Original Article

A Fixed Nitrous Oxide and Oxygen Mixture for Analgesia in Children With Leukemia With Lumbar Puncture–induced Pain: A Randomized, Double-blind Controlled Trial

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Abstract

Context. Leukemia is the most common cancer in the childhood population. Lumbar puncture (LP) plays central role in the diagnosis and treatment process, but options for analgesia are limited.

Objectives. The present study aims to evaluate the efficacy of a fixed N_2O/O_2 mixture to reduce pain in children with leukemia during LP as compared with placebo.

Methods. A double-blind, placebo-controlled, and randomized clinical trial involving children who needed LP for diagnosis or treatment was conducted in the pediatrics department of the General Hospital of Ningxia Medical University. Eligible patients were randomly assigned to inhale either a fixed N_2O/O_2 mixture or O_2. The primary endpoint was the maximal pain level felt by the patient during the procedure measured using a numerical rating scale (0–10).

Results. One-hundred fourteen consecutive patients were enrolled in this study and randomized. Pain scores during the procedure showed a significant decrease in N_2O/O_2 mixture–treated patients to 1.05 ± 1.40 versus 8.00 ± 2.13 in controls ($P < 0.01$). No serious adverse effects were attributed to N_2O/O_2 mixture inhalation. Analysis of the satisfaction of patients receiving N_2O/O_2 mixture indicated that medical staff were satisfied with this treatment.

Conclusions. This study demonstrated that self-administered fixed N_2O/O_2 is efficient to reduce pain related to LP in children with leukemia. J Pain Symptom Manage 2019;57:1043–1050.

Key Words

Lumbar puncture, nitrous oxide, procedural pain, analgesia

Background

Leukemia is the most common cancer in the childhood population,[1] accounting for more than one-third of the total number of cancer cases in many developed countries.[2] Over 70% of leukemia cases in children involve acute leukemia.[3,4] Over the past decade, development of new therapy techniques has allowed the cure of pediatric acute leukemia.[5] The five-year survival rate of childhood acute leukemia has improved to over 80% in the U.S. and 70% in China.[6,7] However, increasing evidence shows that children and

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Trial registration: China Registry of Clinical Trials (ChiCTR-INR-16007989).

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Table 1
Patients' Inclusion and Exclusion Criteria

Inclusion Criteria
Patient aged five to 14 years
Patient suffering from acute leukemia
Patients need lumbar puncture
Written informed consent for participation obtained before any study procedures
Exclusion Criteria
Patient with mental disorder and altered mental status
Patient has difficulty to report pain
Other N_2O/O_2 contraindications, such as abdominal distension or suspected bowel obstruction, air embolism, and pneumothorax

their parents exhibit high levels of stress and uncertainty after diagnosis and subsequent treatment.[8] In China, treatment of pediatric acute leukemia has been estimated to require approximately 12 cycles of bone marrow aspiration and over 15 lumbar punctures (LPs) for intrathecal chemotherapy.[8] These repeated painful invasive procedures cause a common and distressing symptom among the pediatric population.

Unrelieved pediatric pain, as one of the most unbearable symptoms reported, significantly impairs patients' overall quality of life accompanied by negative physiological and psychological consequences.[9] Studies demonstrate that many children with acute leukemia undergoing LPs and bone marrow aspirations without optimal interventions report high levels of anxiety and pain.[10] As a consequence, the risk of failures increases in undertreated patients because of patient movement and noncooperation.

The World Health Organization three-step analgesia and clinical practice guidelines are widely used to control all kinds of pain.[11] Numerous studies focus on pharmacologic and nonpharmacologic measurements to control children procedural pain.[12,13] However, the lack of a specific reference standard for pediatric procedural pain management has led to poor management of LP pain in Northwest China.[8]

The use of a fixed self-administered inhaled N_2O/O_2 mixture has been well studied in control burn dressing debridement pain, breakthrough cancer pain, trauma pain, and other medical conditions.[14–18] It has potent analgesic properties without causing loss of consciousness. The safety of self-administered N_2O/O_2 mixture for pain management has also been demonstrated in previous studies.[19,20] In the present study, we aim to test the hypothesis that a fixed N_2O/O_2 mixture can provide the same analgesic effect in controlling pain in patients with acute leukemia during their LP procedure.

