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Original Contributions

ANALGESIC EFFECT OF NITROUS OXIDE/OXYGEN MIXTURE FOR TRAUMATIC PAIN IN THE EMERGENCY DEPARTMENT: A RANDOMIZED, DOUBLE-BLIND STUDY

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☐ **Abstract—Background: Acute pain is the most common complaint in Emergency Department (ED) admissions, and options for analgesia are limited. Nitrous oxide/oxygen possesses many properties showing it may be an ideal analgesic in the ED. Objectives: The aim of this study is to evaluate the safety and analgesic effect of the fixed nitrous oxide/oxygen mixture for trauma patients in the ED. Methods: We enrolled 60 patients in this double-blind, randomized study. The treatment group received conventional pain treatment plus a mixture of 65% nitrous oxide/oxygen. The control group received the conventional pain treatment plus oxygen. Primary outcome was the reduction in pain intensity at 5 and 15 min after the start of intervention. Secondary outcomes include adverse events, physiological parameters, and satisfaction from both patients and health care professionals. Results: Initial pain scores for the nitrous oxide/oxygen group (6.0 [5.0–8.0]) and the oxygen group (6.75 [5.0–9.0]) were comparable ($p = 0.57$). The mean numerical rating scale scores at 5 min were 3.4 ± 1.8 and 7.0 ± 1.8 for nitrous oxide/oxygen and oxygen, respectively ($p < 0.01$). The mean pain intensity at 15 min in the treatment group was 3.0 ± 1.9, compared with 6.3 ± 2.2 in the control group ($p < 0.01$). Both patients' (8.0 [7.0–9.0] vs. 4.0 [2.0–6.0], $p < 0.01$) and physicians' (8.5 [8.0–9.0] vs. 4.0 [3.0–6.0], $p < 0.01$) satisfaction scores in the treatment group were significantly higher than the oxygen group. No serious adverse events were observed. Conclusions: This study gives supporting evidence for the safety and effectiveness of using self-administered nitrous oxide/oxygen mixture in the ED for moderate-to-severe traumatic pain.** © 2019 Published by Elsevier Inc.

☐ **Keywords—trauma; analgesia; acute pain; nitrous oxide**

INTRODUCTION

Although there are many experiences of pain-related visits and analgesic options for good pain management, oligoanalgesia (untreated or under-treated pain) remains an extremely serious problem in the emergency department (ED) (1). Pain is widely recognized as the fifth vital sign and is the most frequent complaint in patients who arrive at an ED seeking medical care (2). A prospective, multicenter investigation study demonstrated that only 60% of patients were treated with analgesics after waiting for an average of 90 min (3). Furthermore, up to 74% of patients complained about moderate-to-severe pain when discharged. Another prospective survey found that only half of patients received analgesics, even though 63%

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experienced severe pain (4). Of these, analgesics were administered after a mean time of almost 2 h of delay. These results reflect that, despite a high prevalence of pain in the ED, suboptimal pain management remains prevalent.

Several barriers have been related to poorly managed pain. Limited knowledge, insufficient pain assessment and reassessment, wrong analgesics perceptions, inadequate analgesics prescriptions, and the busy emergency environment all lead to inadequate pain management (5,6). In fact, for those trauma patients, emergency physicians dread concealing, delaying, or obscuring diagnosis, and thus the treatment of pain is not traditionally a priority for them (7). Trauma patients require pain relief rapidly across the spectrum of emergency medical settings; regrettably, in many EDs, that need is not met (8). Patients with untreated or unrelieved pain may experience adverse psychological and physiological effects, such as anxiety, increased blood pressure and heart rate, impaired immune function, and altered release of pituitary, neuroendocrine, and other hormones (9,10). These, in turn, may result in longer hospital stays, more readmissions, decreased patient satisfaction, and increased pain sensitivity (1,11). Therefore, pain management should be valued by emergency medical workers.

