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Analgesic effect of premixed nitrous oxide/oxygen on removal of vacuum assisted closure dressings: randomized controlled trial study protocol

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Abstract

Background Vacuum assisted closure (VAC) is an effective treatment that promotes wound healing in clinical practice. However, the pain caused by Vacuum assisted closure VAC dressing removal is still a challenge for patients and medical staff. The purpose of this study was to investigate the analgesic effect and safety of premixed nitrous oxide/oxygen in the treatment of pain caused by VAC dressing removal.

Methods/design This study is a single center, randomized, placebo-controlled, double-blind clinical trial. A total of 100 patients requiring VAC dressing removal were recruited and randomly divided into an intervention group and a control group. The intervention group will receive routine treatment plus a premixed nitrous oxide/oxygen mixture, and the control group will receive routine treatment plus oxygen. Participants and researchers are all blind to the operation process. The results of each group will be monitored at baseline (T0), 5 min after intervention (T1), and 5 min after finishing intervention (T2), 15 min after finishing intervention (T3). The primary outcome measure was pain intensity. Secondary outcomes included physiological parameters, adverse reactions, operators, and patients' satisfaction.

Discussion This study will explore the analgesic effect of oxide/oxygen mixture on VAC dressing removal. If it is beneficial to patients with VAC dressing change, it will be helpful for pain management of VAC dressing removal.

Trial registration Chinese Clinical Trial Register ChiCTR2200056742. Registered on February 13, 2022.

Keywords Nitrous oxide, Analgesia, Vacuum assisted closure, Procedure pain

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Introduction

Negative Pressure Wound Therapy (NPWT) refers to applying sub-atmospheric pressure, usually 125 mm Hg, to the wound through a foam dressing system and adhesive film to promote wound healing. Its core technologies include vacuum sealing drainage (VSD) and vacuum-assisted closure (VAC) ([1, 2]). In clinical practice, VAC is increasingly applied to treat a variety of different wounds, such as skin grafts, diabetic foot ulcers, pressure ulcerations, and chronic wounds ([3–6]). Existing clinical practice has also confirmed its application effect in orthopedics ([7]). At present, VAC is widely used in orthopedic practice, mainly including open fractures, fasciotomy wounds and skin transplantation, and is also developing ([8]).

However, although studies have demonstrated the effectiveness of VAC in wound healing, less attention has been paid to the pain it produces. Minimally invasive procedures such as simple dressing changes can also be a potential cause of procedural pain ([9]). Clinical studies have pointed out that during VAC treatment, including application of suction and the removal and application of dressings and films, may cause varying degrees of pain to patients, and some patients even discontinue treatment due to severe pain ([10]). Severe pain is associated with various stress responses and negative emotions in the body, resulting in decreased immunity, increased risk of infection, anxiety, depression, and ultimately may delay wound healing. Inadequate pain management will also affect patient response and treatment compliance ([11]). No matter what analgesic method is adopted, if the pain is not prevented, minimized and properly treated, it may cause more severe pain for the patient's subsequent operation, or even develop into chronic pain ([9]). A review by Waldie K included several studies comparing the effects of different wounder fillers or drugs on VAC-related pain, but there did not provide sufficient evidence to support how to reduce the pain of VAC dressing removal ([12]). Previous methods included injecting lidocaine through a catheter 20 min before removing the dressing. Although it can play a certain analgesic effect, it also brings the risk of reverse infection to patients while waiting for the drug to take effect ([12, 13]). Hurd T et al. compared gauze-based VAC with lower pain scores during dressing removals than foam-based dressings, but this did not completely eliminate patients' experiences of pain ([14]). This is similar to the research results of Fraccalvieri M ([15]). The characteristics of the foam dressing material mainly made of polyurethane include flexible, strong plasticity, large pore size, not easy to block, and good absorption effect of exudate. However, using gauze as the filling dressing has the disadvantages of poor absorption and increased dressing change frequency ([16]). This may lead to the extension of healing time and the increase of treatment costs. In a qualitative study, 6 out of 17 interviewed patients reported significant pain during the use of VAC and dressing changes ([17]). A recent study applied TENS to VAS adjuvant removal and investigated its analgesic effect. The results suggest that the analgesic effect of TENS is inadequate and that the effectiveness of TENS may vary depending on the mode and parameters of TENS application ([18]).