Methods

Design

The present study was a randomized, double-blind, and placebo-controlled trial. Patients who met the described criteria were randomly assigned to receive standard pain management plus N_2O/O_2 mixture or standard pain management plus O_2. This study was evaluated and approved by the General Hospital of Ningxia Medical University Ethics Service Committee (2015-130), and the trial was registered in the China Registry of Clinical Trials (ChiCTR-INR-16007989). Patients' consent was obtained in accordance with national regulations. This article was drafted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations (Additional File 1).

Study Participants

Patients aged five to 14 years and suffering from leukemia, needing LP, capable of reporting pain, and able to provide consent were recruited between February 2015 and July 2016 at the General Hospital of Ningxia Medical University. The specific inclusion and exclusion criteria are shown in Table 1.

Treatments

Eligible patients received local injection of lidocaine for standard pain management. They also received a pre-prepared N_2O/O_2 mixture in the treatment group or O_2 in the control group 5 minutes before the procedure started and lasted until the treatment finished. The N_2O/O_2 mixture was self-administered by each patient through a self-demand mask with a one-way valve. In this way, overdose is nearly impossible because the patient's consciousness controlled their ability to inhale the gas.[17]

Randomization, Allocation Concealment, and Binding

A total of 114 patients were assigned to the treatment or control groups by using a computer-generated randomization list. Thirty-eight patients received standard pain management plus O_2, and 76 patients were allocated to standard pain treatment plus N_2O/O_2 mixture. The randomization list was sealed and kept by an independent program director, who took charge of the gas distribution for each enrolled patient. Besides the program director, no other medical worker or data collector knew of the

intervention allocation. The project participants were blinded to the list.

Sample Size Determination

The sample size was based on a previous randomized study showing analgesic superiority of nitrous oxide/oxygen mixture over placebo (O_2) in adult patients undergoing LP. The patient material consisted of 33 patients in each group. To enhance power and provide substitution for possible dropouts, we decided to recruit 114 patients in treatment and control groups in a ratio of 2:1, 38 patients to control group and 76 patients to treatment group.

Measurement

The patient's demographic data, including age, sex, and nationality, were recorded by the researchers. Our primary outcome was the numerical rating scale score measured 5 minutes before the procedure (T0), during the procedure (T1), and 5 minutes after the procedure (T2). The patients were instructed to rate their pain with a self-rating tool (ranging from 0 to 10, 0 = no pain, 10 = worst pain).[21] The secondary outcome was measured by focusing on the patients' blood pressure, heart rate, O_2 saturation, and satisfaction of the medical staff. Satisfaction was assessed by a five-point scale (5, very satisfied; 4, satisfied; 3, uncertain; 2, dissatisfied; and 1, very dissatisfied). Patients' anxiety during the procedure was assessed using a numerical rating scale (0–10, with 0 equal to the absence of anxiety and 10 equal to high anxiety). The measurement of anxiety occurred at the same time as pain assessment.

Statistical Analysis

Statistical analysis was performed using SPSS 24.0 (SPSS Inc., IBM Company, Chicago, IL, USA) following the intention to treat principle that includes all interventions of the patients. We used the Kolmogorov-Smirnov test to determine whether the study data were normally distributed or not. Student's *t*-test was applied to determine differences in terms of age. We used the chi-squared test to determine gender differences between the two groups. Heart rate, blood pressure, O_2 saturation, and pain score were assessed using repeated-measures analysis of variance. The last observation carried forward method was applied in case of missing data.

Statistical significance was considered at $P < 0.05$.

Results

From 1 February 2015 to 23 July 2016, among the 134 patients who were eligible and provided consent for participation, a subset of 114 patients were randomly assigned to the two groups in this study and 109 patients were analyzed (Figure 1). Overall, 84 male and 30 female patients aged five to 14 years (9.55 ± 3.41 years) were included. Seventy-six patients were allocated to the N_2O/O_2 group, and 38 patients were enrolled in the control group. No difference was observed between the two groups in terms of age and gender. Table 2 shows the patients' demographic and baseline characteristics. No differences with respect to pain score at T0 (no pain) was noted.