The analgesic properties of nitrous oxide/oxygen, such as used in ED application, have been in use for more than 200 years (12). Nitrous oxide/oxygen possesses analgesic properties without loss of consciousness, few adverse events, ease of administration, and no need for intravenous procedure, so it is safe and noninvasive (13). Advantages of nitrous oxide/oxygen also include rapid onset of action (1–2 min) and rapid offset (35–45 s) after discontinuation, owing to its low solubility in blood (14). These qualities indicate that it may be particularly promising for ED use. Several studies have demonstrated the efficacy of 50% nitrous oxide/oxygen for the treatment of acute trauma pain in the prehospital setting in some countries (15). However, our previous study has shown that 50% nitrous oxide/oxygen is less effective for pain control during change of burn wound dressing in China. Hence, we performed clinical trials to compare the efficacy of different concentrations of nitrous oxide/oxygen mixture on patients during burn wound dressing change and found that a 65% concentration of nitrous oxide/oxygen mixture was more effective for our patients (16).

The main objective of this pilot clinical trial is to determine the clinical analgesic effectiveness of the fixed nitrous oxide/oxygen mixture relative to a placebo in trauma patients with acute pain in the ED. Secondary objectives include the safety of the fixed gases, and satisfaction of patients and emergency medical workers concerning analgesia. We postulate that a 65% nitrous oxide/oxygen mixture can provide superior analgesic effect for these patients.

METHODS

Study Design

This is a double-blind, randomized controlled study of trauma patients with moderate-to-severe pain. This study was approved by our Ethics Committee (2014-179) and has been registered in the Chinese Clinical Trial Registry (ChiCTR-INR-16007807).

Study Setting and Patients

We conducted the present study in the ED of General Hospital, an urban, public, 3684-bed tertiary-care teaching hospital with an ED census of 179,117 annually. Consecutive patients attending the ED were considered eligible if they were Chinese speaking, ranged from 18 to 65 years old, with moderate to severe acute pain caused by trauma, and were willing to participate in the study. The exclusion criteria were patients with disturbance of consciousness, hemodynamic instability (heart rate not within 60–110 beats/min, blood pressure <90/50 mm Hg or >180/100 mm Hg, and oxygen saturation < 94%), polytrauma (e.g., intracranial hematoma, cerebral contusion, multiple rib fractures, pulmonary contusion, visceral organ rupture, hemorrhage), large vascular injury, pregnancy, and a contraindication for the premixed gas use (air embolism, abdominal distension or suspected bowel obstruction, recent ophthalmic surgery, pneumothorax/hemothorax, intestinal obstruction, epilepsy, emphysema, sinusitis, maxillofacial injuries and retinal detachment), or anyone included in another study.

Randomization and Blinding

Randomization. The patient's allocation sequence was decided by a computer-generated randomization list, which was numbered by an independent data manager. Eligible participants meeting the inclusion criteria were randomly allocated to the treatment group (A) or the control group (B) with a 1:1 ratio.

Blinding. The randomization schedule was sealed in an opaque envelope, which was kept and restricted by a project manager. She was responsible for the sequence allocation but wasn't involved in collecting and analyzing data. Once a participant was recruited and enrolled, the project manager opened the envelope sequentially and then assigned participants to the groups. The trained investigators who implemented the intervention were instructed by the project manager to administer the intervention, and the outcome assessor collected data during the study

period. To maintain the blinding of the investigator and outcome assessor, the gas cylinders we used were in exactly identical packaging by Ningfeng Oxygen Company; they were identified only by a label (A or B). Throughout the treatment, apart from the project manager, no other outcome assessors or investigators or patients knew the data allocation, which gas was contained in each gas-holder, or what the letters A and B stood for. Only after all the trials were completed would the randomization list and the meaning of labels A and B be revealed to all the researchers.