Nitrous oxide has been used in clinics for more than 150 years and has been applied in many fields. It provides analgesia, anxiolysis, and hypnosis in the awake state of patients and does not cause serious side effects. N_2O has been shown to be effective for pain in various procedures, such as labor, dental treatment, burn dressing, lumbar punctures, cancer patients with breakthrough pain and gastrointestinal endoscopy ([19–25]). The minimum alveolar concentration of N_2O is 104%. N_2O does not combine with hemoglobin and has low solubility, so it can pass in and out of the lungs. The patient can get the lowest efficiency anesthesia without losing consciousness ([26–28]).

There is currently no trial evaluating the efficacy of N_2O in VAC dressing removal. Reasonable analgesia is required for patients who receive VAC dressing removal. Therefore, the purpose of this study is to evaluate the analgesic effect of inhaling N_2O during patients' removal of VAC excipients through a randomized double-blind controlled trial. We assume that compared to placebo, its analgesic properties will alleviate pain during the VAC dressing removal with minimal side effects.

Methods

Study designs

The study is a randomized, double-blind, placebo-controlled clinical trial to investigate the analgesic effect and safety of N_2O for VAC dressing removal. The study protocol was drafted with SPIRIT ([29]) Trials guideline and following the checklist of the Consolidated Standards of Reporting Trials (CONSORT) ([30]) statement. Eligible participants will be randomly assigned to the intervention group or the control group in a 1:1 allocation ratio based on computer-generated random numbers. Flow chart of the study design is shown in Fig. 1, and the schedule of enrolment, interventions, and assessment is presented in Table 1.

Participants

All participants will be enrolled from a large comprehensive hospital in China. The patient used the consumables for the vacuum-assisted closure therapy system produced by KCI Company of the United States. The researchers will evaluate participants' eligibility based on the inclusion and exclusion criteria as follows.

