Nitrous oxide provides safe and effective analgesia for minor paediatric procedures – a systematic review

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ABSTRACT

INTRODUCTION: Pain and distress during minor hospital-related procedures is a familiar problem in many children. Inadequate relief of children's procedural pain and distress not only affects the experience of the children and their parents, but also adversely impacts procedural success. We aimed to review the safety and efficacy of nitrous oxide during brief, but painful paediatric procedures and to compare nitrous oxide with some of the commonly used pharmacological and non-pharmacological treatments for relieving anxiety and mild to moderate pain in Denmark.

METHOD: We searched MEDLINE (PubMed) and the Cochrane Database of Systematic Reviews with the MeSH term *nitrous oxide* combined with *midazolam, surgical procedures minor*, *analgesia* or *conscious sedation*. The references in the articles acquired that were not found in the MEDLINE search were further investigated. Only articles written in English and published after 1980 were included to ensure optimal data collection.

RESULTS: Nitrous oxide is an effective sedative/analgesic for mildly to moderately painful paediatric procedures. Furthermore, it is safely administrated, particularly for short procedures (< 15 min.). Serious and potentially serious adverse events are rare and occur in less than 0.5% of cases, while minor events typically occur amongst 4-8% of patients.

CONCLUSION: Nitrous oxide is a safe and effective method to achieve analgesia and sedation during minor, but painful procedures. It can be safely administered by a dedicated staff member. This helpful method is still underused in Denmark, and we believe that it could be an alternative or the first choice of treatment in emergency and paediatric departments.

Historically, in the middle of the 1960s surgical procedures on infants were performed without sufficient analgesia on the assumption that infants were insensitive to pain, because the nervous system was underdeveloped [1]. Previous studies have also reported that children were given less analgesics than adults [2, 3]. Accumulating evidence during the past few decades has confirmed that pain is perceived early in life and that children's memories of painful experiences can shape their future reactions to painful procedures [4, 5]. Pain and distress during minor, but painful procedures such as peripheral venous cannulation, lumbar puncture and laceration repair is a familiar problem for many children. Inadequate relief of children's procedural pain and distress not only affects the experience of children and their parents, but also adversely impacts procedural success [6]. There is always a risk that children are undertreated for pain and distress due to difficulties in distinguishing what the pain sensation actually is within the complex mixture of sensations of pain, stress, fear and constraint in children [7, 8]. There is also a risk that our limited knowledge about the pharmacokinetics and pharmacodynamics of the drugs administered results in under-treatment of the children [9-11].

The aim of this article was to review the safety and efficacy of nitrous oxide during brief, but painful minor paediatric procedures. We therefore have not reviewed published data regarding environmental exposure to medical personnel administering nitrous oxide. Nitrous oxide was compared with some of the commonly used pharmacological and non-pharmacological treatments for relief of anxiety and mild to moderate pain outside the operating room in Denmark. Midazolam is one of the most common procedural sedatives used in this context in Denmark.

We therefore chose primarily to compare midazolam to nitrous oxide in our study.

METHOD

We searched MEDLINE (PubMed) and the Cochrane Database of Systematic Reviews for literature on nitrous oxide. The MeSH term "nitrous oxide" (MeSH) was combined with ("midazolam" (MeSH) OR "surgical procedures, minor" (MeSH) OR "analgesia" (MeSH) OR "conscious sedation"(MeSH)). The search identified 1,332 publications.

! ABBREVIATIONS

BoNT-A = botulinum toxin type A
CP = cerebral palsy
EMLA = eutectic mixture of local analgetics
GABA = gamma-aminobutyric acid
LP = lumbar puncture
N_2O = nitrous oxide
VAS = visual analogue scale

SYSTEMATIC REVIEW

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Dan Med J 2013;60(6):A4627

The following inclusion criteria were then applied: 1) Clinical Trial; Controlled Clinical Trial; Meta-Analysis; Randomized Controlled Trial, 2) papers addressing the subject: safety and efficacy of nitrous oxide during minor, but painful paediatrics procedures, 3) research papers published after 1980, 4) research papers published in English, 5) available abstract and 6) Child: birth-18 years. Articles emphasizing the use of nitrous oxide as general anaesthesia, among adults, during dental treatment, colonoscopy, or major surgery were read, but only the most important articles were included.

Several Cochrane analyses were excluded due to this criterion. Additional searches were performed from the reference lists of the selected literature.