INTERVENTIONS

Generally, all patients entering the ED received assessments by clinicians. The patients who met all prespecified inclusion and exclusion criteria were introduced to this study. The investigators explained the purpose, benefits, and potential risk of the study in detail to the qualified patients and told them they had the right to decide whether to participate in this study. Patients who agreed to participate in this study were asked to sign a consent form; the relevant treatment was then carried out immediately. Participants were randomly allocated to either treatment group or control group, according to the randomization list. The treatment group received nitrous oxide/oxygen mixture plus conventional pain treatment, and the control group received oxygen plus conventional pain treatment. At present, the conventional approach is a "generalized pain medication" such as an acetaminophen, nonsteroidal anti-inflammatory drug (NSAID), or opioid (17). Patients with traumatic pain in the ED were evaluated and routinely given analgesics according to the pain severity.

The portable device consists of a cylinder, a gas regulator with a flowmeter attached, and a facial mask with a one-way demand valve. Both gases were stored in the preprepared and exactly identical cylinders. A specially designed demand valve was responsible for safe gas delivery, and careful attention was paid to its status and function during the implementation of the intervention. It was not opened unless negative pressure was applied by the patient. In this method, the rate of gases taken in was controlled by the patient's consciousness level, which decreased the risk of overdose.

Prior to intervention, all patients were taught to use the self-administered apparatus that provides a fixed concentration of nitrous oxide/oxygen mixture (65% nitrous oxide and 35% oxygen) or oxygen at 100% concentration. They inhaled the gas through the facial mask until the pain was controlled or 15 min maximum inhalation time was reached. The investigators successively included participants until they reached the target sample size.

Sample Size Calculation

Based on our previous studies on cancer breakthrough pain and burn-dressing pain, pain severity was used as the primary endpoint measure for sample size calculation (16,18,19). According to the preliminary study, pain intensity was assessed with nitrous oxide/oxygen mixture or oxygen in 20 consecutive patients. It was found that 65% of patients in the experimental group experienced pain relief at 5 min (T1) after the beginning of the intervention, vs. 8% in the control group (a decrease in pain intensity of at least 30% was recommended as the pain relief) (20). We used the formula to calculate that a minimum of 30 patients were required (21,22). In practice, we finally decided on 60 samples (30 per group) to improve the power of this study.

Outcome Measures

The primary endpoint measures were the changes in the pain numerical rating scale (NRS) at 5 min (T1) and 15 min (T2) after the beginning of the intervention. Using a verbal NRS, the data collector asked patients to rate their pain intensity on a numerical scale that usually ranged from 0 (indicating "no pain") to 10 (indicating the "worst pain imaginable") and correlated well with the Wong-Baker FACES Pain Rating Scale. The pain score was assessed and recorded at baseline (enrollment, T0), T1, and T2.

The secondary outcome measures included the vital signs, the incidence of adverse events, and the satisfaction of both patients and physicians. Pulse rate, blood pressure, and oxygen saturation were monitored via an electronic manometer (OMRON, HEM-7120; Omron Healthcare, Haryana, India) and oximeter (Heal Force, PC-60B; Kerikang company, Shenzhen China) at T0, T1, and T2. The satisfaction was assessed by a 10-point satisfaction scale at T2. All the observed adverse effects, such as nausea, vomiting, dizziness, drowsiness, and headache, were carefully evaluated and recorded during the inhalation of gases. All the above measurements were recorded by a data collector on a standardized case report form.

Data Analysis

Data were analyzed according to the intention-to-treat principle. All quantitative statistical analysis was undertaken with SPSS version 22.0 (SPSS Inc., IBM Company, Chicago, IL). Continuous data were described with medians (interquartile ranges), means (standard deviations), and proportions (exact binomial 95% confidence intervals), based on different needs. Repeated-measures analysis of variance was used to compare the differences in

pain scores and physiological parameters at baseline, T1, and T2 between the two groups ('experimental' and 'control'). We used the Mann–Whitney test to compare the satisfaction score from both patients and physicians. The χ^2 test was performed to compare the incidence of the side effects of the two groups. Statistical significance was considered for $p < 0.05$.

