Premixed nitrous oxide/oxygen as an analgesic for dressing in patients with perianal abscess after surgery: study protocol for a randomized, within-patient, controlled trial

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Study protocol

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Abstract

Background: Perianal abscess is mainly treated by surgery in the clinic. However, the pain induced by dressing is the most prominent problem in postoperative patients and available analgesics is limited. The short-acting analgesia, premixed nitrous oxide/oxygen, may be an ideal analgesic for acute pain induced by dressing change after perianal abscess surgery. This study aims to evaluate the safety and analgesic efficacy of premixed nitrous oxide/oxygen mixture for patients with dressing change after surgery around the anus. **Methods/design:** This protocol for a randomized, double-blind, placebo-controlled trial will be implemented in the Anorectal Department, Yinchuan Hospital of Traditional Chinese Medicine affiliated to Ningxia Medical University. Study subjects are hospitalized patients underwent perianal abscess surgery and suffered from moderate to severe pain due to dressing. Two hundred subjects will be selected and randomly assigned to other intervention or control group. The intervention group will get regular pain treatment plus premixed nitrous oxide/oxygen and the control group will be treated with regular pain treatment plus oxygen. The patients, medical staffs or investigators are blinded to the nature of the gas mixture in each cylinder and the randomization list. Data will be collected at baseline (T0, 2 min before dressing) and at 5 min (T1) after the beginning of intervention and at 5 min (T2) past dressing. The primary outcome will be the change in pain score at T1 and T2. Secondary outcomes cover physiological parameters, adverse events, patients and medical staffs' satisfaction as well as patients' acceptance. **Discussion:** The findings of this trial will provide a valuable therapeutic regimen for pain caused by dressing after perianal abscess surgery and identify the efficacy and safety of the gas.

Background

Perianal abscess, a collection of infected fluid under the skin around the anus, is an acute suppurative disease of soft tissue caused by bacteria [1]. Its incidence is difficult to accurately count because there are many uncertainties. A previous study showed that anorectal diseases account for about 15% of all surgical diseases, and the incidence of perianal abscess was 0.4% [2]. It's reported that 90% of cases are caused by anal gland infection [1, 3]. As of now, surgery is the main method for the treatment of perianal abscess [4].

Painful dressing are frequently required during the treatment of wounds. Patients may suffer the severe pain caused by reduplicative dressing change. The pain caused by dressing is the most prominent clinical problem in patients with perianal abscess [5]. Uncontrolled dressing pain may induce anxiety and reluctance to participate in their wound care, thus lead to the delayed recovery and condition to deteriorate. The influence of pain on patients is not restricted to prolong hospitalization, urinary retention, defecate difficulty, and other complications, but is also evident among pathophysiological changes, such as emotional tension, increased heart rate, and elevated blood pressure [5–7]. Postoperative dressings play an important role in the overall process of anorectal treatment. The successful dressing or not is directly related to the incidence of wound infection, the length of the and the degree of wound healing [8].

Although there are many analgesic methods for postoperative dressings, the efficacy is not ideal. Local injection of analgesics (such as intravenous morphine, the onset of action is 3 minutes and the blood concentration peaks after 10 minutes, is an effective analgesic treatment for acute pain [9]) can relieve pain in time. But in most cases, it is not recommended due to invasive administration. As for oral opioids, studies [10, 11] have shown that medical staffs and patients still have many misconceptions about its addiction, tolerance and toxic side effects like acute respiratory depression, ulcers, bleeding, which give rise to the insufficient use of analgesia. In China, the situation is even more pronounced. There is a statistical statement that China ranks 83rd (among 179 countries list) in per capita opioid consumption, far behind some small countries and regions [12].

The premixed nitrous oxide/oxygen stored in the cylinder is a self-service inhaled gas. The inhalation system consists of a whistle, mask and breathing valve that is one-way. Its analgesic effects have been known for nearly two centuries. Studies [13–15] have confirmed the safety of premixed nitrous oxide used pain management. In addition, the main advantage of this analgesic gas is that it can't cause loss of consciousness, and thus patients can control their own maintenance of gas flow [16]. In addition, there is few side effects due to its poorly blood/gas solubility and bound to proteins as well as characterized by rapid onset (1–2 minutes) and transient effects (< 1min) after withdrawal [17, 18]. Even if it occurs, usually, it disappears quickly after exposure to air [16]. There are no reports of the use of nitrous oxide/oxygen mixture to relieve pain caused by dressing after perianal abscess surgery yet. So, we hypothesize that the premixed nitrous oxide/oxygen is a optional, safe and effective gas as an analgesic for dressing after perianal abscess surgery. We designed this study protocol to test and verify this hypothesis.