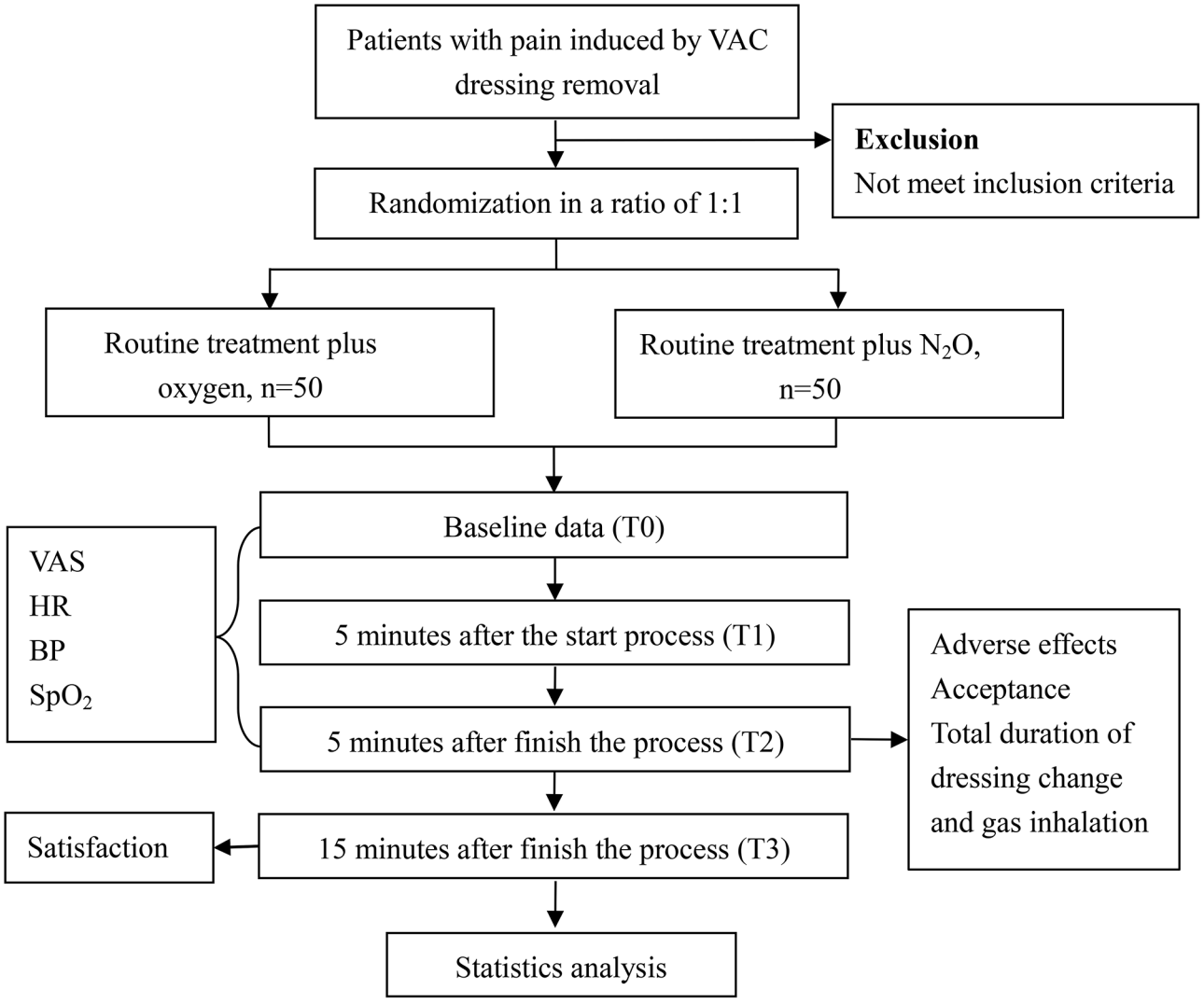

Fig. 1 Research design roadmap. VAC: vaccume assisted closure; VAS: visual analogue scale; SpO_2: percutaneous oxygen saturation; HR:heart rate; BP: blood pressure

This study will calculate the sample size based on the results of a pilot trial. Following the inclusion and exclusion criteria, the pilot trial uses pain severity (VAS) as the indicator for calculating the sample size. A total of 20 patients using VAC will be enrolled and randomly assigned in a 1:1 ratio to the experimental group (diluted nitrous oxide) or the control group (oxygen). After completing the trial and collecting data, the sample size will be calculated using Gpower software, with a two-sided α value of 0.05 and a test power of 80%.

Inclusion criteria

1. 18 years old and above;
2. A wound requiring at least once VAC dressing removal during a hospital admission;
3. Volunteered to participate and signed the informed consent.

Exclusion criteria

1. Pregnant woman;
2. The Patient with intestinal obstruction, pneumothorax, air embolism, and obstructive respiratory disease;
3. The Patient suffers from sinusitis, middle ear disease, eardrum transplant and other ENT diseases;
4. The Patient with a history of epilepsy;
5. The Patient with other severe compound injuries, such as organ damage;
6. The Patient with a history of abuse of analgesics, such as morphine, demerol, etc.;
7. The Patient with painless chronic wounds.

Table 1 Schedule of enrolment, interventions, and assessments

Table 1 Schedule of enrolment, interventions, and assessments

	Study period				
Timepoint	Enrolment	Post-allocation		Close-out	
	VAC patients with pain	Baseline (T0)	5 min after intervention (T1)	5 min after finishing intervention (T2)	15 min after finishing intervention (T3)
Enrolment					
Eligibility screening	√				
Informed consent	√				
Allocation	√				
Demographic information	√				
Interventions					
Control group			√		
Treatment group			√		
Assessment					
Pain score		√		√	
Blood pressure		√	√	√	
Oxygen saturation		√	√	√	
Heart rate		√	√	√	
Satisfaction					√
Side effect		√		√	

Randomization

A total of 100 participants who meet the inclusion criteria will be randomized into intervention or control group in a ratio of 1:1, one treatment groups (65% nitrous oxide/oxygen mixture), $n = 50$, and one control group (oxygen), $n = 50$. The assignment of each Patient is determined by a computer-generated schedule, which is sequentially numbered. Each number will be placed in an opaque, sealed envelope. Open envelopes and determine the participant's group before accept the treatment.