RESULTS

A total of 249 consecutive patients with moderate-to-severe traumatic pain in the ED of the General Hospital were enrolled between November 1, 2016 and June 2, 2017. Of these participants, 47 eligible patients withdrew consent to participate in the study, 116 patients met various exclusion criteria, and 6 patients were excluded for other reasons. Ultimately, 60 patients were enrolled and randomly assigned to two groups in the study. The CONSORT flow diagram for participant enrollment is shown in Figure 1. All the patients completed the intervention.

Demographic characteristics and baseline characteristics of all patients were detailed in Table 1. Between the nitrous oxide/oxygen groups and oxygen groups, no significant difference in age (45 [31–48] and 46 [36–59] years, respectively), gender (males/females: 10/20 and 6/24, respectively), initial pain scores (6.0 [5.0–8.0] and 6.8 [5.0–9.0], respectively), or other characteristics (etiology of pain) were noted. The most common etiology of pain was extremity pain.

The analyses of pain intensity (NRS) for each group are shown in Table 2 and Figure 2. The mean pain scores at T0, T1, and T2 were 6.7 (± 1.6 SD), 3.4 (± 1.8 SD), and 3.0 (± 1.9 SD), respectively, in the nitrous oxide/oxygen group, and 6.9 (± 1.9 SD), 7.0 (± 1.8 SD), and 6.3 (± 2.2 SD), respectively, in the oxygen group. As observed in Figure 2, the differences in NRS scores between the groups were significant at T1 ($p < 0.01$) and T2 ($p < 0.01$).

The vital signs between the two groups are also shown in Table 2. There was no significant difference between the two groups concerning blood pressure, oxygen saturation, and heart rate. The satisfaction from both patients (8.0 [7.0–9.0] vs. 4.0 [2.0–6.0], $p < 0.01$) and physicians (8.5 [8.0–9.0] vs. 4.0 [3.0–6.0], $p < 0.01$) in the nitrous oxide/oxygen group was significantly higher than the oxygen group (Figure 3).

The number and types of adverse events are reported in Table 3. We observed no severe side effects related to the gas inhalation during the whole intervention. Four subjects experienced adverse events (nausea in 1 patient, somnolence in 1 patient, dizziness in 2 patients) in the nitrous oxide/oxygen group. Dizziness in 1 patient was observed in the oxygen group. All of these were mild to moderate and fully reversible after the inhalation was discontinued. There was no significant difference in the incidence of side effects between the groups (Table 3).

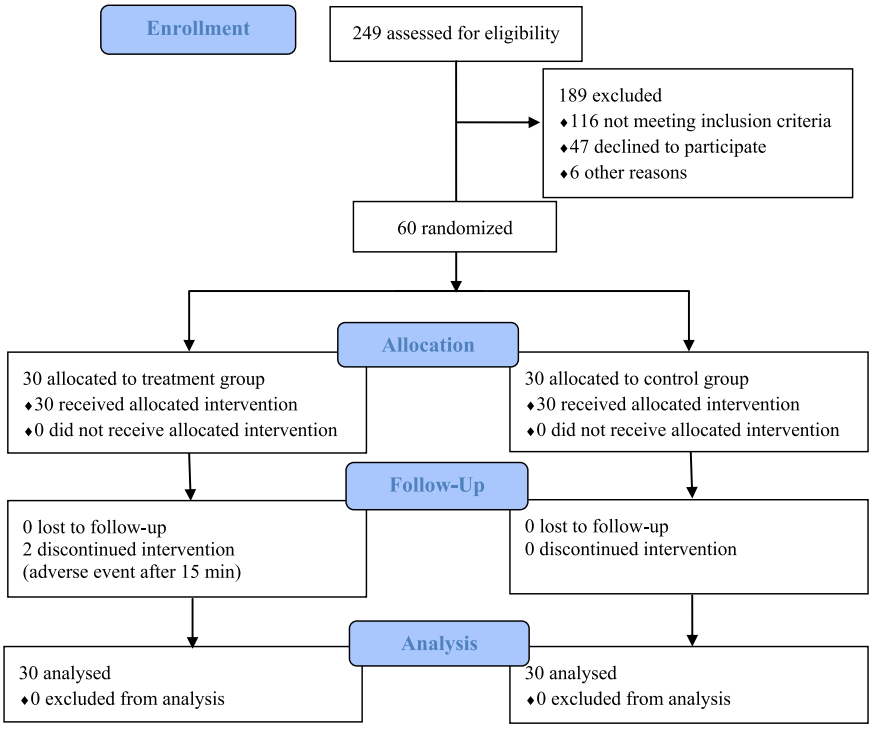

Figure 1. Participants flow diagram.