Methods

Study design

This study protocol is a randomized, within-patient, controlled, double-blind, single- center trial (See Fig. 1). This clinical trial was designed on the basis of interventional Trials SPIRIT [19] guidelines (See Additional file 1) as well as abiding by the checklist set out in the Consolidated Standards of Reporting Trials (CONSORT 2010) [20] statement (see Additional file 2). The study have obtained an official authorization from the Ethics Committee of Ningxia Medical University (2018–231) and was registered in the China Clinical Trial Registration Center (NO.ChiCTR1900021374) for the clinical trial protocol. We will summarize the complete schedule of participant enrollment, intervention, and evaluation in table 1.

Study setting

This study will be conducted by a trained researcher in the Anorectal Department, Yinchuan Hospital of Traditional Chinese Medicine affiliated to Ningxia Medical University. The department is the only national-level anorectal specialty in our district, with visiting more than 6,000 outpatient and inpatient

approximately 1200 people annually. Hence, we have sufficient patient to achieve a suitable and cross-sectional sample size.

Study population

According to the study design, a total of 200 eligible participants will be recruited from 28 April 2019 in the Anorectal Department. To eliminate the complex factors that may interfere with dressing, we will recruit patients with relatively consistent or close of wound conditions as far as possible.

Inclusion criteria

- Chinese-speaking and ranging from 18 to 60 years old;
- Meeting the diagnosis of perianal abscess [21] and are suffering from acute pain (moderate to severe intensity) induced by dressing after perianal abscess surgery.
- Being able to take deep breaths to use self-managing devices (similar to oxygen mask);
- Signing the informed consent.

Exclusion criteria

- Having contraindications to the use of nitrous oxide/oxygen (such as intracranial hypertension, maxillofacial traumatism, gas embolism, unventilated gas in the body, requiring pure oxygen inhalation) [22];
- Impairing cognitive function and being difficult to report pain;
- Being diagnosed with other life-threatening situations or instability of vital signs.

Randomization, allocation concealment, and blinding

A total of 200 participants will be randomly assigned to either intervention or control group in a 1:1 fashion with a computer-generated list. Taking into account selection bias and confounding factors, the random numbers of each participant will be generated by an independent statistical expert who works for the School of Public Health and Management, Ningxia Medical University with applying Random Allocation Software version 1.0.0 [23]. The expert will not be involved in the recruitment, gas distribution, data collection. Then, the random numbers will be stored and sealed in a designated research office to ensure concealment [15]. In order to maintain a double-blind environment, nurses and researchers are blinded and not allowed to touch the random numbers unless they can put forward justifiable reason and get the approval from the project supervisor. Only the project leader who is in charge of gas distribution

and treatment delivery can have access to the envelope [23]. In addition, the two gas cylinders (Ningfeng Oxygen Company, Yinchuan, China) containing premixed nitrous oxide/oxygen and oxygen are strictly identical on the package, and all cylinders are marked with the letters A or B. The intervention group will receive premixed nitrous oxide/oxygen contained in gas cylinders tag the letter A. While the control group will obtain oxygen stored in cylinders with B. No medical staffs, researchers and patients know what the letter indicates. The treatment method (the nature of the gas inhaled by patients) is blind for everyone. According to study rules of the protocol, the investigators will know the answer until completing all the trials.

Interventions

To build the same conditions, dressing for all post-operative wounds is performed by a regular surgeon who has received medicine college education for 5 years or longer and more than 3 years of clinical experience in the Anorectal Department. The patients will receive an informed consent form and get an explanation from investigators regarding the aim, benefits and possible risks of the trial before the study is carried out. Eligible patients will be randomly allocated into two groups, inhaling premixed nitrous oxide/oxygen or oxygen with a one-way valve, specially designed oral–nasal mask [15]. The patients hold the self-administered mask that can be controlled by their own negative pressure to inhale gas until the dressing is over. Regular pain treatment will also be conducted as usual. In this study, we designed that the intervention group will get nitrous oxide/oxygen plus conventional analgesic therapy comparing with the control group receives oxygen plus conventional analgesic therapy. In general, inhalation of these two gases is a safe intervention strategy with no severe adverse effects on patients. Even if any undesired events during the nitrous oxide/oxygen intervention happen, short and mild, which usually disappear when the patients are exposed to the air [16]. Finally, each participant is endowed with undeniable right to withdraw from the study at any time, of course, the reason of dropout will also be recorded and analyzed by the Data Monitoring Committee (DMC) and the data collector.