After this procedure, a total of 26 studies were selected for review (see PRISMA flow diagram in **Figure 1**).

RESULTS

The results from this systematic review are presented under the following subheadings: "Classical strategies for pain relief", "The optimal duration of inhalation and concentration of nitrous oxide" and "Effectiveness of nitrous oxide during different procedures".

Classical strategies for pain relief

Non-pharmacological treatments

The predominant strategies are cognitive behavioural therapy [12], use of music [13] or topical freeze sprays [14].

Pharmacological treatments

An ideal agent for children should be easy to administer, have a rapid onset and offset, produce no residual symptoms, have minimal side effects, and should be cost-effective. Pharmacological options for children are available in different forms classified as invasive or non-invasive drugs. In Denmark, either eutectic mixture of local analgetics (EMLA), midazolam or nitrous oxide or a combination of these has typically been used.

Topical anaesthesia

EMLA cream the most frequently used anaesthetic cream in Scandinavia. It contains two dermal anaesthetics: lidocaine and prilocaine [15].

Orally, nasally and rectally administered sedatives

In Denmark, benzodiazepines have typically been used, and midazolam has become more popular than other benzodiazepines as it has a shorter half-life and is more potent than the alternatives [16, 17]. Rectal administration has primarily been used, but midazolam can also be administered orally [18], intranasally, buccally, intravenously or intramuscularly. The main effects of benzodiazepines are sedation, hypnosis, anxiolysis, anterograde and retrogade amnesia, centrally mediated muscle relaxation and anti-convulsant activity [19, 20]. Although the efficacy of midazolam has been demonstrated, the inter-individual variation of effects and its elimination are high and dose-dependent [21]. The anterograde and retrograde amnesia after midazolam is frequently cited as an advantage of midazolam [22, 23]. This has been questioned because the amnesic effect mainly affects explicit memory, but leaves implicit memory intact [20]. This means that the child remembers a scary experience, but cannot put it into words. A well-known side effect is post-procedure agitation, which occurs in 17% of paediatric patients pre-medicated with midazolam (0.3-0.5 mg/kg) [24].

The drug exerts its clinical effect by binding to a receptor complex which facilitates the action of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Practically all effects of the benzodiazepines result from their actions on the ionotropic GABA receptors. Benzodiazepines do not activate GABA receptors directly, but they require GABA [22, 25].

Inhaled analgesia-sedative agents

Nitrous oxide (N_2O) is an oxide of nitrogen and a compressed liquefied, colourless non-flammable gas, with a slightly sweet odour and taste. During the past few years, N_2O and an oxygen mixture have gained renewed interest. N_2O is the only inhaled anaesthetic that possesses analgesic properties at a sub-anaesthetic concentration [26]. Several studies have demonstrates the improved efficacy of sedation and pain control of N_2O compared with placebo and behavioural management during minor procedures [27-31].

N_2O primary effects are exerted on the central nervous system and the analgesic action is dependent on the inhibition of supraspinal GABA receptors and the activation of spinal GABA receptors [32]. The analgesic effects of N_2O consist of an interaction between the endogenous opioid system and the descending noradrenergic system. It seems that N_2O-induced release of endogenous opioids causes dis-inhibition of brain stem noradrenergic neurons, which release norepinephrine into the spinal cord and inhibit pain signalling [32].

Administration of N_2O is simple and painless, it has a rapid onset and a short duration of action, and its effects are analgesic, anxiolytic and sedative [33, 34]. The euphoric effect of N_2O is induced by dopamine release and the activation of dopaminergic neurons [35].

Epidemiological studies have linked chronic occupational exposure to N_2O to specific health problems, including reproductive risks [36, 37]. These studies remain controversial and are rarely dedicated to short procedural pain management outside the operating room [32, 38]. However, in order to respect occupational exposure

limits, an appropriate scavenging system should be used while giving N_2O. Different kinds of systems with masks and ventilation have been studied with good results [39]. However, they can limit the use of N_2O due to the necessity for the child to accept the mask during the whole procedure. These compliance challenges explain why treatment with N_2O is primarily used in children older than four years of age.

The optimal duration of inhalation and concentration of nitrous oxide

Although the safety of fixed 50% N_2O/50% oxygen mixture for procedural sedation has been demonstrated in studies encompassing thousands of patients [33, 40, 41], less information is available regarding the safety of N_2O administered at a higher concentration [41-43]. Babl et al [42] conducted a prospective observational study and enrolled a total of 762 patients who were aged from 1 to 17 years. The children had received either N_2O 50% or N_2O 70%. They found that 63 (8.3%) patients sustained mild and self-resolving adverse events and that there was no significant difference in adverse event rates between N_2O 50% and N_2O 70%. There are, however, some limitations as there were no independent observers and the staff involved in the procedural sedation might have underreported adverse events.