Patients pretreated with the N_2O/O_2 mixture reported low pain intensity compared with the control group (1.05 ± 1.40 vs. 8.00 ± 2.13, $P < 0.01$) (Figure 2). In the N_2O/O_2 mixture group, heart rates decreased from 88.21 ± 13.03 (T0) to 86.04 ± 12.00 (T1) and 85.99 ± 13.54 (T2). In the O_2 group, heart rates increased from 90.03 ± 15.23 (T0) to 125.42 ± 16.66 (T1) and 94.84 ± 13.50 (T2). The systolic and diastolic blood pressures of the O_2 group were higher than those of the N_2O/O_2 mixture group at T1. The mean O_2 saturation levels at T0, T1, and T2 in the N_2O/O_2 mixture group were 98.37 ± 0.88, 98.51 ± 0.84, and 98.66 ± 0.70, respectively; by comparison, those of the control were 98.50 ± 0.78, 99.00 ± 0.79, and 98.97 ± 0.56, respectively (Table 3). Analysis of the satisfaction of patients receiving N_2O/O_2 mixture indicated that medical staff were satisfied with this treatment ($Z = -11.96$, $P < 0.01$). The anxiety level of patients receiving N_2O/O_2 significantly decreased during the procedure (2.32 ± 2.14 vs. 8.24 ± 0.88, $P < 0.001$).

No serious adverse events related to N_2O/O_2 mixture treatment were observed (Table 4). Among patients with mild side effects (such as nausea and vomiting), no treatment was usually required. All adverse effect symptoms disappeared 4 hours after completion of the procedure.

Discussion

Multiple procedures, especially LP, are performed in children in pediatric department for the treatment of acute leukemia. Relieving pediatric pain and anxiety related to invasive procedures, such as LP aspirates for acute leukemia, is a shared goal. Several studies have shown that poor management of pain may place children at high risk for depression and anxiety.[22,21,8] Recent studies also show that many families report dissatisfaction with the light-sedation regimen when their children undergo painful procedures.[23,22,24] Therefore, controlling procedural pain in children is critical. A recent review offered numerous strategies to alleviate pain related to invasive procedures, and the literature indicates that both pharmacologic and nonpharmacologic interventions are effective.[12]

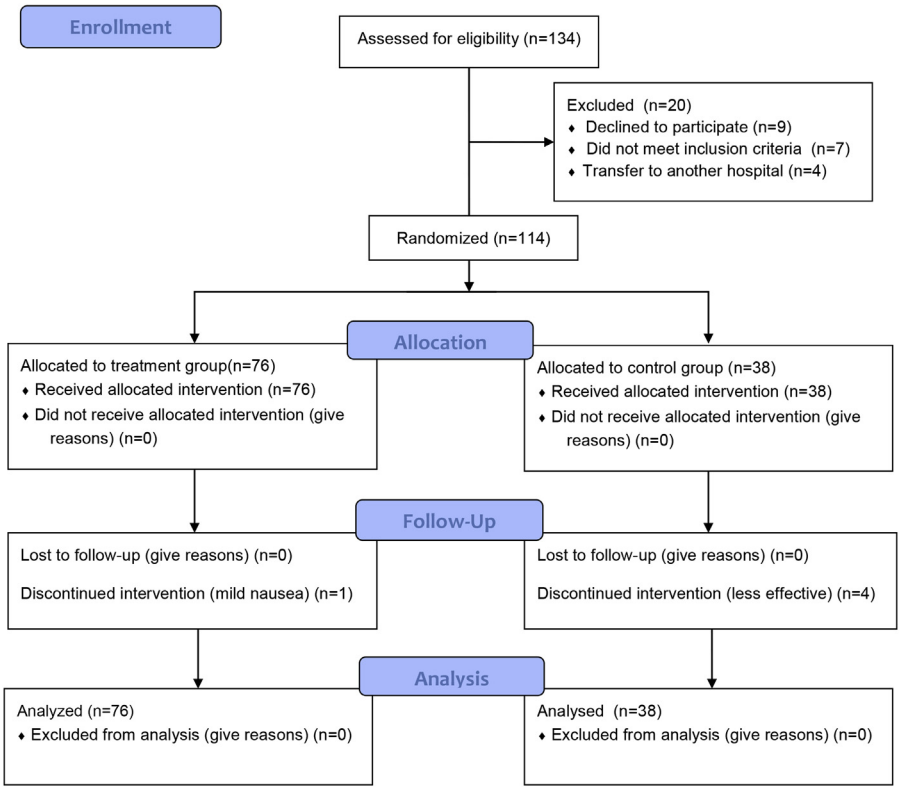

Fig. 1. CONSORT 2010 flow diagram.