Outcome measurement

1. Baseline data

Demographic details of each patient (age, sex, nationality, weight, height, education level, occupation, etc.) and clinical characteristics (such as classification of perianal abscesses and post-operation wound size) will be recorded using in-house-designed questionnaire at baseline (T0). Physiological parameters including blood pressure, heart rate, respiratory rate, oxygen saturation and temperature will also be collected.

2. Primary outcome measure

The primary outcome is the change in pain score assessed on the Changhai Pain Rating Scale (it combines the characteristics of the Faces Pain Scale Revised, Numerical Rating Scale and Visual Analogue Scale). The researchers will measure and record the primary measure with the patients self-report scale at T0 (3 min before dressing), T1 (5 min after the beginning of dressing) and T2 (5 min after dressing finished) respectively. The percentage change in pain score at T1 and T2 will be then calculated.

3. Secondary outcome measures

Secondary outcomes measures cover physiological parameters, adverse events, patients and medical staffs' satisfaction, Ramsay sedation score and patients' acceptance. Noninvasive electronic manometer (OMRON, HEM-7120) and digital monitoring of oxygen saturation (OXIMETER, PC-60B) will be used to monitor the physiological parameters. And these parameters will be recorded by data collector at T0, T1 and T2. However, adverse events in secondary outcome measures, such as nausea, vomiting, numbness, drowsiness, over sedation and dizziness [14] will be carefully recorded after performing inhalation gas and handled properly. Patients and medical staffs' satisfaction (a five-point satisfaction scale, 1 = very dissatisfied; 5 = very satisfied) with pain management will be obtained at T2. Also, acceptance from the patients (they are asked if they would still accept this new analgesic gas in case of acute pain with moderate to severe, yes / no) will be recorded at 5 min after the whole intervention. Finally, total time of the patient inhales gas will be also minuted.

Sample size determination

The determination of its sample size was on the basis of preliminary experimental data collected in the Anorectal Department for 30 patients. and our previous studies involved burn-dressing and cancer breakthrough pain [15, 24]. The data indicated that 55% of participants receiving premixed nitrous oxide/oxygen had a meaningful change in pain score (a drop at least one-third of pain score [25]) at T1 and T2, while 15% of patients receiving oxygen was. That is, we designed the intensity of pain as the primary outcome of this trial, so when the difference between the two groups is the most obvious and decimal in two places, the pilot experiments showed that the mean $\pm$ standard deviation of the control group is 7.67 ± 0.67 , while the experimental group is 4.47 ± 0.86 . To assess the efficacy of the new analgesic gas, statistical power of 90% ($\beta = 0.10$) and type-1 error rate of 0.05 (a two-tail test) is needed. So a sample size of 87 is sufficient. Considering a possible 15% dropout rate, ultimately, we decided that 200 patients in total will be recruited to meet the Chinese Food and Drug Administration standard.

Data management

In order to ensure the quality of the collected data and the smooth implementation of the study protocol, all the researchers will obtain professional and targeted training concerning aim, design (randomized and double-blind), data collection and the management of adverse effects as well as withdrawal records and analysis involved in the trail before the study [23]. Not just have the DMC and auditing system been set

up to monitor data collection and patients safety throughout the study, but double check method of data has been established for quality control. The monitors and auditors are responsible for checking this password-protected database periodically, but they are blind to random allocation. They are not involved in research design, data collection and management, manuscript writing and publication, etc. Microsoft Office 2010 (Redmond, WA, USA) will be elected to input data, this is the responsibility of the data collector [23]. During the database established, anonymity runs the study and personal information (name, number, etc.) of participants are kept confidentiality in other locked cabinet. In other words, all data involved in the study will be entered by two people independent of the protocol through double password entry. Only when the final statistical analysis is performed, the researchers can be access to the database. If there is missing data, a sensitivity analysis is necessary. All original records will be kept at least 3 years, both electronic and paper.