Zier & Liu [41] enrolled 5,779 children ranging in age from 33 days to 18 years, with a median age of 5.0 years. N_2O administration began at 60% with titration to either a higher or lower concentration within two to 3 min. based on the patient's response to the procedure. The maximal allowable N_2O concentration was 70%. Minor adverse events included nausea (1.6%), vomiting (2.2%) and diaphoresis (0.4%). Nine patients (0.14%) had potentially serious adverse events among which four patients had brief oxygen desaturation from 79% to 89%, and three other children experienced brief (< 3 min.), generalized tonic-clonic seizures, one during N_2O administration and two while receiving 100% oxygen after the procedure. Two of the children had previously experienced seizures, while the last child was otherwise healthy. All events were either self-limiting or resolved promptly with increased supplemental oxygen. There was no difference in adverse events between N_2O administered at less than or equal to 50% compared with above 50%. The incidence of adverse effects was, however, higher when N_2O was administered for more than 15 min. The authors felt that N_2O seemed safe for children of all ages. The present study, however, has some limitations. Adverse events were based on nurse reports and particular minor ones may be underreported [44]. Dental "nasal mask" and not a full face mask was used for gas delivery. While it was possible to cover both the mouth and the nose of smaller patients, older patients were instructed to breathe through the nose while keeping the mouth closed. Room air may have been entrained resulting in decreased, inspired N_2O concentrations compared with the flow meter setting [45]. This study is therefore not completely comparable with studies in which highly concentrated nitrous oxide was administered through a "full face mask" system.

Effectiveness of nitrous oxide during different procedures

Several randomized studies have compared midazolam and N_2O and conclude that both N_2O and midazolam provide a safe and effective sedation in children [46-52]. In the following, we mainly focus on the efficacy of nitrous oxide during some of the most common minor paediatric procedures.

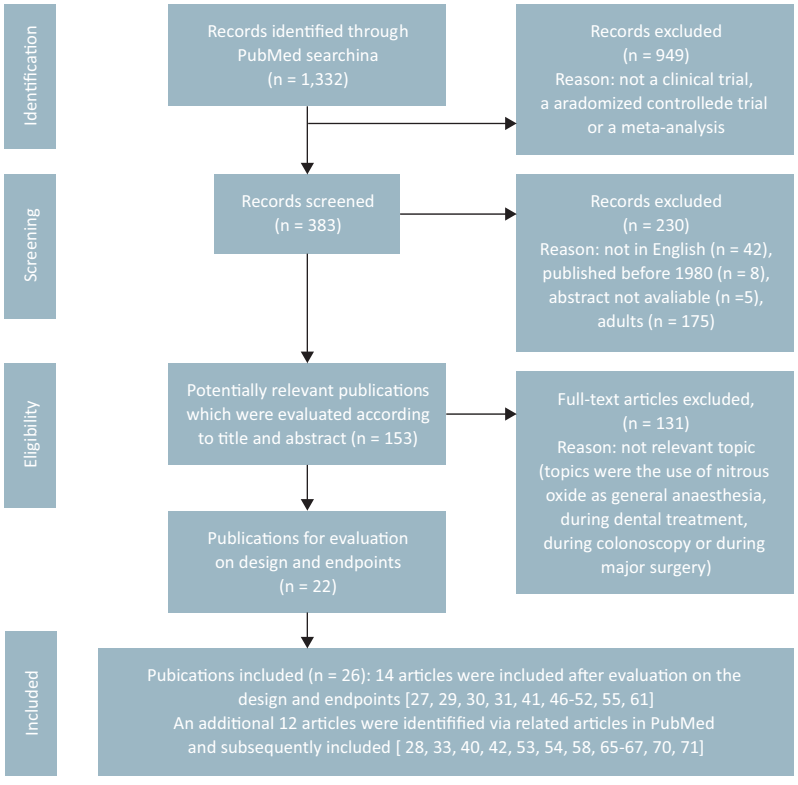
Nitrous oxide used for peripheral venous cannulation