Table 2
Clinical Characteristics of Patients at T0 by Group

Variable	Group		*P*
	N_2O/O_2 ($n = 76$)	O_2 ($n = 38$)	
Age (yrs)[a]	9.94 ± 3.30	9.11 ± 3.59	0.218
Males[b]	60 (80%)	24 (63.2%)	0.072
Heart rate ($minute^{-1}$)[a]	88.21 ± 13.03	90.03 ± 15.23	0.516
Systolic blood pressure (mm Hg)[a]	108.67 ± 13.65	109.03 ± 13.12	0.866
Diastolic blood pressure (mm Hg)[a]	73.54 ± 11.84	74.28 ± 7.50	0.580
SpO_2 (%)[a]	98.37 ± 0.877	98.50 ± 0.775	0.393
Number of prior LPs experienced by each patient before the study procedure			
0	25 (32.9%)	14 (36.8%)	0.804
1	19 (25.0%)	9 (23.7%)	
2	14 (18.4%)	8 (21.1%)	
3	12 (15.8%)	3 (7.9%)	
≥4	6 (7.9%)	4 (10.5%)	

Results are expressed as n (%) or means ± standard deviation.
[a]Based on *t*-test.
[b]Based on chi-square test.

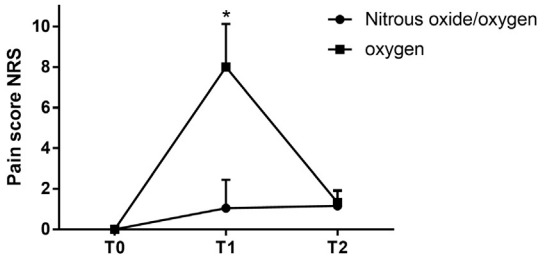

Fig. 2. Pain score based on NRS for the case and control groups at T0, T1, and T2. NRS = numerical rating scale. *$P < 0.01$ (based on *t*-test).

In the present study, we found that the pre-prepared N_2O/O_2 mixture is an effective analgesic for management of LP pain in children when used in conjunction with local injection of lidocaine. LP is an extremely painful procedure for pediatric patients. This procedure is usually performed after local injection of anesthetic infiltration.[25–27] Studies demonstrate that using eutectic mixture of local anesthetics patch for at least 1 hour is efficient and avoids the first puncture of anesthetic injection.[28] A randomized control trial of patients with procedural pain who accepted buffered lidocaine solution or unbuffered preparations for LP biopsy procedures revealed that the former did not make LP biopsy less painful than the latter.[29] In a prospective trial, pretreatment with tramadol plus local injection of 2% lidocaine was reportedly associated with less pain intensity than placebo, thereby indicating that it could be a good local anesthetic for LP biopsy combined with local lidocaine injection.[30] Studies demonstrate that lidocaine administration usually causes mild local skin reactions, such as edema, pallor, or erythema, although other severe complications, such as methemoglobinemia, cardiotoxicity, and central nervous system toxicity, can also be encountered.[31]

Intravenous sedation, such as with lorazepam, midazolam, or diazepam, has been recommended for pain reduction during LP for this group of patients.[32,33] In this case, the child should be in the operating room and anesthetized by anesthesiologists to prevent complications. A prospective observational study of propofol/fentanyl in 202 patients aged six months to 14 years for short-term painful procedures in the pediatric oncology ward demonstrated that children benefit from general anesthesia by propofol and fentanyl, although 11.9% of them displayed complications, such as vomiting, agitation, and headache.[34] Moreover, this medication is much expensive, and some families cannot afford it.

Physiological variables, such as heart rate and blood pressure measurements, have been well studied for signs of acute pain in children.[35–38] Statistical analysis by repeated-measures one-way analysis

Table 3

Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure, and O_2 Saturation (SpO_2) at T0, T1, and T2 in All Patients

