In children, nitrous oxide decreases pain on injection of propofol mixed with lidocaine

[Le protoxyde d'azote diminue la douleur de l'injection d'un mélange de propofol et de lidocaïne chez des enfants]

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Purpose: To investigate if 50% nitrous oxide reduces the pain during injection of propofol mixed with lidocaine in children.

Methods: Healthy children undergoing iv induction of general anesthesia for elective surgery were recruited into this prospective, randomized, double-blind study. None of the patients received any premedication except for eutectic mixture of local anesthetics cream. Before induction of anesthesia with propofol 1% mixed with lidocaine 0.05% (propofol dose 3 mg·kg⁻¹), the treatment group received 50% N₂O in O₂ and the control group received 100% oxygen. Pain due to propofol administration was rated with a four-point behavioural scale: none, mild, moderate or severe.

Results: There were 28 subjects in the control group and 26 subjects in the treatment group. Demographic data were similar in both groups. The incidence of pain at induction was 4% after N₂O and 36% in the control group, $P < 0.01$. No patients had severe pain. Most patients had mild pain. Three of the ten patients with pain in the control group had moderate pain. The number needed to treat was 3:1.

Conclusion: Nitrous oxide reduces pain during induction with propofol mixed with lidocaine in healthy children.

(3 mg·kg⁻¹ de propofol), les enfants du groupe expérimental ont reçu un mélange de N₂O et de O₂ à 50 % et les enfants témoins, 100 % d'oxygène. La douleur causée par l'administration de propofol a été cotée selon une échelle en quatre points : aucune douleur, douleur légère, modérée ou sévère.

Résultats : Le groupe témoin comprenait 28 sujets et le groupe expérimental, 26. Les données démographiques étaient comparables entre les groupes. L'incidence de douleur à l'induction a été de 4 % après l'administration de N₂O et de 36 % chez les témoins, $P < 0,01$. Aucun patient n'a éprouvé de douleur sévère. La plupart n'ont subi que de légères douleurs. Trois des dix patients qui ont présenté des douleurs dans le groupe témoin ont eu des douleurs modérées. Le nombre nécessaire pour traiter a été de 3:1.

Conclusion : Le protoxyde d'azote réduit la douleur pendant l'induction de l'anesthésie avec un mélange de propofol et de lidocaïne chez des enfants en bonne santé.

Objectif : Vérifier si du protoxyde d'azote à 50 % peut réduire la douleur de l'injection d'un mélange de propofol et de lidocaïne chez des enfants.

Méthode : Des enfants en bonne santé devant subir l'induction intraveineuse d'une anesthésie générale, pour une intervention non urgente, ont participé à une étude prospective, randomisée et à double insu. Aucun enfant n'a reçu de prémédication, sauf un mélange eutectique de crème anesthésique locale. Avant l'induction de l'anesthésie avec un mélange de propofol à 1 % et de lidocaïne à 0,05

PROPOFOL has many beneficial pharmacodynamic and pharmacokinetic properties. However, one of its major adverse effects is injection pain. Incidence of propofol injection pain in children varies between 28% and 85%.¹ Lidocaine is commonly mixed with propofol to reduce pain of propofol administration. This, however, does not completely remove the pain in all cases. We hypothesized that 50% N₂O in O₂ would further reduce the pain of propofol administration in children.

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Methods

Patient population

With Ethics Committee approval and parental consent, we recruited 54 healthy children (ASA I or II) from three to 12 yr of age, scheduled for elective surgery, for a prospective, randomized, double-blind, controlled study. Patients with known allergy to propofol or its constituents, allergy to local anesthetics, or who refused *iv* induction, or in whom we failed to establish *iv* access before induction were excluded from the study.

Anesthetic management

Eutectic mixture of local anesthetics (EMLA) cream was applied to the dorsum of both hands at least one hour before scheduled operation time. No other premedications were given. Upon arrival at the operating room, an *iv* cannula of 22 or 24 gauge was placed in the dorsum of the subject's hand. A circle system with fresh gas flow of 300 mL·kg⁻¹·min⁻¹ was used for administering the gases. The circuit was primed for 30 sec before use.

Subjects were randomized into two groups, by using a computer generated randomization table: Group A (treatment group) had O₂ and N₂O in equal ratios for two minutes before injection of propofol with 0.05% lidocaine; Group B (control group) had 100% O₂ for two minutes before injection of propofol with 0.05% lidocaine.

