Scandinavian Journal of Pain 7 (2015) 28–34

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Clinical pain research

Nitrous oxide analgesia for bone marrow aspiration and biopsy – A randomized, controlled and patient blinded study

Anna-Maria Kuivalainen[a,*], Freja Ebeling[b], Eira Poikonen[b], Per H. Rosenberg[a]

[a] Department of Anaesthesiology and Intensive Care Medicine, University of Helsinki, PO Box 20, FIN-00014 Helsinki, Finland
[b] Cancer Center, Division of Haematology, Helsinki University Central Hospital, PO Box 372, FIN-00029 HUS Helsinki, Finland

HIGHLIGHTS

- Bone marrow sampling is a painful procedure.
- Inhaled 50% N_2O was not a better analgesic than 50% O_2 during the procedure.
- Patients in both groups were equally satisfied with the analgesia method.
- Nitrous oxide inhalation was safe and did not cause any serious adverse effects.

ARTICLE INFO

Article history:
Received 26 October 2014
Received in revised form
28 December 2014
Accepted 5 January 2015

Keywords:
Nitrous oxide
Bone marrow examination
Pain
Anxiety

ABSTRACT

Background and aims: Bone marrow aspiration and/or biopsy (BMAB), performed under local anaesthesia in adults, is a common and often painful procedure. Anxiety is known to intensify pain during the procedure. Nitrous oxide (N_2O), known for its sedative and analgesic benefit in various short medical procedures and labour pain, could be advantageous also for pain relief during bone marrow examination. N_2O acts rapidly and is eliminated in a couple of minutes once the inhalation is stopped, and occasional side effects (e.g. dizziness and nausea) are mild. The aim of this study was to compare the analgesic effects of inhaled 50% mixture of nitrous oxide and oxygen to 50% oxygen during bone marrow examination.

Methods: In this randomized, controlled, patient and observer blinded study patients received either 50% mixture of nitrous oxide and oxygen or 50% mixture of oxygen in air during bone marrow examination, in addition to local analgesia. Both patient groups comprised 35 adult patients. Pre-procedural anxiety and procedural pain were rated on the Numeral Rating Scale (NRS 0–10). Cognitive function was measured before and 30 min after the procedure. Possible side effects were recorded. A telephone interview was performed 24 h later.

Results: There were no statistically significant differences in pain scores of the procedural steps (median NRS ranging 3.0–4.0) between the study groups. High pain scores of 8–10 comprised 0% vs. 8.6% of the scores during infiltration, 2.9% vs. 5.7% during puncture, 11.4% vs. 14.3% during aspiration and 2.9% vs. 2.9% during biopsy in N_2O and 50% O_2 groups, respectively (NS). Pre-procedural anxiety (median NRS 3.5 in both groups), measured in the outpatient clinic just prior to procedure, correlated with pain intensity during bone marrow aspiration ($P = 0.045$). There were no significant differences between side effects. During the BMAB four patients (3 in N_2O group, 1 in 50% O_2 group) reported dizziness and one patient in the N_2O group reported nausea. Gas inhalation did not affect the cognitive function of the participants. In both groups the majority (>80%) of the patients was satisfied with the inhalation technique. During the 24 h interview, most of the participants were pain free and they did not report any serious adverse effects.

Conclusions: In spite of similar moderate to strong procedural pain in both groups and no benefit of N_2O, most patients were satisfied with the inhalational techniques. We assume that the bedside presence of an anaesthesiologist and the distraction caused by the inhalational arrangements introduced positive context-sensitive therapeutic effect independent of the gas used. Pre-procedural anxiety predicted pain associated with bone marrow aspiration.

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2015.01.008.
* Corresponding author. Tel.: +358 50 427 2805; fax: +358 9 47174017.
E-mail addresses: anna-maria.kuivalainen@helsinki.fi (A.-M. Kuivalainen), freja.ebeling@hus.fi (F. Ebeling), eira.poikonen@hus.fi (E. Poikonen), per.rosenberg@hus.fi (P.H. Rosenberg).

http://dx.doi.org/10.1016/j.sjpain.2015.01.001

Implications: Inhaled 50% nitrous oxide was not an effective analgesic during bone marrow examination in our unselected outpatient population. Further studies should concentrate on its use with patients predicted to be at increased risk of suffering intense pain during the procedure, such as very anxious patients or those who have a painful history of previous bone marrow examinations.

1. Introduction

Analgesia for bone marrow aspiration and/or biopsy (BMAB) in adults is usually provided by local infiltration anaesthesia alone. The bone and bone marrow are poorly anaesthetized and therefore BMAB is often painful [1,2]. Anxiety and fear are known to increase the pain associated with BMAB [1,3]. Premedication with sedatives [4,5] and various analgesics [6,7] have been found to attenuate, but not eliminate pain during BMAB.

