will receive their drug with the dedicated strata bottle code in sequence (i.e. from 1 to 49). Each patient receives a total of 10 bottles with the same code; one or two bottles delivered each week.
**Blinding (investigator's opinion)**
Double blinded
**Blinding description**
The three letter codes assigned to each strata (chemotherapy and no-chemotherapy) are printed with consecutive numbers (from 1 to 49 for each strata) and provided to the principal investigator, which in turn prints out each number with it's unique three letter code on a discrete paper. Then papers are enveloped and numbered from 1 to 49. Eligible patients in each strata are sequentially provided bottles starting from number 1 by admission order. The corresponding codes for each patient is recorded and delivered to the pharmacist on a weekly basis.
**Placebo**
Not used
**Assignment**
Parallel
**Other design features**

## Secondary Ids

empty

## Ethics committees

### 1

**Ethics committee**
**Name of ethics committee**
Health Research Center, Babol University of Medical Sciences
**Street address**
Daneshagh Sq.
**City**
Babol
**Province**
Mazandaran
**Postal code**
4717647754
**Approval date**
2024-08-11, 1403/05/21
**Ethics committee reference number**
IR.MUBABOL.HRI.REC.1403.076

## Health conditions studied

### 1

**Description of health condition studied**
Malignant neoplasm of head, face and neck
**ICD-10 code**
C76.0
**ICD-10 code description**
Malignant neoplasm of head, face and neck

## Primary outcomes

### 1

**Description**
Grade 3 mucositis
**Timepoint**
Before intervention and every week after intervention for at least 5 weeks
**Method of measurement**
According to CTCAE v.5

## Secondary outcomes

### 1

**Description**
Grade 1 and 2 mucositis
**Timepoint**
before intervention and every week during intervention for at least 5 weeks
**Method of measurement**
According to CTCAE v.5

### 2

**Description**
Grade 3 and 4 mucositis
**Timepoint**
before intervention and every week during intervention for at least 5 weeks
**Method of measurement**
According to CTCAE v.5

### 3

**Description**
Mucositis onset
**Timepoint**
Every week during intervention for at least 5 weeks
**Method of measurement**
The day of the first evidence of grade 1 mucositis detected by history or examination from the day of treatment initiation - according to CTCAE v.5

### 4

**Description**
Tube or Intravenous nutrition
**Timepoint**
Before intervention and every week during intervention for at least 5 weeks
**Method of measurement**
History and examination

### 5

**Description**
Opioid Use
**Timepoint**
Every week during intervention for at least 5 weeks
**Method of measurement**
Any opioid use detected by subjectively

### 6

**Description**
Hospitalization
**Timepoint**
Every week during intervention for at least 5 weeks
**Method of measurement**
Subjective - Inquired

### 7

**Description**
Mucositis recovery time
**Timepoint**
Every week during intervention for at least 5 weeks, and the two post-intervention weeks
**Method of measurement**
The day mucositis score reaches zero from treatment termination - according to CTCAE v5.0

### 8

**Description**
Mortality
**Timepoint**
Every week during intervention for at least 5 weeks
**Method of measurement**
Subjective - Inquired

### 9

**Description**
Overall survival
**Timepoint**
The duration of survival after 24 months (730 days) from the moment of randomization
**Method of measurement**
Subjective - Inquired

## Intervention groups

### 1

**Description**
Silymarin group: Patients Swish mouth with 15 ml of 0.2% silymarin solution (Silybum marianum extract, Zardband pharmaceuticals, Tehran, Iran) every 8 hours for two minutes and spit the remainder.
**Category**
Treatment - Drugs

### 2

**Description**
Benzydamine group: Patients Swish mouth with 15 ml of 0.15% Benzydamine solution (Benzylagine – Exir Pharmaceutical Company, Tehran, Iran) every 8 hours for two minutes and spit the remainder.
**Category**
Treatment - Drugs

## Recruitment centers

**1**

**Recruitment center**

**Name of recruitment center**
Shahid Rajaee Hospital
**Full name of responsible person**
Davoud Jahansouz
**Street address**
Shilat Sq., Shariati St
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babolsar
**Province**
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**Postal code**
4741999879
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**Email**
rajaee@mubabol.ac.ir

## Sponsors / Funding sources

**1**

**Sponsor**

**Name of organization / entity**
Babol University of Medical Sciences
**Full name of responsible person**
Mehdi Rajabnia
**Street address**
Daneshgah Sq.
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**Postal code**
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**Phone**
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**Email**
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**Grant name**

**Grant code / Reference number**

**Is the source of funding the same sponsor organization/entity?**
Yes

**Title of funding source**
Babol University of Medical Sciences

**Proportion provided by this source**
30

**Public or private sector**
Public

**Domestic or foreign origin**
Domestic

**Category of foreign source of funding**
*empty*

**Country of origin**

**Type of organization providing the funding**
Academic

## Person responsible for general inquiries

**Contact**

**Name of organization / entity**
Babol University of Medical Sciences
**Full name of responsible person**
Davoud Jahansouz
**Position**
Physician
**Latest degree**
Specialist
**Other areas of specialty/work**
Radiotherapy
**Street address**
Shilat Sq., Shariati St.
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## Person responsible for scientific inquiries

**Contact**

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**Position**
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**Other areas of specialty/work**
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## Person responsible for updating data

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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**
Yes - There is a plan to make this available
**Study Protocol**
Yes - There is a plan to make this available
**Statistical Analysis Plan**
Yes - There is a plan to make this available
**Informed Consent Form**
Yes - There is a plan to make this available
**Clinical Study Report**
Undecided - It is not yet known if there will be a plan to make this available
**Analytic Code**
Yes - There is a plan to make this available
**Data Dictionary**
Undecided - It is not yet known if there will be a plan to make this available
**Title and more details about the data/document**
All of the deidentified data are to be released after publication of the study
**When the data will become available and for how long**
Within one year after paper publication
**To whom data/document is available**
Any academic institution can have access to data
**Under which criteria data/document could be used**
There is no restriction
**From where data/document is obtainable**
Any interested institution is expected to send a formal email to the Health Research Institute of Babol University of Medical Sciences. Email: hribabol@gmail.com Phone & Fax: +98-11-32190557 Website: hri.mubabol.ac.ir
**What processes are involved for a request to access data/document**
The documents would be delivered to the applicant by email, after one business week. In some cases, a Research Vice Chancellor and/or Ethics Committee approval for data access may be needed in which the aforementioned time may stretch up to three weeks. Applicants are not required to do additional tasks in such cases.
**Comments**