ORIGINAL ARTICLE

Efficacy Evaluation of Nitrous Oxide as Analgesic in the Pediatric Age: Prospective Study

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Abstract

Introduction: Inhaled nitrous oxide has been primarily used as a sedative but also as an analgesic in pediatric painful procedures. This study characterises the use of nitrous oxide in this age group and evaluates its effectiveness, safety and acceptance.

Methods: Observational and prospective study performed based on the application of a questionnaire to pediatric patients in which nitrous oxide was administered (50% mixed with oxygen). Wong-Baker and FLACC-R (face, legs, activity, cry, consolability – revised) scales were used for pain assessment by the patient and the physician, respectively. Statistical analysis was performed using non-parametric tests and a significance level of 0.05 was considered.

Results: A total of 65 patients with a median age of 8 years were evaluated. In 46 patients (70.8%), it was used in acute disease, mainly in fractures reduction (n = 33; 50.8%). The median of onset duration was 3 minutes and the action duration 7 minutes. There were reported side effects in 21 patients (32.3%), all mild and temporary. Twenty patients (30.8%) underwent supplemental analgesia during the procedure. During the procedure, in the context of acute illness, pain was lower than previous pain when evaluated by the patient ($p < 0.001$). Patients who were 5 years of age or older reported less pain during the procedure than patients who were of a younger age ($p < 0.001$). All the patients would accept its use again.

Discussion: Nitrous oxide is an effective, safe, easy to use and quick-action analgesic. Efficacy was higher in patients older than 5 years of age and was well accepted by the patients.

Keywords: Analgesia; Child; Nitrous Oxide/administration & dosage; Pain/prevention & control; Pain Measurement; Portugal; Surveys & Questionnaires

Introduction

Painful procedures in children are challenging due to the low collaboration inherent with this age group, associated with a high level of fear and stress.[1-3] Pain control during these procedures is often overlooked in quick techniques.[4] On the other hand, there is still a lack of knowledge regarding the pharmacokinetics and pharmacodynamics of the analgesic drugs used in those of pediatric age which often leads to inappropriate pain treatment in this age group.[1,5] However, not only poorly controlled pain negatively influences the procedure success,[5] the way a child deals with the pain at an early age also affects future reactions in painful procedures.[3,6] The negative effect that pain and stress experienced by children in this context can have in their development is also recognised.[7-9] The Portuguese Directorate-General of Health issued, in 2010, a guideline on the control of pain in children, with the aim of alerting and providing health professionals with skills in this area.[10]

The intravenous administration of analgesia is safe and fast-acting, although invasive due to the need of venipuncture, which is also painful. Nitrous oxide (N_2O) is a gas with analgesic and sedative properties[11,12] and has long been used in the pediatric age by dentists, stomatologists and anaesthesiologists in operating rooms.[13-15] It is a colourless and odourless gas that is easy to use, with no need for venous access, fast-acting and with a good safety profile.[4,16,17] In fact, the most frequent side effects, including dizziness, drowsiness, euphoria, nausea and vomiting, are light and quickly reversible.[18] These characteristics made the N_2O administered by inhalation an alternative analgesic option[19] increasingly used in various painful procedures performed in children and adolescents outside of the operating room, particularly in the context of emergency care.[16,20-23]

There are several international studies in centres that use inhaled N_2O as a sedative and analgesic in painful procedures that demonstrated the safety of its use in samples of a significant size.[19,21,24-28]

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In Portugal, to date, there are no prospective studies evaluating the efficiency and safety of N_2O during painful procedures. The primary goals of this study were to characterise the use of N_2O as pain reliever in painful procedures and assess its efficiency and safety in pediatric patients in a Portuguese hospital. The secondary goal was to determine the acceptance of inhaled N_2O use by patients.

Methods

An observational, cross-sectional and prospective study was performed during eight months (February to September) in 2017, in pediatric emergency and day hospital departments of a Portuguese level II hospital. The study included children and adolescents who, during painful procedures, were submitted to the administration of inhaled N_2O in the form of compressed gas: a mixture of 50% N_2O and 50% oxygen.

