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Patient-Administered Nitrous Oxide/Oxygen Inhalation Provides Safe and Effective Analgesia for Percutaneous Liver Biopsy: A Randomized Placebo-Controlled Trial

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OBJECTIVE: Although percutaneous liver biopsy (PLB) can be a painful procedure, common practice has not included intravenous sedation or analgesia. Patient-administered nitrous oxide/oxygen (N_2O/O_2) inhalation has demonstrated analgesic efficacy in various procedures associated with mild to moderate pain. The aim of this study was to investigate the safety and efficacy of analgesia with N_2O/O_2 inhalation for PLB.

METHODS: One hundred consecutive patients undergoing a first PLB (for chronic hepatitis C: 56, for alcoholic liver disease: 23, for miscellaneous reasons: 21). Patients were randomly assigned to self-administrate from a facial mask with a demand valve, for 5 min before and during biopsy, either a breathing mixture of 50% N_2O/O_2 (N_2O group, n = 51), or a breathing oxygen placebo (P group, n = 49). Liver biopsy was performed at bedside after adequate local anesthesia with xylocaine. At the end of the procedure, patients were asked to self-evaluate pain experienced using a visual analogue scale (VAS) with scoring from 0 to 100 mm.

RESULTS: N_2O/O_2 administration resulted in the absence of pain in a significantly higher number of patients treated than in patients of the P group: 19 *versus* 2, respectively ($p = 0.0001$). Patients receiving N_2O/O_2 had significantly lower pain scores than those of the P group: 12 ± 12 *versus* 28 ± 19 mm ($p < 0.0001$). No serious complication was observed. Side effects of N_2O/O_2 were minor and reversible. The average cost per biopsy was 4 US dollars.

CONCLUSIONS: Patient-administered N_2O/O_2 inhalation provides safe and effective analgesia, at a reasonable cost, for PLB. Its routine use could be useful for the management of patients with chronic liver disease undergoing PLB as it may enhance patients compliance with future biopsies. (Am J Gastroenterol 2001;96:1553–1557. © 2001 by Am. Coll. of Gastroenterology)

INTRODUCTION

Percutaneous liver biopsy (PLB) is a well-established procedure, widely used in clinical practice for the diagnosis of liver diseases. In experienced hands, its morbidity is low (1, 2). Although it is invasive and usually considered painful by patients, PLB is performed by many physicians without preprocedure sedation or systemic analgesia, as it may hinder patient cooperation for breath-holding during the procedure (3). However, in a recent pilot study aimed at grading the intensity of pain experienced during PLB by means of a visual analogue scale (VAS) scoring from 0 to 100 mm, we observed that the mean pain score was close to 30 mm and that 20% of patients experienced severe pain (*i.e.*, VAS $>$ 40 mm) (4). These data suggest that pain experienced during percutaneous liver biopsy should be taken into consideration and that patients should be provided adequate prophylactic analgesia.

A gaseous mixture of 50% nitrous oxide and oxygen (N_2O/O_2), originally introduced for use by women in labor, has demonstrated its analgesic efficacy and safety in various procedures associated with mild to moderate pain, including minor surgery (5, 6), emergency transportation (7–9), venous canulation (10), colonoscopy (11, 12), and dentistry (13). It is fast acting, with analgesia noted approximately 60 s after inhalation and of short duration of action, most of the gas being eliminated via the lungs in 1 to 5 min (14). It can be easily self-administered by the patient under the supervision of a trained nurse, allowing the patient to follow instructions and to cooperate for respiratory movements. As a result of these properties, N_2O/O_2 seems to be a suitable analgesic for use in PLB.

We conducted a randomized placebo-controlled study aimed at investigating the analgesic efficacy and safety of patient-administered N_2O/O_2 inhalation for PLB.

MATERIALS AND METHODS

Patients

The study was carried out during a 6-month period in the Hepatology unit of Bicêtre hospital. All patients over 18 yr old undergoing a first PLB were eligible. They were enrolled after written informed consent was obtained. The study protocol conformed to the ethical guidelines of the

1975 Declaration of Helsinski and was approved by the ethics committee of our institution.

Exclusion criteria were as follows: 1) clotting disorders, such as prothrombin levels less than 50% of normal, or Kaolin-activated partial thromboplastin time exceeding 1.5 times normal control time, or platelet count below 10^5 per cubic millimeter, or Ivy's bleeding time exceeding 4 min; 2) abdominal ultrasound revealing a contraindication such as intrahepatic bile duct dilation, focal liver lesion, hydatid disease, or massive ascites; 3) ongoing analgesic treatment; 4) comprehension difficulty; 5) psychiatric disturbance; and 6) contraindications to nitrous oxide administration such as pulmonary emphysema and chronic respiratory failure.