Blinding

All gas cylinders used in two groups are identical in appearance, and the numbers 1 and 2 are used to distinguish gases. Throughout the intervention, neither the participants nor the researchers know what the numbers 1 and 2 indicate.

Intervention

Before intervention, training programs for researchers and data collectors should be implemented to ensure the accuracy and precision of data collection. The trained researcher will re-evaluate patients to determine if they meet inclusion criteria and inform them of the purpose, methods, potential risks, and rights of the participants. Patients who meet the inclusion criteria will sign the informed consent form after agreeing to participate in the trial and will be grouped according to the randomly assigned list, and the trial will be conducted in the treatment room. Before the trial (T0), the researcher will record the baseline characteristics of the patient; assess the patient's pain intensity; measure heart rate, blood pressure, and oxygen saturation, and teach the patient to use a mask to inhale gas. When the patient wears the upper mask to inhale the gas, the trail will start timing. The researcher will evaluate the patient's physical indicators at 5 min after the start of the dressing change (T1). Five minutes after the surgery (T2), the patient's various physiological indicators will be re evaluated. After 15 min of surgery, the satisfaction of the surgical personnel and patients will be asked. During the whole intervention period, the researchers will closely monitor the awareness and condition of patients. Standardized protocols have been created and implemented for VAC dressing removal that includes pain management strategies.

Outcomes measures

Baseline data

We will use a form to record the demographic information of each patient, including age, gender, weight, height, wound location and size. In addition, the patient's pain intensity and physiological parameters (blood pressure, heart rate, and oxygen saturation) at baseline will be collected.

Primary outcome measure

The primary outcome was the intensity of pain during the intervention, represented by VAS (range = 0 to 10). Data collectors will collect patients' pain scores at baseline and T2. Finally, baseline and T2 pain changes will be compared. The measurement tools used in this study have proven valid and reliable ([31]). A continuous evaluation process is implemented to refine and improve pain management strategies.

Secondary outcome measure

Secondary outcomes included adverse effects, satisfaction of patients and operators, and physiological parameters (blood pressure, heart rate, oxygen saturation). Regularly collect and analyze patient feedback to improve pain management strategies. Adverse effects and satisfaction will be collected at T2. Physiological parameters will be collected at baseline, T1, and T2. Collect other variables that may affect the results, such as wound location and cause, for multivariate analysis. Finally, the total duration of dressing removal and gas inhalation will be recorded.

Monitoring adverse effects

Establish protocols for monitoring and managing adverse effects to ensure patient safety. Adverse effects of N_2O include nausea, vomiting, dizziness, drowsiness, headache, hypotension and decreased oxygen saturation, but resolve within 5 min of terminating [12]. During the intervention, if the patient has any adverse reaction, it will be terminated immediately and given oxygen. Investigators will document all adverse reactions during the trial.

Date collection

Train data collectors using clear guidelines and training courses to ensure they are unaware of intervention measures and accurately record data. The collected data will be input into the database by two people to ensure accuracy. The Data Monitoring Committee (DMC) will also review the data regularly to ensure the quality of the data. Participants' privacy will be strictly protected throughout the research process. All participants' personal and disease information will be kept confidential.

Statistical analysis

The test data will be statistically analyzed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics will be analyzed by medians (inter-quartile ranges, IQR), means (standard deviations, SD), and proportions (exact binomial 95% confidence interval, CI). A chi-square test will be used to compare group differences in dichotomous variables of baseline characteristics. For normally distributed data, within-group, and between-group comparisons will be made using repeated measures analysis of variance (ANOVA) by assessing changes in continuous variables at different time points before and after the intervention. Multiple imputation and/or last observation carried forward (LOCF) will be used to handle the missing data in randomized patients. We will consider statistical significance when the P value is less than 0.05. Missing data will be handled using multiple imputations if less than 10% of the data is missing; otherwise, LOCF will be used.