For data collection, a questionnaire filled in by the health care professional (either a doctor or nurse) was elaborated, which accompanied the patient during the procedure. The questionnaire consisted of six short open-ended questions or multiple choice questions, which included information regarding the patient (date of birth, gender, acute or chronic disease), information regarding the procedure (place, date, type of procedure, administration of N_2O, effect onset and duration of the procedure in minutes as evaluated by the healthcare professional, need for additional analgesia, side effects), analgesia efficacy evaluated by the patient, analgesia efficacy evaluated by the health care professional, acceptance for use in future interventions.

For pain assessment, scales recommended by the Portuguese Directorate-General of Health were used [9] - Wong-Baker faces scale (Fig.1) in the evaluation of pain by the patient and FLACC-R scale (face, legs, activity, cry, consolability - revised) for the evaluation of pain by the health care professional. The modified FLACC-R (Table 1) scale was used so that it could be applied to disabled children and adolescents. Both scales assess the pain intensity on a scale of 10 points (0 to 10), in which zero is equivalent to not having pain and 10 corresponds to maximum pain. The patient and health care professional evaluated the pain at three points: before, during and after the procedure.

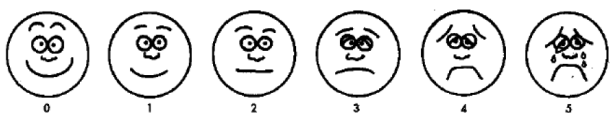

Figure 1. Wong-Baker Faces Scale used to evaluate pain by the patient.

A prior pilot study including 32 patients was conducted in order to verify the questionnaire applicability and it obtained good results.

Inclusion criteria were being a patient with the need to undergo a painful procedure, aged between 2 and 17 years old, and having signed informed consent agreeing to participate in the study. Cases were excluded when patients or their legal representatives had difficulty in understanding the goals of the study or the questions in the questionnaire as well as those with incomplete questionnaires. Cases of children or adolescents with chronic illnesses unable to assess the intensity of the pain by applying the Wong-Baker faces pain scale were excluded only from the statistical evaluation of the efficacy of N_2O by the patient.

The data collected were included in an electronic database in Excel® and analysed using SPSS 24®. Statistical analysis was performed with a non-parametric test (Chi-square test) with a 0.05 significance level.

Results

The sample included 65 patients, with a predominance of males (n = 43; 66.2%) and a median age of 8 years (minimum 2 years; maximum 17 years). During the period of the study, inhaled N_2O was administered in an emergency setting in 38 cases (58.5%) and in the day hospital in 27 cases (41.5%).

In most cases, the N_2O was administered in the context of acute illness (n = 46; 70.8%). In all other cases, (n = 19; 29.2%) N_2O was used to perform painful procedures in patients with chronic illnesses. The majority were patients with cerebral palsy (n = 15), followed by two patients with a brain tumour, one patient with autism spectrum disorder and one patient with sickle-cell disease.

The painful procedure that motivated the greatest use of N_2O was the reduction of closed limb fractures (n = 33; 50.8%). This was followed by venepuncture (n = 13; 20%) and administration of botulinum toxin (n = 13; 20%), suture (n = 3; 4.6%), lumbar puncture (n = 1; 1.5%), nail removal (n = 1; 1.5%) and intra-articular therapy (n = 1; 1.5%) (Fig. 2).

In the studied cases, the median onset of action of inhaled N_2O was 1 minute (minimum 1 minute; maximum 13 minutes). The median procedure duration was 7 minutes (minimum 2 minutes; maximum 30 minutes). In 45 cases (69.2%), inhaled N_2O was the only analgesic therapy used to perform the painful procedure, since the physician considered the pain under control. In 20 cases (30.8%), additional analgesia was administered. In 16 cases, additional topical analgesia (EMLA®) was used and, in four cases, intravenous analgesia (morphine/ketorolac) was used.