Protocol

Before starting the procedure, patients were taught in a standard way by the same assessor how to use a validated 100-mm VAS to grade the intensity of pain experienced during biopsy (15, 16). On that scale, the left endpoint, 0, was defined as no pain, the right endpoint, 100, as the worst pain the patient could imagine. There were no further marks on the line. The intensity of pain was indicated by the distance in millimeters from the left endpoint.

After grading of anxiety using VAS (0 = totally calm; 100 = extremely anxious), patients were randomized (using random numbers) to receive during biopsy either 1) a breathing mixture of equal parts of nitrous oxide and oxygen (Air Liquide Santé, Paris, France) (N_2O group) or 2) a breathing oxygen placebo (P group). Gas was self-administered by the patient from a facial mask with a demand valve (Robertshaw valve) so that the gas did not flow unless a negative pressure was applied to the inspiratory port. If the patient became drowsy, his grip on the mask would relax, thus breaking the airtight seal, and consequently, gas flow would stop. Gas (*i.e.*, mixture or placebo) was administrated 5 min before and during biopsy under the control of a nurse unaware of randomization group.

PLB was performed at bedside by the same senior operator according to the Menghini technique (17) using a 1.8-mm-diameter needle (Hepafix, Braun, Melsungen, Germany) after local anesthesia with 10 ml xylocaine 1% (*i.e.*, infiltrated first subcutaneously, then into the intercostal area, and finally down to the diaphragm and capsule of the liver, care being taken to infiltrate each layer adequately). At the end of the procedure, gas administration was discontinued. Once the effect of gas administration had disappeared, patients were asked by a nurse unaware of randomization group to grade on VAS the intensity of pain and discomfort experienced during biopsy (D0). They were asked the same question the next day at discharge (D1) by a nurse unaware of randomization group to take into account the recollection of pain experienced during biopsy. They were also asked to report incidents such as nausea, vomiting, headache, and dysphoria.

After procedure, patients were required to remain recumbent for at least 6 h after biopsy. Their vital signs were monitored as for a conventional liver biopsy (*i.e.*, every 15 min for 1 h, every 30 min for the next 2 h, then every hour for the next 3 h). Cost of N_2O/O_2 use was also considered.

Table 1. Clinical Characteristics of the Patients (Mean ± SD) and Anxiety Scores Measured Before the Biopsy by VAS

Characteristics	N_2O Group (n = 51)	P Group (n = 49)	*p*
Age (yr)	46 ± 13	42 ± 11	NS
Sex ratio (M/F)	26/25	34/15	NS
Indications			
Chronic hepatitis C	29	27	NS
Alcoholic liver disease	10	13	NS
Others	12	9	NS
Anxiety (VAS)	35 ± 30	35 ± 30	NS

NS = not significant.

Statistical Analysis

Data were expressed as mean ± SD for VAS and age. The two groups were compared by the χ^2 test or Fischer's exact test for qualitative variables and by Mann-Whitney nonparametric test for VAS. Correlation between pain scores at D0 and at D1 were done using Spearman's test. A p value < 0.05 was considered significant.