Ethics statement and study registration

The ethics committee of the hospital has approved the ethics approval (approval number: 2021-59, date: May 17, 2021). Before enrollment, the researcher will explain the study objectives, benefits and potential risks in detail to the participants and should sign an informed consent form.

The study protocol has been registered in the clinical trials registry with the identification code ChiCTR2200056742 (registration date: February 13, 2022).

Discussion

VAC is considered an effective method to promote wound treatment, and many studies have also confirmed its application effect in various fields. The application of VAC can promote wound healing by increasing blood flow, promoting granulation tissue formation, preventing secondary infections, removing substances produced by necrotic tissue, and reducing wound surface area ([3, 32–34]). However, the removal of the VAC is one of the sources of patient pain. During the use of VAC, granulation tissue at the wound may adhere to the sponge dressing or grow into the sponge. When the VAC is removed, the granulation tissue in the wound bed is broken with the removal of the sponge dressing, which causes the patient to feel severe pain ([35]). It is particularly important to control the pain of such patients. The previous literature compared various methods to relieve such pain, including local anesthesia, filling dressing replacement, adjustment of pressure value, injecting cold, sterile water into the VAC sponge, and transcutaneous electrical never stimulation (TENS) ([18, 35, 36]). These methods have been proven to have a certain degree of analgesic effect on VAC dressing removal. At the same time, the above methods generally have some defects that limit their clinical application. Therefore, further clinical studies are needed to determine other possible pain management measures.

Nitrous oxide (N_2O) is a non-invasive inhaled analgesic that can be controlled by patients without the involvement of an anesthesiologist. It is usually mixed with oxygen in a different proportion to play an analgesic role in clinical operations ([37, 38]). It provides analgesia, anxiolysis, and hypnosis in the awake state of patients and does not cause serious side effects. N_2O has the characteristics of low blood solubility and non-protein binding, which can onset and recover quickly. It does not mask the signs and symptoms that may be necessary for disease diagnosis ([26–28]). Li et al. ([21]) applied nitrous oxide-oxygen mixtures in analgesia for burn patients during dressing changes and demonstrated the ability of nitrous oxide-oxygen mixtures to provide more rapid analgesia in wound care. Xing et al. ([39]) conducted a meta-analysis of the analgesic effects of N_2O in adult patients in the emergency department, which showed nitrous oxide's analgesic effect and provided the capability of shortening the operation time and evidence of fewer adverse effects.

In summary, nitrous oxide may provide good analgesia, shorter operation time, and fewer adverse effects in patients with VAC adjuvant removal. Therefore, this study investigated whether N_2O can reduce pain during VAC dressing removal. Statistical analysis of the data collected in the study will determine the efficacy and safety of N_2O for pain relief during VAC dressing removal.

To our knowledge, this is the first randomized controlled trial to investigate the effects and safety of premixed nitrous oxide/oxygen in the treatment of pain during VAC dressing removal. Suppose the results of this study demonstrate the benefit of premixed nitrous oxide/oxygen for patients with VAC dressing removal. In that case, it will provide an effective and safe analgesic option for such patients and an evidence base for further research.

Limitations

This study has limitations. This study will be conducted in a hospital in China. One potential bias is the single-center design, which may limit generalizability. Future studies should aim to include multiple centers and a larger sample size to mitigate this bias.

Trial status

Recruitment of patients will begin on February 14, 2022. Due to the prevalence of COVID-19, the trial was originally scheduled to be completed in December 2022 and is expected to be completed in December 2023. At the time of submitting the manuscript, 95 participants had been recruited for this study. This is protocol version 2.0, dated October 22, 2023.

Abbreviations

NPWT	Negative pressure wound therapy
VSD	Vacuum sealing drainage
VAC	Vacuum-assisted closure

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Author contributions

YHX is mainly responsible for conducting experiments and writing papers. YLH assists with the experiment project, writes and revises the paper. CL writes and revises the paper. WFW assists in the experiment. CJF assures the overall control of the project direction and the smooth implementation of the experiment. LT is responsible for the overall control of the project direction, the smooth implementation of the experiment, and the revision of the paper.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent for publication

Not paalicable.

Competing interests

The authors declare no competing interests.

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