Propofol with 0.05% lidocaine was prepared by mixing 0.5 mL of 1% lidocaine with 9.5 mL of propofol, to a total of 10 mL. This was done within half an hour of use. 3 mg·kg⁻¹ of propofol were used for induction. Study gases were administered with a face mask gently held on the subject's face but with an effective seal. The subject was blinded to the gases administered. Propofol was injected rapidly over 20 sec after the gases were given over two minutes. An independent rater blinded to the gases administered, rated pain of propofol administration with the four-point behavioural pain scale proposed by Cameron *et al.*:² 0 = no pain; 1 = mild pain (grimace); 2 = moderate pain (grimace + cry); and 3 = severe pain (cry + withdrawal).

Statistical analysis

Demographic data, such as age, sex, duration of gas administration, propofol injection time, incidence and severity of pain, were analyzed with Chi-square test, Mann-Whitney U test and Student's *t* test. For alpha and beta values of 0.05 and 0.2 respectively, and predicting that the intervention would reduce the incidence of pain due to propofol administration by 20%, the sample size calculated was 54 subjects.

Results

Sixty-three subjects were enrolled into the study. Nine subjects were excluded from the study because of failure to establish *iv* access. Of the remaining 54 subjects, 26 were in the treatment group and 28 in the control group. Demographic data were similar (Table). There was a statistically significant difference in the incidence of pain between the two groups ($P < 0.01$). One (4%) out of 26 subjects in the nitrous oxide group had mild pain. Ten (36%) of the 28 subjects in the control group had pain. Of these, seven subjects had mild pain and three had moderate pain. None of the subjects had severe pain. The number needed to treat was 3:1, i.e., three subjects had to be treated to prevent pain in one subject.

Discussion

Pain associated with propofol administration is an ongoing problem. The exact cause is not known but seems to be related to the effect of propofol on the vascular endothelium. Many strategies to reduce propofol injection pain have been studied, including various combinations of lidocaine with propofol, the use of meperidine, metoclopramide, short acting opioids, non-steroidal anti-inflammatory drugs, different sites of injection, speed of injection, dilution of propofol, changing the temperature of propofol, etc.¹ Lidocaine is the most effective agent in reducing this pain especially if given first with a venous tourniquet inflated to 50 mmHg.^{3,4} The strategy most commonly used clinically, however, is mixing lidocaine with propofol. The amount of lidocaine mixed with propofol varies but in adults, 0.1 mg·kg⁻¹ seems to be effective,⁵⁻⁸ whereas children seem to need about 0.2 mg·kg⁻¹.^{2,9} However, none of these strategies is always successful.

N₂O is a centrally-acting sedative and analgesic agent. It is perhaps not surprising that it should reduce the pain due to propofol injection. N₂O has been used for *iv* cannulation in children^{10,11} and for other short painful procedures both in and outside operating rooms in hospitals.^{12,13} High concentration of N₂O such as 70%,

TABLE Demographic and induction characteristics

	N ₂ O	Control	P value
Age (yr)	6.9 ± 2.1	7.3 ± 2.1	0.59
Male:female	18:8	15:13	0.24
Duration of study	139 ± 35	138 ± 42	0.93
drug administration before propofol injection (sec)			
Duration of propofol administration (sec)	23 ± 9	22 ± 5	0.57

Values are expressed as mean ± standard deviation.

may cause side effects such as excitement, dysphoria, nausea, restlessness and opisthotonic movements,¹⁰ explaining why we chose to use a concentration of 50%. N₂O is widely available and easy to administer. It is inexpensive and relatively free from side effects. At the same time as giving N₂O, 50% of oxygen is also given to the patients. Hence there is some 'preoxygenation'. It may have been possible that a fresh gas flow of 300 mL·kg⁻¹·min⁻¹ was inadequate to ensure that all subjects were breathing 50% N₂O, because the minute volume at increased respiratory rates could exceed this flow rate. In this case, it was more likely that less than 50% of N₂O was administered. So, although this remains a limitation of the study, it should further strengthen our conclusions.

All the subjects in this study had propofol with 0.05% lidocaine. Thirty-six percent of the control group had pain due to propofol injection. This figure is similar to that in adult subjects who received propofol with 0.05% lidocaine in the studies by King and Gajraj.^{5,7}

In the course of the study, we had to exclude nine recruited patients because of failure to establish *iv* access. This is a fairly high failure rate and was possibly due to the vasoconstrictive effect of EMLA cream. We used EMLA cream as it was used in previous studies on propofol injection pain.^{2,9} EMLA cream does not appear to affect the incidence of propofol injection pain but this issue remains unclear. The use of amethocaine gel, which is vasodilating, would have introduced another variable and rendered comparisons with similar studies more difficult.

Assessing pain in children is often difficult and some sort of behavioural or biological method must be used. We chose to use the scale devised by Cameron *et al.*^{2,14} because it had been used for similar studies.

In conclusion, 50% nitrous oxide markedly reduces the pain due to the administration of a propofol-lidocaine admixture in healthy children. There was a fairly high incidence of pain in the control group although the pain was only mild to moderate.

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