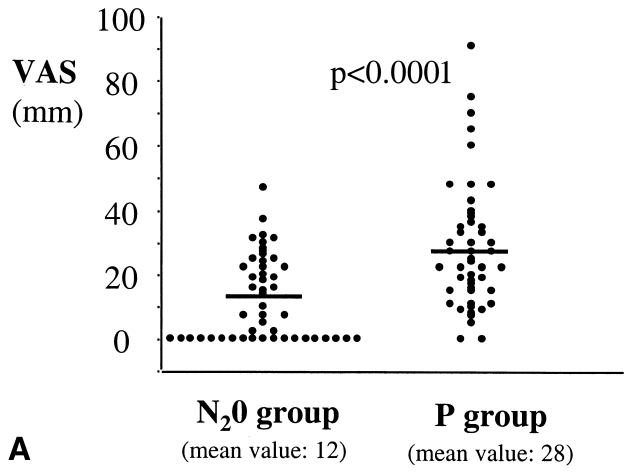
RESULTS

One hundred consecutive patients (N_2O group: n = 51, P group: n = 49) were enrolled. There were 60 male and 40 female patients (mean age: 44.4 ± 12.5 yr; range: 21–77 yr). None of the patients had clinical or biological evidence of liver failure. Indications for liver biopsy were as follows by number of patients: chronic hepatitis C, 56; alcoholic liver disease, 23; miscellaneous, 21 (this category included the following diagnoses: nonalcoholic steatosis: five patients, drug-induced hepatitis: four patients, hemochromatosis: three patients, unexplained hepatic tests abnormalities: three patients, chronic hepatitis B: two patients, autoimmune hepatitis: one patient, primary sclerosing cholangitis: one patient, idiopathic portal hypertension: one patient, light-chain deposition disease: one patient). Both groups were similar with respect to age, sex ratio, indication for liver biopsy, and anxiety before procedure (Table 1).

VAS pain scores (mean ± SD) are presented in Table 2. For each group, mean pain scores were similar at D0 and D1: N_2O group, 12 ± 12 mm at D0 and 14 ± 18 mm at D1 ($r = 0.84$, $p < 0.0001$); P group, 28 ± 19 mm at D0 and 31 ± 22 mm at D1 ($r = 0.66$, $p < 0.0001$). N_2O/O_2

Table 2. Pain Scores Measured by VAS, Given as Mean ± SD (Range)

Pain Measurement Day	N_2O Group (n = 51)	P Group (n = 49)	*p*
D0	12 ± 12 (0–47)	28 ± 19 (0–91)	<0.0001
D1	14 ± 18 (0–51)	31 ± 22 (0–95)	<0.0001



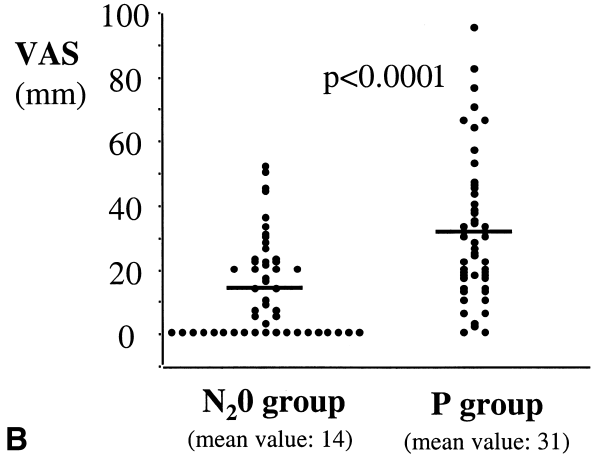


Figure 1. (*A*) Pain scores measured in millimeters by visual analog scale (VAS) at the end of procedure (D0) in the two groups. Dots represent individual data, and bars, mean values. (*B*) Pain scores measured in millimeters by VAS the next day (D1) in the two groups. Dots represent individual data and bars, mean values.

administration resulted in the absence of pain (VAS = 0) in a significantly higher number of patients treated than in patients of the placebo group at D0 and at D1: 19 *versus* 2 ($p = 0.0001$; Fig. 1). In patients of the N_2O group, pain scores were significantly lower than in patients of the placebo group at D0 (12 ± 12 *vs* 28 ± 19 mm; $p < 0.0001$) and at D1 (14 ± 18 *vs* 31 ± 22 mm; $p < 0.0001$); only one patient (2%) experienced severe pain (*i.e.*, VAS > 40 mm), as compared with nine (18%) in the placebo group ($p < 0.02$).

Incidence of side effects and complications is reported in Table 3. None of the patients developed severe complication. Side effects observed with N_2O/O_2 were all minor (headache in three patients, dysphoria in two patients, and nausea in one patient) and reversible once administration ended. Two transient vasovagal reactions were observed in the placebo group.

The cost of N_2O/O_2 use was estimated as follows: a 1.4-m^3 cylinder of N_2O/O_2, which allowed treatment of 20 patients, cost 80 US dollars. Therefore, the average cost per biopsy was 4 US dollars.

