Clinical Trial Protocol
Iranian Registry of Clinical Trials

09 Nov 2026

Title : Investigating the Effect of 50% Nitrous Oxide on Opioid-Induced Hyperalgesia (OIH) after Isoflurane-Remifentanil Administration or Quantitative Sensory Testing (QST) in Patients Undergoing Septorhinoplasty Surgery

Protocol summary

Study aim
To determine the effect of 50% nitrous oxide on reducing opioid-induced hyperalgesia (OIH) following isoflurane-remifentanil administration in patients undergoing septorhinoplasty surgery.

Design
This was a phase 2–3, randomized, double-blind, parallel-group, controlled clinical trial conducted on 56 patients. Randomization was performed using the RAND function in Excel.

Settings and conduct
Double-blind RCT at Rasoul Akram Hospital, Tehran, on 56 patients aged 18-55, ASA I, septorhinoplasty. Block randomization (size 4, Excel) into intervention (50% N_2O+50% O_2) and control (100% O_2). Induction: midazolam, fentanyl, propofol, atracurium, lidocaine. Maintenance: isoflurane (BIS 40-60) + remifentanil 0.1 µg per kg per minute. Pressure pain threshold measured by algometer at nose, cheek, forearm before and 5 min post-PACU. Shivering, morphine use, extubation time, PONV recorded. Blinding: patients and outcome assessor; anesthesiologist aware.

Participants/Inclusion and exclusion criteria
Inclusion Criteria: Patients with ASA physical status I Age between 18 and 55 years Candidates for elective septorhinoplasty surgery under general anesthesia Provision of written informed consent to participate in the study Exclusion Criteria: History of chronic pain Substance or alcohol abuse Diagnosed psychiatric disorders Obesity (Bodu mass index more than 30) Use of any analgesic or opioid within 48 hours prior to surgery Known allergy or contraindication to any study medication Any contraindication to nitrous oxide including: proven or suspected pneumothorax, bowel obstruction, middle ear disease (e.g., acute infection or barotrauma), increased intracranial pressure, or history of allergy to N_2O

Intervention groups
Intervention Group: Receives 50% N_2O + 50% O_2 at 2 L per minute during maintenance. Control Group: Receives 100% O_2 at 2 L per minute.

Main outcome variables
Opioid-Induced Hyperalgesia

General information

Reason for update

Acronym

IRCT registration information
IRCT registration number: **IRCT20240519061842N2**
Registration date: **2026-07-01, 1405/04/10**
Registration timing: **prospective**

Last update: **2026-07-01, 1405/04/10**
Update count: **0**

Registration date
2026-07-01, 1405/04/10

Registrant information

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Name of organization / entity

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Iran (Islamic Republic of)

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Recruitment status
recruiting

Funding source

Expected recruitment start date
2026-07-21, 1405/04/30
Expected recruitment end date
2027-01-20, 1405/10/30
Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
Title : Investigating the Effect of 50% Nitrous Oxide on Opioid-Induced Hyperalgesia (OIH) after Isoflurane-Remifentanil Administration or Quantitative Sensory Testing (QST) in Patients Undergoing Septorhinoplasty Surgery

Public title
Investigating the Effect of 50% Nitrous Oxide on Opioid-Induced Hyperalgesia (OIH) in Patients Undergoing Septorhinoplasty Surgery
Purpose
Supportive
Inclusion/Exclusion criteria
Inclusion criteria:
Patients with ASA physical status I Age between 18 and 55 years Candidates for elective septorhinoplasty surgery under general anesthesia Provision of written informed consent to participate in the study
Exclusion criteria:
History of chronic pain Substance or alcohol abuse Diagnosed psychiatric disorders Obesity (Body mass index more than 30) Use of any analgesic or opioid within 48 hours prior to surgery Known allergy or contraindication to any study medication Any contraindication to nitrous oxide including: proven or suspected pneumothorax, bowel obstruction, middle ear disease (e.g., acute infection or barotrauma), increased intracranial pressure, or history of allergy to N_2O
Age
From **18 years** old to **55 months** old
Gender
Both

Phase
2-3
Groups that have been masked

- Participant
- Outcome assessor

Sample size
Target sample size: **56**
Randomization (investigator's opinion)
Randomized
Randomization description
Patient randomization in this clinical trial is performed using block randomization with a block size of 4 and an allocation ratio of 1:1. The unit of randomization is individual. The random sequence is generated using Microsoft Excel with the RAND function. For each patient, a random number between 0 and 1 is generated using the RAND function; patients are then sorted in ascending order based on these values and allocated into blocks of four to groups A (intervention) and B (control). For allocation concealment, the generated sequence is placed by an individual independent of the research into opaque, sealed, sequentially numbered envelopes from 1 to 56. After tracheal intubation and before initiating maintenance anesthesia, the attending anesthesiologist opens the corresponding envelope and adjusts the respiratory gases according to the allocation inside. The anesthesiologist is the only individual aware of the group assignment, while the outcome assessor performing QST measurements remains completely blinded to group allocation.
Blinding (investigator's opinion)
Double blinded
Blinding description
This study is designed as a double-blind trial, meaning that two main groups of individuals are unaware of the patient's group allocation: the patients and the outcome assessor. Blinding of patients: All patients are enrolled without knowing which type of respiratory gas they receive. Since maintenance anesthesia is initiated after tracheal intubation while the patient is already unconscious, patients are naturally unaware of the gas composition. During the recovery period, patients also have no information about their group assignment. Blinding of the outcome assessor: The researcher performing QST measurements using a pressure algometer at T_0 (before surgery) and T_1 (5 minutes after PACU admission) is completely blinded to patient group allocation. This researcher is not present in the operating room and has no access to allocation documents. Additionally, the recovery room nurse who records shivering intensity, nausea/vomiting, and morphine consumption is also blinded to group assignment. Practical blinding in the operating room: To ensure uniform appearance, the respiratory gas circuits and ventilators are covered so that the type of gas (presence or absence of N_2O) cannot be identified by the device's appearance or sound. The anesthesiologist responsible for adjusting the gases is the only individual aware of the allocation and is instructed not to disclose group information to other team members, the surgeon, or especially the outcome assessor. No group indicators are recorded on data collection forms; only the patient's identification code is used.
Placebo
Not used
Assignment
Parallel
Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee
Name of ethics committee