During various minor diagnostic or therapeutic medical procedures N_2O has been shown to be an effective analgesic [8,9]. It is widely used during labour as well [10,11] but its analgesic efficacy varies [11]. Its anxiolytic efficacy has been demonstrated during dental procedures [12], intravenous cannulations [13], and in women undergoing Caesarean section under spinal anaesthesia [14]. The analgesic mechanism of nitrous oxide may be mediated by activation of opioid receptors and descending antinociceptive pathways; the anxiolytic effect may be mediated with activation of $GABA_A$ receptors [15]. Nitrous oxide has a fast onset of action [16] due to its low solubility in blood and adipose tissue [17]; in addition, inspiratory and alveolar partial pressures equilibrate rapidly. It is quickly eliminated to the alveoli and further to the exhaled air after the inhalation is ceased. The side effects are usually minor including headache, dizziness and sometimes nausea. With higher concentrations (>70%) diffusion hypoxaemia may occur when the N_2O inhalation is ceased.

Nitrous oxide has been effective in paediatric patients during various medical procedures, including BMABs [18]. Promising results have also been reported in adults undergoing BMAB [19–21]. However, these studies have been relatively small and only one of them [19] was randomized, blinded and placebo-controlled. Thus, to enable evidence-based use of nitrous oxide during BMAB, more clinical data are needed.

The aim of this study was to find out if inhalation of a 50% mixture of N_2O and oxygen is effective in relieving procedural pain during BMAB compared to 50% oxygen. The primary outcome was pain intensity during BMAB. The secondary outcome was the occurrence of any side effects, such as nausea, dizziness or headache.

2. Methods

The ethics committee of Helsinki and Uusimaa Hospital District approved the study (Diary number 323/13/03/01/2012). The Finnish Medicines Agency (Fimea) was notified of the study. The EudraCT number of the study is 2012-004285-18 (https://www.clinicaltrialsregister.eu/ctr-search/search). The patient data were collected between May 2013 and March 2014 in two outpatient clinics of the Division of Haematology of the Helsinki University Hospital.

2.1. Patients and blinding

Outpatients from the Division of Haematology undergoing bone marrow aspiration and/or biopsy were considered for inclusion. Patients having unstable coronary artery disease, emphysema or chronic obstructive pulmonary disease, pneumothorax, Alzheimer's disease or dementia, or obesity (body mass index > 32 kg/m^2) were excluded. Inability to speak and understand Finnish or Swedish led to exclusion as well. The other reasons leading to exclusion and the flow of patients are presented in Fig. 1. There were no losses after randomization and thus the whole patient data was analyzed.

The sample size was based on a previous randomized study showing analgesic superiority of a 50% mixture of N_2O and O_2 over placebo (O_2) in adult males undergoing BMAB [19]. The patient material consisted of 48 patients. In order to enhance power and provide substitution for possible dropouts, we decided to recruit 70 patients, 35 patients to both groups.

One of the researchers phoned the patients on the previous day and informed them about the study. After arrival at the outpatient clinic, the patient received further written information and patients willing to participate gave their informed, written consent. The randomization was performed using sealed envelopes. Each envelope contained a randomization key (nitrous oxide or 50% oxygen). After the key was inserted, the envelope was sealed and then the

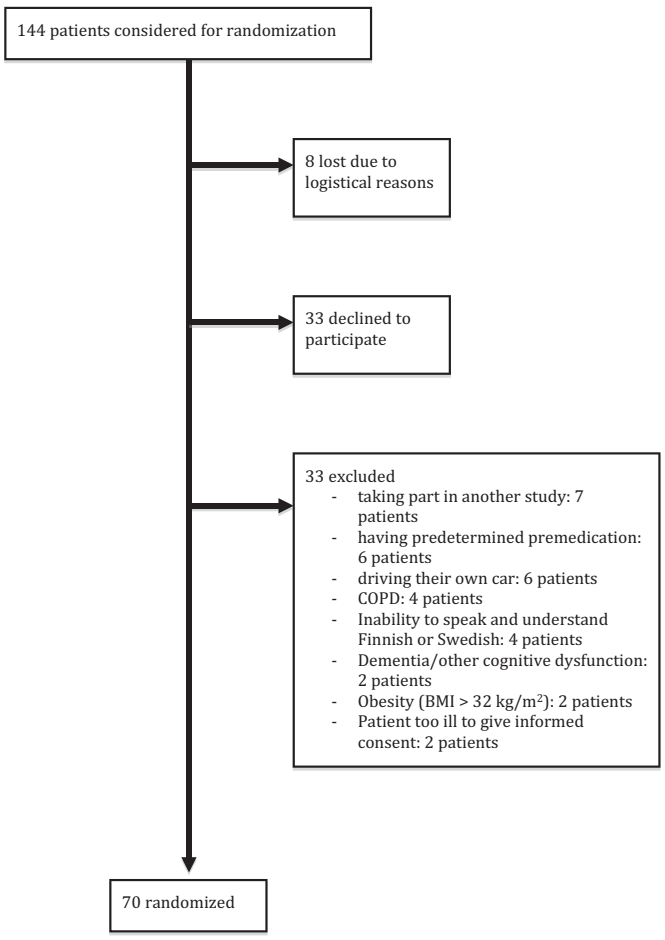

Fig. 1. The flow chart.