Data analysis

The statistic analysis of the data will be conducted by a statistician with SPSS version 22.0 (Chicago, IL, USA) in the light of the CONSORT statement [20]for guiding control randomized trials (CRTs). Multiple imputation and/or last observation carried forward (LOCF) will be used to handle the missing data. Descriptive statistics (such as population demographic data) will be performed by medians (inter-quartile ranges, IQR), means (standard deviations, SD), and proportions (exact binomial 95% confidence interval, CI). Comparison of mean between two groups will be analyzed by *t*-test (normal distribution, homogeneity of variance) or Mann-Whitney test (non-normal distribution, two-sample), while categorical variables (comparison of proportions for the two groups) will be assessed by Chi-squared tests or Fisher' s exact test. When *P* values (two-sided) is less than 0.05, we will consider that there is significantly statistical.

Discussion

"Access to pain management is a fundamental human right", as the Declaration Montreal in International Pain Summit at 2010 announced [26].It is an obligation for all medical staff to consider making the treatment resources reasonably available to relieve pain within their own professional practice scope. However, many studies [10, 11]indicates that health care professionals are reluctant to offer adequate pain management for people with pain (moderate or severe) due to adverse effects of morphine. In addition, they are lack of knowledge about the mechanisms and management of pain [26], so there is a tendency for healthcare professionals to focus on the underlying pathology but ignore pain [27].Moreover, there is very strict control over the use of opioids. The medical consumption per capita ranks the bottom of The International Narcotics Control Board (INCB) list [12].Traditional Chinese culture encourages people to be brave by enduring the pain [28].These lead to inadequate pain management. However, study also shows that some technologies can reduce pain to tolerable levels, even in low-resource settings [27]. In fact, existing researches have revealed that not just can mixture of nitrous oxide/oxygen as an analgesic descend opioids consumption [29, 30], but it is safety and effective in the process of pain

management [14, 24]. Of course, there is report that inhalation of nitrous oxide can't show significant analgesic effectiveness for advanced cancer patients with breakthrough pain [31].

The planned trial aims to identify the the clinical safety and analgesic efficacy of the nitrous oxide/oxygen mixture on patients with acute pain induced by dressing. If the finding of this study has an active effect on dressing induced pain, the result could help to generate preliminary pain guidelines in patients with acute pain and improve patients' overall satisfaction with the Anorectal Department in China. We be firmly convinced that the result may be disseminated to domestic and overseas journals and conferences.

Trial status

Currently, patient recruitment is ongoing. Trial registration: ChiCTR1900021374. Registered on 17 February 2019. Eligible participants will be recruited from 28 April to 28 December 2019 in the Anorectal Department.

Abbreviations

CONSORT: Consolidated Standards of Reporting Trials; CRTs: control randomized trials; DMC: Data Monitoring Committee; INCB: International Narcotics Control Board; LOCF: last observation carried forward; SPIRIT: Standard Protocol Items for Randomized Trials.

Declarations

Ethics approval and consent to participate

This study has obtained ethical approval from the Ningxia Medical University Ethics Committee (2018–231). Patients voluntarily signed a conformed consent to participate, prior to the study. We tend to disseminate international journals and conferences.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

Authors declare that there is no conflict of interest.

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Author contributions

Study concept and design: Dr. Y-X L, J-Q Y; Acquisition of subjects and/or data: MS. H-X G, K M, Y-L D, Y Y, Z-J L and Z-M G; Analysis and interpretation of data: Dr. L-L G, Q Land MS. W-Q B, J-Y M; Preparation of manuscript: Dr. Y-X L and MS. J-J Z and T-T Z.

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Table 1

Table 1 Schedule of enrolment, interventions, and assessments.

Time points	Study period				
	Enrolment	Post-allocation		Close-out	
	suffering from acute pain induced by dressing after surgery	T0	T1	T2	Data collection measurements
Patients					
Eligibility screen	√				
Informed consent	√				
Allocation		√			
Interventions					
Control group			√		
Treatment group			√		
Assessments					
Pain score		√	√	√	Changhai Pain Rating Scale
Blood pressure		√	√	√	Noninvasive electronic manometer
Heart rate		√	√	√	Noninvasive electronic manometer
Oxygen saturation		√	√	√	Digital monitoring
Side effect			√	√	Yes_/no
Acceptance				√	Yes/no question
Satisfaction				√	Five-point scale

Figures

Figure 1

Research design roadmap. BP: blood pressure; HR: heart rate; SpO₂: oxygen saturation; NOOM: nitrous oxide/oxygen. At baseline: 3 min before dressing.

Supplementary Files

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- [SPIRITChecklist.doc](#)