Table 3. Side Effects and Complications Observed in the Two Groups

Complication	N_2O Group (n = 51)	P Group (n = 49)
Nausea	1	0
Vomiting	0	0
Headache	3	2
Dysphoria	2	0
Vasovagal reaction	0	2
Serious complication (bleeding)	0	0

DISCUSSION

Over the past decade, the importance of PLB for diagnosis, therapeutic decisions, and monitoring has grown considerably. Chronic liver diseases, and especially chronic hepatitis C, represent the main indication for PLB (18). With over 160 million people infected by hepatitis C virus worldwide (19), with new treatment options becoming available (20–22), and with the need to repeat liver biopsy during follow-up of patients with chronic liver disease, it is likely that the number of PLB will continue to increase in the near future. So far, the standard patient preparation for PLB includes only local anesthesia (3, 23–25). Although intravenous sedation with midazolam may be given safely in frightened patients (26, 27), its use in clinical practice has remained rather limited since (18). Sedation is not routinely given because it may interfere with patients' cooperation and possibly increase the complication rate and also because pain experienced during PLB is deemed minor by most physicians. However, analysis of the placebo group in this study has shown unacceptable high pain scores despite adequate local anesthesia with xylocaine, with 18% of patients experiencing severe pain, a finding in keeping with the results of our previous pilot study (4). Moreover, a significant degree of anxiety, with a mean score close to 40 on VAS, was observed before procedure in both groups of patients. Such experiences often limit the willingness of patients with chronic liver disease, particularly those with hepatitis C who are young and asymptomatic, to undergo subsequent follow-up biopsies.

The results of the present study, conducted on a large cohort of patients undergoing PLB, many of them for chronic hepatitis C, show that patient-administered N_2O/O_2 inhalation provides safe and excellent analgesia. Evaluation of patients' pain was performed using VAS, which is the validated and recommended method for pain assessment (11, 15, 16). Similarity in mean pain scores in each group at D0 and D1 confirms the reproducibility of our results and that N_2O/O_2 use did not result in amnesia of pain. Although we did not use a double-blinded design, confidence in results can be considered similar to that of a double-blind study because the gas mixture was self-administrated by

blinded patients with self-assessment of the pain they experienced. We chose to compare N_2O/O_2 to a placebo because of the significant differences observed in clinical practice with respect to sedation for PLB and also because of the lack of standardized protocols between institutions (18, 28). The monitoring of patients after biopsy included a stay overnight at the hospital, a common practice in France, as shown in a recent survey (29).

An important issue for the use of sedation during PLB is patient cooperation because an untoward movement when the biopsy needle is in the hepatic parenchyma can lead to a tear of the liver and capsula and subsequent torrential bleeding (3). Interestingly, N_2O/O_2 inhalation through a demand valve, safeguarding the patients from relative overdose of the gas, allowed them to cooperate with breath-holding and to follow the instructions given by the physician during PLB, and it was not associated with an increased risk of procedure-related complications. Indeed, none of the patients in our study developed severe complication.

Side effects observed with N_2O/O_2 were all minor and reversible once administration ended, as reported elsewhere (10, 12). When mixed with equal parts of oxygen to avoid hypoxia, nitrous oxide does not cause respiratory or cardiovascular depression and does not impair protective reflexes (30). It has been shown to be safe even under adverse cardiac conditions (31). Its low blood and fat solubility is responsible for its relatively low anesthetic potency, with a rapid onset of action and a fast recovery once the inhalation stops (14). Furthermore, nitrous oxide is considered to be physiologically inert: the absence of hepatic or renal metabolism does not lead to accumulation of active metabolites and therefore allows its use in patients with chronic liver disease. However, fears have been raised about the long-term risks of nitrous oxide for medical personnel. Chronic exposure to nitrous oxide can cause impairment of the vitamin B12–dependent enzyme methionine synthetase, which may in turn result in bone marrow depression, megaloblastic changes, and neurological dysfunction (32, 33). These problems have been documented only in abusers of nitrous oxide or in medical personnel chronically exposed to high concentrations of nitrous oxide used for anesthesia. There should be no hazard in a well-ventilated hepatology unit, but regular monitoring of atmospheric gas concentration would nonetheless be a wise precaution.

In our experience, N_2O/O_2 presented other outstanding advantages: 1) its administration does not require the presence of an anesthetist and can be conducted at bedside, under the supervision of a trained nurse; 2) its limited contraindications allow for widespread use; 3) and its use remains cheap, with an average cost of 4 US dollars per biopsy. The investment of 700 US dollars required for the delivery equipment regulator, Robertshaw valve, and facial mask can be redeemed rapidly, particularly if shared among several hospital facilities.

In conclusion, the results of our study suggest that patient-administered N_2O/O_2 inhalation provides safe and effective analgesia at a reasonable cost for PLB. Its routine use could be useful for the management of patients with chronic liver disease undergoing PLB, as it may enhance patients' compliance with future biopsies.