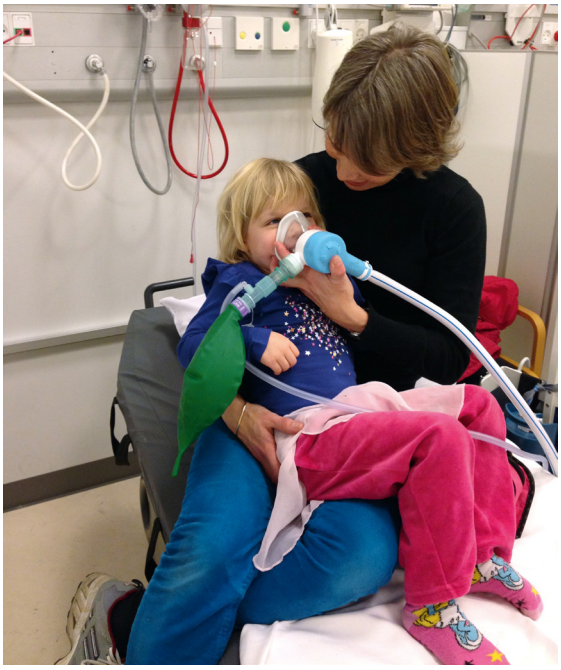
The large studies have successfully used N_2O during peripheral venous cannulation [33, 40, 41], but they have not specifically described the effectiveness of N_2O during this procedure.

However, a prospective, randomized study by Furuya et al [53] randomly allocated 73 children into one of four equally sized groups prior to peripheral intraven-

FIGURE 1

PRISMA flow diagram of the literature search of the study.





Nitrous oxide induction before undergoing a minor emergency department procedure: stabilization of a simple fracture of the right arm. The child is waiting 3 min. for full nitrous oxide effect.

Use of nitrous oxide during the procedure. The mother is helping by having a good contact with the child while the nurse is performing the procedure.

ous cannulation: Group 1: 50% N_2O for 3 min.; Group 2: 50% N_2O for 5 min.; Group 3: 70% N_2O for 3 min. or Group 4: 50% N_2O for 5 min. They found that a concentration of 70% N_2O was more effective in reducing pain than was 50% N_2O, but pain scores did not differ between those who breathed N_2O for 3 min. and those who breathed N_2O for 5 min. They found no significant difference between the four groups regarding the number or severity of adverse effects.

In a randomized trial by Ekbom et al [54], 70 children were allocated to either EMLA or EMLA plus N2O prior to venipuncture. Children who received N_2O and EMLA were reported to have statistically less pain assessed by a visual analogue scale. The authors found no difference between the two groups in regard to the total time required to complete the procedure. However, this study had several limitations as randomization and allocation concealment were not well explained.

Ekbom et al [55] randomly assigned 90 patients to receive either midazolam or 50% N_2O prior to peripheral intravenous cannulation. All patients received EMLA. The primary end point was efficiency, measured as total procedure time and number of attempts required to set up two intravenous lines. Secondary endpoints were patients' and parents' evaluations. They found that treatment with 50% N_2O was the most efficient with regard to total procedure time ($p < 0.001$) and the number of successfully placed intravenous lines. The patients' evaluations were also significantly more positive for 50% N_2O than for midazolam.

Nitrous oxide used for lumbar punctures

Although lumbar puncture (LP) is one of the most commonly performed painful procedures in paediatric departments, several studies show that most children are not adequately relieved of pain [56, 57]. Large studies have successfully used N_2O during LP [33, 40, 41], but they have not specifically described the effectiveness of N_2O during this procedure. We only found one study that specifically addressed the effectiveness of N_2O during LP [58]. Patients received either only 50% N_2O or a combination of EMLA and 50% N_2O. This study was, however, small and it was unclear whether the patients were randomized or if there were any differences between the two treatment groups. Both groups experienced adequate relief of pain.

Nitrous oxide used for intramuscular injections

Several studies have demonstrated the benefit of intramuscular botulinum toxin type A (BoNT-A) injections in the management of spasticity in children [59, 60], and children undergoing BoNT-A injections for spasticity often receive multiple injections at regular intervals [61]. Several reviews of BoNT-A injections in children note the lack of consensus between medical centres about use of pre-injection interventions, ranging from no intervention, to topical anaesthesia only, and oral sedation or general anaesthesia [62, 63]. The safety and efficacy of N_2O for sedation of patients with intellectual disability for outpatient dental treatment has been demonstrated [64]; however, the published data on the effectiveness

of N_2O during BoNT-A injections in patients with cerebral palsy (CP) are more ambiguous:

While large studies have successfully used N_2O during botulinum toxin injections [33, 41], they have not specifically described the efficacy of N_2O during this procedure. We only found smaller studies that specifically dealt with the effectiveness of N_2O during intramuscular injections.