Table 1. Baseline Characteristics of Patients Entering the Study

Variable	Group		*p*-Value
	Nitrous Oxide/Oxygen (n = 30)	Oxygen (n = 30)	
Age (years)*	45 (31–48)	46 (36–59)	0.17
Gender n (%)†			0.24
Female	10 (33)	6 (20)	
Male	20 (66)	24 (80)	
Etiology of pain (n, %)			
Extremity pain	15 (50)	12 (40)	
Fracture	9 (30)	10 (33)	
Abdominal pain	4 (13)	6 (20)	
Thoracodorsal pain	1 (3)	0	
Head pain	1 (3)	2 (7)	
Pain scores rating on NRS at baseline (median, IQR)*	6.0 (5.0–8.0)	6.8 (5.0–9.0)	0.57

NRS = Numerical Rating Scale; IQR = interquartile range; SD = standard deviations.
Results are expressed as n (%), median (IQR) or means ± SD.
Significance set at $p < 0.05$.
* Based on Mann–Whitney test.
† Based on χ^2 test.

DISCUSSION

In this randomized controlled trial, the use of nitrous oxide/oxygen mixture was superior to that of placebo in the reduction of pain intensity in adult trauma patients with moderate-to-severe pain. In addition, we observed a low rate of side effects, with no serious complications.

During our implementation of intervention, few and mild side effects were observed (nausea, 6.9%; somnolence, 3.4%; dizziness, 3.4%), and all of them were transient and vanished within 5 min after removing the inhalation device. No serious side effects were noted. These observations were consistent with previous studies (1,15). The randomized controlled study administered by Ducasse et al. found that about 7% of patients (4 of 60) experienced nausea that was fully reversed 5 min after the termination of gas inhalation, which suggested that adverse effects associated with nitrous oxide/oxygen

Table 2. Pain Scores and Vital Signs Recorded at T0, T1, and T2 in all Patients

Variables	Group		*p*-Value*
	Nitrous Oxide/Oxygen (n = 30)	Oxygen (n = 30)	
Pain Scores Rating on NRS			
T0	6.7 ± 1.6	6.7 ± 1.9	0.000†
T1	3.4 ± 1.8	7.0 ± 1.8	
T2	3.0 ± 1.9	6.3 ± 2.2	
Systolic blood pressure (mm Hg)			
T0	130.50 ± 18.55	123.23 ± 10.88	0.517
T1	127.80 ± 17.62	131.43 ± 10.57	
T2	127.20 ± 18.13	123.90 ± 7.77	
Diastolic blood pressure (mm Hg)			
T0	81.07 ± 14.75	78.57 ± 12.34	0.304
T1	80.63 ± 16.60	77.20 ± 11.65	
T2	78.97 ± 14.85	74.90 ± 11.41	
Heart rate (beats/min)			
T0	82.47 ± 14.85	89.80 ± 15.90	0.023
T1	81.43 ± 13.54	91.90 ± 14.41	
T2	80.20 ± 16.04	87.07 ± 14.06	
Oxygen saturation (%)			
T0	95.73 ± 1.57	96.56 ± 1.94	0.662
T1	96.13 ± 1.81	95.43 ± 1.91	
T2	96.53 ± 1.53	96.90 ± 2.02	

Results are presented as mean ± SD and median (IQR). SD = standard deviations; IQR = interquartile range; NRS= Numerical Rating Scale; T0 = at baseline; T1 = 5 min after the beginning of intervention; T2 = 15 min after the beginning of intervention.
* Determined using repeated-measures analysis of variance.
† Statistically significant, $p < 0.01$.