Ethics Committee of the Faculty of Medicine, Iran University of Medical Sciences

Street address

Iran University of Medical Sciences, Shahid Hemmat Highway, between Sheikh Fazl-allah and Chamran Expressways, Tehran, Iran

City

Tehran

Province

Tehran

Postal code

14496-14535

Approval date

2026-06-22, 1405/04/01

Ethics committee reference number

IR.IUMS.FMD.REC.1405.293

Health conditions studied

1

Description of health condition studied

Opioid-Induced Hyperalgesia following remifentanil in septorhinoplasty surgery

ICD-10 code

R20.3

ICD-10 code description

Hyperesthesia

Primary outcomes

1

Description

Opioid-Induced Hyperalgesia

Timepoint

Before surgery and 5 minutes after PACU admission

Method of measurement

Pressure algometer (kg/cm²)

Secondary outcomes

1

Description

Postoperative Shivering Intensity

Timepoint

5 minutes after PACU admission

Method of measurement

The standard shivering scale (Grade 0 indicated no shivering; Grade 1 referred to mild shivering localized to the face and neck; Grade 2 denoted visible shivering involving the trunk muscles; Grade 3 represented generalized shivering involving both the trunk and extremities; and Grade 4 indicated severe generalized shivering with an inability to cooperate)

2

Description

Morphine Consumption

Timepoint

During the recovery period

Method of measurement

Recorded from patient file (mg)

3

Description

Extubation Time

Timepoint

From end of surgery to extubation

Method of measurement

Recorded from patient file (minutes)

4

Description

Postoperative Nausea and Vomiting

Timepoint

During the recovery period

Method of measurement

Recorded by nurse (yes/no)

5

Description

Postoperative Pain Intensity

Timepoint

During the recovery period

Method of measurement

Numerical Rating Scale (NRS) from 0 to 10

Intervention groups

1

Description

Intervention group: Patients in this group receive a gas mixture of 50% nitrous oxide (N_2O) and 50% oxygen with a fresh gas flow of 2 L/min during maintenance of anesthesia. Anesthesia induction is performed with midazolam 0.02 mg/kg, fentanyl 0.02 µg/kg, propofol 2 mg/kg, atracurium 0.5 mg/kg, and lidocaine 1 mg/kg. Anesthesia is maintained with isoflurane (adjusted to maintain BIS between 40-60) and remifentanil at a fixed dose of 0.1 µg/kg/min as a continuous intravenous infusion. The surgeon injects 6 mL of 2% lidocaine with 1:100,000 epinephrine into the nasal area at the start of surgery, and at the end of surgery, all patients receive 1 gram of intravenous apotel (tranexamic acid). The nitrous oxide used (N_2O) is medical-grade gas with 99.9% purity, supplied by Darmangaz Co, in Iran.

Category

Treatment - Other

2

Description

Control group: Patients in this group receive only 100% oxygen with a fresh gas flow of 2 L/min during maintenance of anesthesia. Anesthesia induction, maintenance with isoflurane (BIS 40-60) and remifentanil 0.1 µg/kg/min, injection of 2% lidocaine with epinephrine by the surgeon at the start of surgery, and

administration of apotel 1 g IV at the end of surgery are exactly the same as the intervention group. The only difference is that they do not receive nitrous oxide and breathe pure oxygen.

Category
Treatment - Other

Recruitment centers

1

Recruitment center

Name of recruitment center
Hazrat Fatemeh Hospital

Full name of responsible person
Taymaz Amiraslani

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Iran University of Medical Sciences - Faculty of Medicine, Hemat Highway, next to Milad Tower, Tehran

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Sponsors / Funding sources

1

Sponsor

Name of organization / entity
Iran University of Medical Sciences

Full name of responsible person
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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
Iran University of Medical Sciences

Proportion provided by this source
100

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
Iran University of Medical Sciences

Full name of responsible person
Taymaz Amiraslani

Position
Assistant professor

Latest degree
Specialist

Other areas of specialty/work
Anesthesiology

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Person responsible for scientific inquiries

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Position

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Latest degree

Specialist

Other areas of specialty/work

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Sharing plan

Deidentified Individual Participant Data Set (IPD)

Undecided - It is not yet known if there will be a plan to make this available

Study Protocol

Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan

Undecided - It is not yet known if there will be a plan to make this available

Informed Consent Form

Undecided - It is not yet known if there will be 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

Undecided - It is not yet known if there will be a plan to make this available

Data Dictionary

Undecided - It is not yet known if there will be a plan to make this available