Table 1. FLACC-R scale used to evaluate pain by the health care provider

Category	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn or disinterested; appears sad or worried	Consistent grimace or frown; frequent/constant quivering chin; clenched jaw; distressed-looking face; expression of fright or panic
Legs	Normal position or relaxed; usual tone & motion to limbs	Uneasy, restless, tense; occasional tremors	Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking
Activity	Lying quietly, normal position, moves easily, regular & rhythmic respirations	Twitching, moving back and forth, tense; slight agitation	Arched, rigid or jerking, severe agitation, head banging, shivering, breath holding, gasping or sharp intake of breaths, severe splinting
Cry	No cry/verbalisation	Moans or whimpers, occasional complaint, occasional verbal outburst or grunt	Crying steadily, screams or sobs, frequent complaints, repeated outbursts, constant grunting
Consolability	Content or relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort, pushing away carer, resisting care or comfort measures

FLACC-R - face, legs, activity, cry, consolability - revised.

Side effects have been reported in 21 cases (32.3%), all transient and mild. The reported side effects were drowsiness (n = 9), dizziness (n = 7), euphoria (n = 6), tachycardia (n = 2), sweating (n = 2), nausea (n = 1), vomiting (n = 1), hallucinations (n = 1) and asthenia (n = 1) (Fig. 3). The side effects were rapidly reversible after administration was suspended and no therapy or hospitalisation was needed.

When the patient was asked to assess the pain using the Wong-Baker faces scale (0-10), the median of the pain before, during and after the procedure was 4 (minimum 0, maximum 10), 2.5 (minimum 0, maximum 10) and 0 (minimum 0, maximum 5), respectively. When the pain assessment was made by the health care professional, with the FLACC-R (0-10) scale, the median of the pain in the same three moments was 2 (minimum 0, maximum 8), 5 (minimum 0, maximum 10) and 0 (minimum 0, maximum 4) (Table 2). In the context of acute illness, the pain reported by the patient during the painful procedure was significantly lower than before the procedure ($p < 0.001$). However, when the pain intensity was assessed by the health care professional, it was higher during the procedure in comparison with the pain before the procedure ($p < 0.001$). The difference found in the evaluation of pain intensity between the patient/health care professional and temporal relationship with the procedure is shown in Fig. 4. When the patients are stratified by age, the median pain during the procedure was lower in the group aged 5 or higher (2.5) compared with the group aged lower than 5 (3) ($p < 0.001$).

The last question of the survey was aimed at the evaluation of inhaled N_2O acceptance by the children and adolescents. All the patients (n = 65) reported that they would repeat the procedure under this form of analgesia.

Discussion

The inhaled N_2O for analgesia in painful procedures is increasingly being used in those of pediatric age and has been administered in different types of procedures, including: minor surgery, [20,29,30] arterial or venous puncture,[31-33] lumbar puncture,[34] intramuscular injection,[35] catheterisation,[36] fracture reduction,[37] among others.

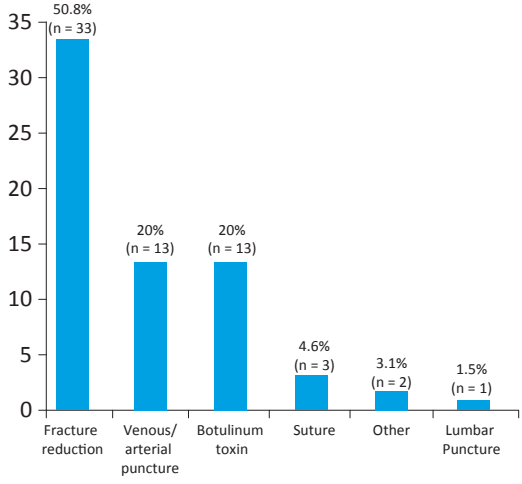

Figure 2. Type of procedure (n = 65).

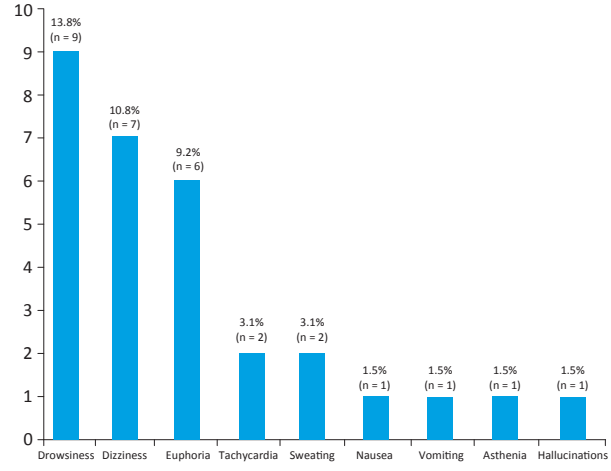

Figure 3. Side effects

Table 2. Pain evaluation in acute disease setting (n = 46)