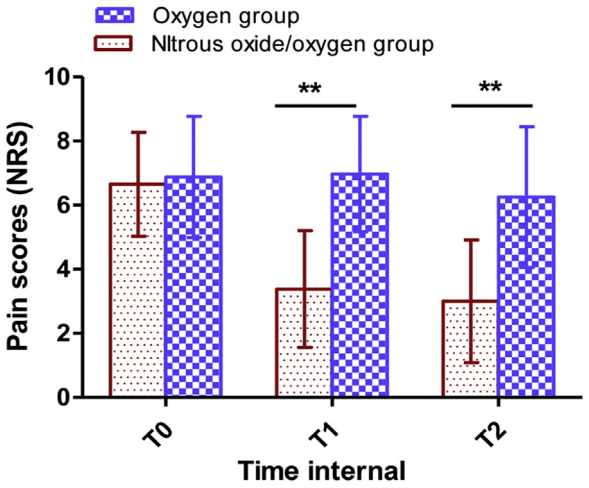

Figure 2. Pain score based on NRS for intervention and control groups at T0, T1 and 2. NRS = numerical rating scale. **Statistically significant, $p < 0.01$ (based on *t*-test).

were mild and rare (15). In another study, Meier et al. documented that only 13.3% of patients (4 of 30) complained of adverse side effects, consisting of headache (3.3%), unpleasant loss of control (6.6%), and dizziness (3.3%), which vanished within minutes; none of the patients underwent deleterious side effects (23). These outcomes of nitrous oxide/oxygen use also showed superiority in the treatment of ED patients.

Abundant studies have tested the safety and efficacy of nitrous oxide, generally compared with other techniques. Kariman et al. compared the analgesic effect of nitrous oxide/oxygen with fentanyl in patients who suffered from isolated extremity trauma (24). This study showed that it has fewer adverse drug effects and equivalent

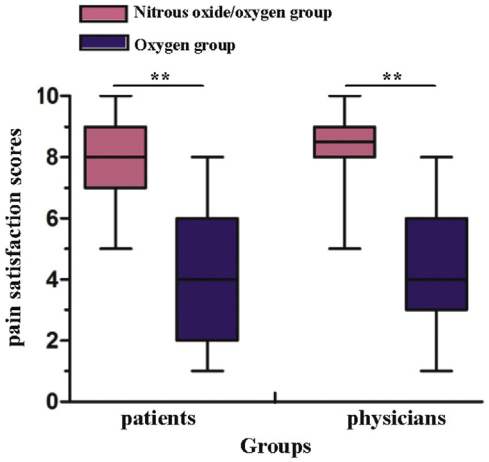

Figure 3. Satisfaction from both patients and physicians in the two groups. **Statistically significant, $p < 0.01$ (Based on Mann–Whitney test).

Table 3. Adverse Events During the Whole Intervention by Groups

Adverse Events	Group	
	Nitrous Oxide/Oxygen (n = 30)	Oxygen (n = 30)
Nausea	1 (3.33%)	0
Somnolence	1 (3.33%)	0
Dizziness	2 (6.66%)	1 (3.33%)
Total*	4 (13.33%)†	1 (3.33%)

Results are expressed as n (%).
* Based on Pearson χ^2 statistic test.
† $p = 0.35$ vs. oxygen group.

analgesic efficacy. It has been reported that the nitrous oxide/oxygen mixture will play the same role as a dose of at least 15 mg of morphine given intramuscularly (17). During the administration of tumescent local anesthesia for endovenous laser ablation, nitrous oxide/oxygen provided significant pain relief compared with the tumescent local anesthesia alone (23). Similar to that found in the previous study, in this study the mean pain severity of the patients in the treatment group was 3.4, whereas the mean pain intensity of those in the control group was 7.0 ($p < 0.01$).