A study by Gambart et al [65] with 40 children undergoing BoNT-A injection found that despite premedication with EMLA and inhalation of 50% N_2O, a total of 55% of the patients showed clinical signs of pain; for 30%, reactions were crying and withdrawal directly related to the injections; and for 25%, manifestations seemed non-specific and mainly related to overall anxiety and discomfort.

A similar prospective study, which included 51 injection sessions, 34 children with a mean age of six years and 209 injected muscles, evaluated the effectiveness of an analgesic protocol with N_2O and EMLA for children undergoing botulinum toxin injections [66]. Pain was evaluated with the Children's Hospital of Eastern Ontario Pain Scale, a visual analogue scale (VAS) and the Face Pain Scale for the children and with a VAS for the parents. The combination of N_2O and EMLA was only effective for 50% of the children.

In a double-blinded, placebo-controlled study conducted by Zier et al [61], 50 children were randomized to either sedation with N2O or midazolam (dose 0.35-0.5 mg/kg). The groups were similar in type of CP and Gross Motor Function Classification System level. N_2O was found to be more effective in reducing pain than midazolam as measured using the Face, Legs, Activity, Cry, Consolability scale ($p = 0.010$), parental estimate of pain ($p = 0.009$) and nursing estimate of pain ($p = 0.007$).

In a randomized, double-blinded, multicentre study conducted by Carbajal et al [67], 55 children received palivizumab intramuscular injections. Each child randomly received three different analgesic interventions during the first three monthly injections: 1) application of EMLA plus air inhalation; 2) 50% N_2O plus application of a placebo cream; and 3) 50% N_2O plus EMLA. Each child was his or her own control. Procedural pain was assessed through videotapes with the Modified Behavioural Pain Scale. This study found that administration of 50% N_2O to infants and young children was effective in decreasing the pain associated with intramuscular injections. The combined 50% N_2O plus EMLA cream was more effective than either EMLA cream or 50% N_2O alone.

DISCUSSION

Inadequate relief of children's procedural pain and distress not only affects the experience of the children and their parents, but also adversely impacts procedural success [6]; and children's memories of painful experiences can shape their future reactions to painful procedures [4, 5]. Pain and distress should be avoided and any medication should be easy to administer, have a rapid onset and offset, produce no residual symptoms, have minimal side effects, and should be cost-effective.

! LEARNING POINTS

Pain and distress during minor, but painful procedures is a familiar problem for many children.

Inadequate relief of children's procedural pain and distress affect the experience of children and their parents and impacts procedural success. Inhalation of nitrous oxide combined with oxygen is a well-known safe and effective analgesia, without major adverse effects.

Under-treatment with nitrous oxide patients should always be clinically monitored and the staff should be trained in basic airway management.

N2O is an effective sedative/analgesic for mildly to moderately painful paediatric procedures [33, 40, 41, 68-71]. It can also be safely administered, particularly for short procedures (< 15 min.) [33, 40, 41, 69]. When comparing N_2O with midazolam administrated transmucosally, intravenously or orally, the nitrous oxide group may experience significantly shorter induction time, shorter procedure time and shorter recovery time [50-52, 69, 72, 73]. This helpful method is, however, still underused [7].

Adverse effects of nitrous oxide can be categorized as reported by the Paediatric Sedation Research Consortium [74], where serious adverse events include death, cardiac arrest and aspiration. Potentially serious adverse events include those which could progress to poor outcome if not managed well, including stridor, laryngospasm, airway obstruction, wheezing or central apnoea, whereas "minor" events include euphoria, dizziness, headache, nausea and vomiting. Serious and potentially serious adverse events are rare and occur in less than 0.5%, while minor events typically occur among 4-8% of included patients [33, 40, 41] (**Table 1**). A French national survey with 1,019 children, however, observed minor adverse effects during 381 (37%) inhalations, but all side effects were transient and vanished within 5 min. after removing the inhalation device. No serious side effects were noted. The number of adverse events in this study may partially be attributed to the fact that 18% of the children received additional drugs, typically midazolam and nalbuphin.