Temporal relationship with the procedure		Before	During	After
Sick (Wong-Baker faces scale)	median	4	2.5	0
	minimum	0	0	0
	maximum	10	10	5
Health care provider (FLACC-R scale)	median	2	5	0
	minimum	0	0	0
	maximum	8	10	4

FLACC-R - face, legs, activity, cry, consolability - revised.

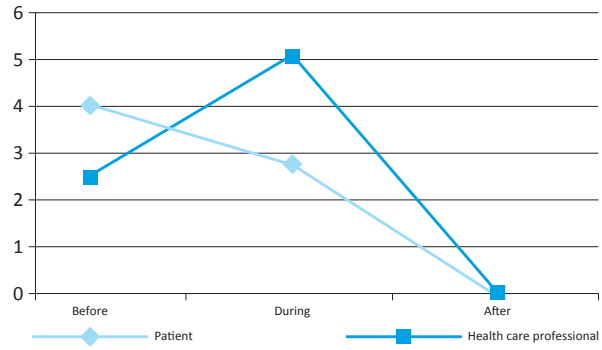

Figure 4. Pain evaluation in the context of acute disease by the patient and health care provider.

According to our literature review, this study is the first in Portugal assessing the efficacy of inhaled N_2O as a pain reliever during painful procedures in those of pediatric age, both from the perspective of the patient and of health care providers.

In the present study, most administrations of N_2O were performed in an emergency setting, in acute illness cases (58.5%), similarly to other published studies.[4,17,29,38-45] In this context, it was primarily used in fracture reduction (50.8%). N2O is also useful in painful procedures in children and adolescents with chronic illness. In the present study, it was mainly used in a day hospital in patients with cerebral palsy who underwent the administration of botulinum toxin (20%), which facilitates and improves the provided care and, consequently, the quality of life of these patients.[46] In fact, N_2O seems effective for pain management during the administration of botulinum toxin,[46] although there are no other studies evaluating its efficacy in painful procedures in chronically ill patients.

The administration of inhaled N_2O is straighforward.[18] On the other hand, the pharmacodynamics of the drug also facilitates its use, with a rapid onset of action (1-2 minutes) and a short duration of action after suspending administration (< 1 minute).[11,24,47-49] In the studied sample, a fast onset of action, of a median of 3 minutes, was observed. The duration of the administration of N_2O is variable and depends on the procedure time.

One of the goals of the study was to evaluate the safety of the administration of inhaled N_2O. There is a low prevalence of side effects reported in the literature,[4,16,17,19,24,25,29,31,33,38,44,50-52], the majority of which is resolved immediately or within a few minutes after the suspension of the gas administration.[16,17,26] In the studied sample, side effects, such as drowsiness, dizziness and euphoria, occurred in approximately one third of cases (32.3%). As shown in the literature, these side effects as well as nausea and vomiting, occur frequently.[4,18,26,29,31] The reported side effects, all of them minor and rapidly reversible with no need for any kind of intervention, are in accordance with the previously reported good safety profile. This safety profile allows the N_2O to be administered by pediatricians without the support of anaesthetists,[22,36,53] which is an important advantage as regards human resources management, especially in emergency settings, where it is more often used.

Serious adverse effects, such as laryingospasm[54] or cardiac arrest[24] are very rare. However, and despite this excellent safety profile, patient cardiorespiratory monitoring should be ensured as well as the existence of resuscitation material and professionals with resuscitation training during administration.[55] The American Society of Anesthesiologists recommends moderate sedation with the use of N_2O with a concentration equal to or less than 50% in order to minimise the risk of serious adverse effects, given that, with this concentration, the circulatory and respiratory functions remain unchanged.[6] In the published studies, the rare cases of more serious adverse effects occurred with the administration of N_2O in concentrations of 70%.[4] The administration of this gas at 50% concentration, which is the formulation currently used in Portugal, is safe and has fewer side effects.[19,26,29]

The effectiveness of inhaled N_2O as a pain reliever during painful procedures in those of pediatric age is widely demonstrated.[4,16,17,20-23,29,31,57] In the present study, inhaled N_2O seems to have been effective, since the intensity of the pain reported by the patient during the procedure was significantly lower than before (p < 0.001). When the patients were stratified by age group,

N_2O was found to be less effective in controlling the pain in the group of children aged younger than 5 years old ($p< 0.001$), a finding which was also reported in other studies.[4,17,58] The authors speculate that this difference is due to the better understanding and cooperation in gas inhalation by the older children, allowing for the greater efficacy of the drug.