Variable	Group	T0	T1	T2	Main Effect of Group[a]	Group × Time Interaction[a]	Main Effect of time[a]
Heart rate	N_2O/O_2 ($n = 76$)	88.21 ± 13.03	86.04 ± 12.00	85.99 ± 13.54	$P < 0.001$ ($F = 78.173$)	$P < 0.001$ ($F = 65.303$)	$P < 0.001$ ($F = 55.921$)
	O_2 ($n = 38$)	90.03 ± 15.23	125.42 ± 16.66	94.84 ± 13.50			
Systolic blood pressure	N_2O/O_2 ($n = 76$)	108.67 ± 13.65	110.90 ± 13.61	104.65 ± 13.09	$P < 0.001$ ($F = 77.702$)	$P < 0.001$ ($F = 64.974$)	$P < 0.001$ ($F = 55.637$)
	O_2 ($n = 38$)	109.03 ± 13.12	130.38 ± 18.70	121.09 ± 17.53			
Diastolic blood pressure	N_2O/O_2 ($n = 76$)	73.54 ± 11.84	73.26 ± 11.79	68.88 ± 9.95	$P = 0.043$ ($F = 4.208$)	$P = 0.001$ ($F = 7.113$)	$P < 0.001$ ($F = 18.376$)
	O_2 ($n = 38$)	74.28 ± 7.50	82.03 ± 7.29	69.56 ± 12.02			
O_2 saturation	N_2O/O_2 ($n = 76$)	98.37 ± 0.877	98.51 ± 0.841	98.66 ± 0.703	$P = 0.002$ ($F = 9.829$)	$P = 0.252$ ($F = 1.385$)	$P = 0.001$ ($F = 7.384$)
	O_2 ($n = 38$)	98.50 ± 0.775	99.00 ± 0.793	98.97 ± 0.560			

Results are presented as mean ± standard deviation and median (interquartile range).
[a]Determined using repeated-measures analysis of variance (ANOVA). Significance set at $P < 0.05$.

Table 4
Adverse Events Over the Entire Course of Intervention by Group

Group	N_2O/O_2 ($n = 76$)	O_2 ($n = 38$)
Nausea	7 (9.2%)	0 (0%)
Somnolence	2 (2.6%)	0 (0%)
Dizziness	3 (3.95%)	1 (2.6%)
Total[a]	12 (15.79%)	1 (2.6%)

Results are expressed as n (%).
[a]Based on chi-squared test. $P < 0.001$.

of variance showed significant differences between the two groups in terms of heart rate and blood pressure. In the present study, the heart rate and blood pressure in the N_2O/O_2 mixture group significantly decreased during the procedure compared with those in the control group ($P < 0.01$). This result indirectly indicates decreased pain in the N_2O/O_2 treatment group.

N_2O, first used in anesthesia in 1772,[39] has been extensively studied in various procedures and areas, such as dental care, pulmonary endoscopy, venous cannulation, clip removal, fractures, and minor procedures (burn dressing and abscess drainage) because of its pain relief properties.[20] N_2O/O_2 mixture is suitable for use as an analgesic in various procedures because of its analgesic properties, safety profile, rapid reversal, and self-administration by patients.[40,41] A randomized, double-blinded trial compared 50% N_2O/O_2 inhalation with medical air inhalation to treat moderate-to-severe acute pain. The median pain scores at 15 minutes were 2 (interquartile range 1−4) in the study group versus 5 (interquartile range 3−6) in the control group ($P < 0.05$).[42] Another randomized double-blinded study that compared a 50:50 ratio of N_2O:O_2 with 50:50 N_2:O_2 (placebo) for cutaneous, muscle, and bone/joint procedure-related pain in 100 patients aged one to 18 years found that pain scores were lower in the 50:50 N_2O:O_2 group than in the placebo group and with rare minor side effects.[43] The effect size in our study is notably higher than that in the adult population possibly because children are sensitive to N_2O than adults. In the present study, the patients also showed rare and minor adverse effects. Overall, N_2O, as one of the earliest analgesics, is a safe and effective analgesic for procedural pain control in children.

Limitations

The limitations of the present study include the recruitment of young patients in a single department. The study findings should be confirmed in different ages of patients, such as older patients, to determine true analgesia effects, adverse drug events, and the satisfaction of both health workers and patients. Another potential limitation is that we did not perform blinding evaluation. Large-sample studies should be implemented to test the analgesic effect of N_2O/O_2 mixture in multicenter randomized controlled trials.

Conclusion

This study aims to demonstrate the efficacy, feasibility, and medical staff satisfaction of N_2O/O_2 mixture plus local anesthesia of lidocaine to treat LP-related pain. We can conclude that N_2O/O_2 provides significant pain relief to children with a low incidence of side effects during procedural pain. Health care providers in low-resource settings should consider inhalation of N_2O/O_2 mixture as an effective approach to alleviate procedural pain in children.

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The authors have no conflicts of interests to declare.

Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpainsymman.2019.02.029.

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