Epileptic seizures have only been described as case reports [75, 76]. In most of the large international studies, there have been no reports of convulsions [34, 40, 42]. In the largest study, enrolling 35,828 children, epileptic seizures only occurred in two cases [33], and Zier & Liu al [41] enrolled 7,802 children and reported

three cases who experienced seizures. Although temporally related to the nitrous oxide administration, causality between N_2O and seizures in the later studies is indeterminate. Only one case report has clearly linked N_2O inhalation with the onset of electroencephalographic and clinical seizure activity in a child [76]. The incidence of epileptic seizures may be underreported, but the risk of seizures may be very small the large studies of children taken into consideration. The clinician should, however, be aware that the risk exists, especially in children with a reduced seizure threshold. Other potential adverse events such as myeloneuropathy associated with N_2O administration to a B12-deficient patient, may be rarer still, and have primarily been described among adults with a long-term abuse of N_2O [77]. Yet, providers offering N_2O sedation should be aware of this potentially serious complication [78].

CONCLUSION

Nitrous oxide is a safe and effective method to achieve analgesia and sedation during minor, but painful procedures. It has a rapid onset, is quickly reversible, does not have major side effects and can be safely administered by a dedicated staff member. It should be underlined that patients should always be clinically monitored and that the staff should be trained in basic airway management. However, nitrous oxide is not equally effective for all children. Staff members should therefore be prepared for another method of pain management in case of treatment failure.

TABLE 1

Identified literature in the present systematic review with emphasis on safety of nitrous oxide.

Study	Country	Study type	Patients, n[a]	Patients' age	Nitrous oxide-oxygen ratio	Major, serious, or potentially serious adverse events, %[b]	Minor adverse events, %[b]	Procedure characteristics
Onody et al [33]	France	Observational multicentre study	35,828[c]	0-1 yrs: 3% 1-4 yrs: 23% 5-10 yrs: 36% 11-18 yrs: 22% ≥ 19 yrs: 16%	50:50	0.08	4.4	Peripheral venous cannulation, lumbar puncture, reduction of luxation/fracture, burn dressings, minor superficial surgery, bone-marrow aspiration, gastrointestinal endoscopy and others
Annaquin et al [40]	France	Observational multicentre study	1,019	Range 0-18 yrs (median 6.4 yrs)	50:50	0	37	Peripheral venous cannulation, lumbar puncture, reduction of luxation/fracture, burn dressings, minor superficial surgery, bone-marrow aspiration and others
Zier & Liu [41]	USA	Observational multicentre study	7,802	0-1 yrs: 116 (1.5 %) 1-4 yrs: 3,751 (48.1%) 5-19 yrs: 3,050 (39.1%) 11-18 yrs: 885 (11.3%)	Up to 70:30	0.14	5.0	Urinary catheterization, peripheral venous cannulation, lumbar puncture, noninvasive procedures (e.g., chocardiogram, computed tomographic scan, enteral tube placement, minor surgical procedure (e.g., abscess incision and drainage, laceration suturing and others
Babl et al [42]	Australia	Observational singlecentre study	762	Range 1-17 yrs (median 6.0 yrs)	Up to 70:30	0.3	8.3	Peripheral venous cannulation, lumbar puncture, reduction of luxation/fracture, laceration repair, foreign body removal, minor superficial surgery and others
Gall et al [70]	France	Observational multicentre study	7,511	0-19 yrs	50:50	0.33	5	Peripheral venous cannulation, lumbar puncture, reduction of luxation/fracture, cast remodulation, burn dressings, minor superficial surgery, bone-marrow aspiration, bronchoscopy/gastroscopy, bladder catheterization and others
Hennequin et al [71]	France	Observational multicentre study	1,205[d]	NA	50:50	0	6.2	Dental procedures

NA = not available.

a) All children unless otherwise specified.

b) Either undefined or defined a priori by the study authors with exception of Onody, who based definitions on standards from the European Agency for the Evaluation of Medical Products and Zier, who categorized adverse effects as reported by the Pediatric Sedation Research Consortium.

c) Includes 29.471 patients from "pediatric units".

d) Includes adults with intellectual disability and children.

Although large studies show that nitrous oxide is effective, further well-performed double-blinded, randomized controlled trials are needed to compare N_2O with other pharmacological sedatives for painful procedures such as venous puncture, lumbar puncture and intramuscular injection.

This helpful method is still underused in Denmark, and we believe that it could be an alternative or the first choice of treatment in emergency and paediatric departments.

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ACCEPTED: 20 February 2013

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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