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REFERENCES

1. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy—a multicentre retrospective study on 68276 biopsies. J Hepatol 1986;2:165–73.
2. Perrault J, McGill DB, Ott BJ. Liver biopsy: Complications in 1000 inpatients and outpatients. Gastroenterology 1978;74: 103–6.
3. Grant A, Neuberger J. Guidelines on the use of liver biopsy in clinical practice. Gut 1999;45(suppl 4):IV1–11.
4. Castéra L, Nègre I, Samii K, Buffet C. Pain experienced during percutaneous liver biopsy. Hepatology 1999;30:529–30.
5. Gamis AS, Knapp JF, Glenski JA. Nitrous oxide analgesia in a pediatric emergency department. Ann Emerg Med 1989;18: 177–81.
6. Griffin GC, Vance D, Campbell F, Jones R. Nitrous oxide-oxygen sedation for minor surgery. Experience in a pediatric setting. JAMA 1981;245:2411–3.
7. Thal E, Montgomery S, Atkins B, Roberts WG. Self-administered analgesia with nitrous oxide. JAMA 1979;242:2418–9.
8. Baskett PJF. Nitrous oxide in pre-hospital care. Acta Anaesthesiol Scand 1994;38:775–6.
9. Baskett PJF, Bennett JA. Pain relief in hospital: The more widespread use of nitrous oxide. BMJ 1971;2:509–11.
10. Henderson JM, Spence DG, Komocar LM, et al. Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. Anesthesiology 1990;72:269–71.
11. Lindblom A, Jansson O, Jeppsson B, et al. Nitrous oxide for colonoscopy discomfort: A randomized double-blind study. Endoscopy 1994;26:283–6.
12. Saunders BP, Fukumoto M, Halligan S, et al. Patient-administered nitrous oxide/oxygen inhalation provides effective sedation and analgesia for colonoscopy. Gastrointest Endosc 1994;40:418–21.
13. Weinsten P, Donato P, Holleman E. The use of nitrous oxide in the treatment of children: Results of a control study. J Am Dent Assoc 1986;112:325–31.
14. Marshall B, Wollman H. General anesthesia. In: Gilman A, Goodman L, Rall T, eds. The pharmacologic basis of therapeutics, vol 7. New York: MacMillan, 1985:89–92.
15. Maxwell C. Sensitivity and accuracy of the visual analogue scale. Br J Clin Pharmacol 1978;6:15–8.
16. Price DD, McGrath P, Rafii A, Buckingham B. The validation

of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17:45–56.
17. Menghini G. One second biopsy of the liver: Problem of its clinical application. N Engl J Med 1970;283:582–5.
18. Gilmore IT, Burroughs A, Murray-Lyon IM, et al. Indications, methods and outcomes of percutaneous liver biopsy in England and Wales: An audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut 1995;36:437–41.
19. Hepatitis C. Wkly Epidemiol Rec 1997;72:65–9.
20. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1493–9.
21. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485–92.
22. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998; 352:1426–32.
23. Sherlock S, Dooley J. Needle biopsy of the liver. Diseases of the liver and biliary system. Oxford, UK: Blackwell Scientific, 1993.
24. Lebrec D. Various approaches to obtaining liver tissue—choosing the biopsy technique. J Hepatol 1996;25(suppl):20S–4S.
25. Degos F, Degott C, Benhamou JP. Biopsie hépatique. In: Benhamou JP, Bircher J, McIntyre N, et al., eds. Hépatologie clinique. Paris: Flammarion Médecine-Sciences, 1993: 320–4.
26. Alexander JA, Smith BJ. Midazolam sedation for percutaneous liver biopsy. Dig Dis Sci 1993;38:2209–11.
27. Brouillette DE, Yoo YK, Chien MC, et al. Use of midazolam for percutaneous liver biopsy. Dig Dis Sci 1989;34:1553–8.
28. Sue M, Cadwell SH, Dickson RC, et al. Variation between centers in technique and guidelines for liver biopsy. Liver 1996;16:267–70.
29. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: Results of a prospective nationwide survey. Hepatology 2000;32:477–81.
30. Baskett PJF, Eltringham RJ, Bennett JA. An assessment of oxygen tensions obtained with pre-mixed 50% nitrous oxide and oxygen mixture (Entonox) used for pain relief. Anaesthesia 1973;28:449–50.
31. Kerr F, Hoskins MR, Brown MG, et al. A double-blind trial of patient controlled nitrous oxide/oxygen analgesia in myocardial infarction. Lancet 1975;1(7922):1397–400.
32. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B12. Br J Anaesthesiol 1987;59:3–13.
33. Koblin DD, Waskell L, Watson JE, et al. Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75–8.