On the other hand, from the perspective of the health care provider, the pain was more intense during the procedure than before ($p < 0.001$). The difference found in the evaluation of the pain by the patient and health care provider can be explained by the sedative and amnesiac properties. In the studied sample, 6.5% (n = 4) of the patients required additional systemic analgesia, a percentage lower than in other published studies.[17,38] In fact, the administration of inhaled N_2O as the only analgesic may not be sufficient for adequate pain control, especially in painful procedures such as fracture reductions.[38,40] The most commonly used drugs as pain relievers are opioids and benzodiazepines.[38] In the studied sample, only four cases required the use of an opioid (morphine), all in fracture reduction cases. On the other hand, a topical analgesic (EMLA®) was used in 13 cases of administration of botulinum toxin and three cases of venous/arterial punctures for catheter placement. The use of EMLA® in association with inhaled N_2O is advantageous in this type of procedure, as it increases the efficacy of pain management.[17,35]

In most cases, the isolated use of inhaled N_2O is effective in the control of pain in painful procedures, allowing for the reduction of the use of other drugs with greater potential for adverse effects which sometimes warrant hospitalisation.

The use of inhaled N_2O was very well accepted by the patients, since all of them reported that they would repeat the procedure. Other authors also concluded that the use of this gas has excellent acceptance by the pediatric patients.[4,29] This result was expected, since inhalation as routes of administration is better tolerated by most children than the intravenous or rectal routes.[19,59]

This study has some limitations. The sample size limited the statistical analysis, namely the comparison of the efficacy of inhaled N_2O in multiple painful procedures.

An original and non-validated questionnaire was used. Nevertheless, the pilot study enabled the assessment of the applicability with good results. No case-control study was performed for ethical issues, since the use of inhaled N_2O in painful procedures is standard practice in the hospital. The evaluation of pain intensity is difficult due to subjectivity and interindividual variation, as numerous factors can influence the way it is felt by the patient,[59] and may constitute a bias in assessing the N_2O efficacy. However, in the studied sample, there is no great variability, since more than half of the cases of N_2O administration occurred in fracture reductions in an emergency setting and only twenty patients needed supplementary analgesia and, most of these, with non-systemic analgesics. The characterisation of the administration of N_2O for painful procedures in patients with chronic pathology was limited by the small number of patients included. Further studies are needed to better characterise the use of inhaled N_2O in these patients.

The use of inhaled N_2O as an analgesic seems to be effective, significantly decreasing the patients' reported pain during the procedure, especially in patients over 5 years old. The gas sedative and amnesiac capabilities can justify the difference found in pain evaluation provider and patient. The inhaled N_2O for painful procedures in those of paediatric age has other advantages: it is easy to use and has a rapid onset of action; the side effects are mostly mild and reversible, with a good safety profile. The administration of inhaled N_2O is well tolerated by patients. The inhaled N_2O is, therefore, a good option for pain control during painful procedures on an outpatient basis, avoiding the use of sedative/anaesthetic drugs associated with a lower safety and reducing the number of hospital admissions. These results are similar to those in international literature that show the effectiveness, safety and tolerability of inhaled N_2O in those of paediatric age, contributing to an improvement in the treatment of pain. A national multicentre study would be an important next step for the drug evaluation at a national level.

WHAT THIS STUDY ADDS

- First Portuguese study demonstrating the inhalation of nitrous oxide as a good option for pain control during painful procedures in those of paediatric age, since it is effective, fast-acting and has a good safety profile.
- The use of inhaled nitrous oxide as an analgesic was very well accepted by paediatric patients.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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