In the present study, blood pressure, heart rate, and oxygen saturation were also monitored throughout this trial. There were no significant differences at the studied moments. Many other studies on nitrous oxide/oxygen mixture found similar results. Cazarim et al. evaluated the analgesia effect of 50-50% N_2O-O_2 gas mixture and pure oxygen on patients undergoing transrectal ultrasound-guided biopsy and showed no significant differences in the values of heart rate, peripheral O_2 saturation, and diastolic blood pressure during the study (25). Wang et al. designed a randomized controlled study to assess the safety and efficacy of nitrous oxide (30%–70% concentrations) and observed similar physiological parameters between the nitrous oxide and pure oxygen groups (26). These results indicated the hemodynamic stability presented by patients in the nitrous oxide group. The use of nitrous oxide had minimal effects on these parameters, similar to the effects of pure oxygen (17).

Managing patients' pain and relieving suffering is the obligation of health care professionals. Numerous studies have suggested that undertreatment of pain or oligoanalgesia remains common in the ED (27,28). For trauma patients in the ED, the most common options for acute pain include opioids and NSAIDs (17). Opioids are effective analgesics that have been used to treat moderate-to-severe pain for nearly 200 years, and are still the mainstay of pain management. NSAIDs are the most frequently used pain killers to control painful conditions such as

musculoskeletal pain. Considering drug safety (adverse effects and diversion or abuse potential to opioids) and dose-related side effects of NSAIDs, they are not suitable for some high-risk patients. Selecting a therapy that takes the patient's risk factors and expectations of pain management into consideration in the ED still remains a major challenge for health care workers. Our previous research suggests that a fixed nitrous oxide/oxygen mixture managed by health care workers for burn dressing and breakthrough pain are safe and effective (16,19). It seems to be a promising adjunct to opioid analgesics for pain relief in the ED.

However, opioids (such as morphine and fentanyl) have not been accepted all over the world. They are mainly used in developed regions, including Britain, France, Australia, America, and South Africa. In China, they are mainly used in obstetric and burns surgery.

Limitations

The present study did not record the pain intensity several hours after the intervention to evaluate the long-term effect. After the end of initial pain management intervention, patients were routinely given medical treatment by clinicians, compounded by the involvement of other treatment. The present study was a preliminary clinical trial and aimed to determine the analgesic effect and safety of the gas mixture in trauma patients with acute pain in the ED. The results may not be generalizable to other departments or patient settings. All the above should be considered in subsequent studies.

CONCLUSIONS

This study demonstrates that 65% nitrous oxide/oxygen seems to be more efficacious than oxygen in treating moderate-to-severe traumatic pain in the ED. The nitrous oxide/oxygen mixture is associated with few side effects, and no severe complications appeared during the study period.

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ARTICLE SUMMARY

1. Why is this topic important?

Pain is widely recognized as the fifth vital sign and is a common complaint in many patients who come to the emergency department (ED). However, the need for timely and adequate pain management isn't met in most EDs. Selecting a safe, quick-acting, and well-tolerated pain management therapy in ED is still a major challenge for health care workers.

2. What does this study attempt to show?

The main objective of this article is to determine the clinical analgesic effectiveness of the fixed nitrous oxide/oxygen mixture relative to a placebo in trauma patients with acute pain in the ED. Secondary objectives include the safety of the fixed gases, and satisfaction of patients and emergency medical workers concerning analgesia.

3. What are the key findings?

As this randomized controlled trial shows, the use of 65% nitrous oxide/oxygen mixture can provide superior analgesic effect for these patients arriving at the ED. Both patients' and physicians' satisfaction in the nitrous oxide/oxygen group were significantly higher than the oxygen group ($p < 0.01$). The researchers have observed no serious adverse effect in the two groups during the intervention.

4. How is patient care impacted?

The results of this study will contribute to manage patient's pain and relieve suffering in the ED. For trauma patients with acute pain in the ED, health care workers should pay more attention to the pain and be familiar with the pain assessment and management strategies.