ORIGINAL ARTICLE

Efficacy of the methoxyflurane as bridging analgesia during epidural placement in laboring parturient

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ABSTRACT

Background: Establishing an epidural in an agitated laboring woman can be challenging. The ideal pain control technique in such a situation should be effective, fast acting, and short lived. We assessed the efficacy of inhalational methoxyflurane (Penthrox™) analgesia as bridging analgesia for epidural placement. **Materials and Methods:** Sixty-four laboring women who requested epidural analgesia with pain score of ≥7 enrolled in an observational study, 56 of which completed the study. The parturients were instructed to use the device prior to the onset of uterine contraction pain and to stop at the peak of uterine contraction, repeatedly until epidural has been successfully placed. After each (methoxyflurane inhalation-uterine contraction) cycle, pain, Richmond Agitation Sedation Scale (RASS), nausea and vomiting were evaluated. Maternal and fetal hemodynamics and parturient satisfaction were recorded. **Results:** The mean baseline pain score was 8.2 ± 1.5 which was reduced to 6.2 ± 2.0 after the first inhalation with a mean difference of 2.0 ± 1.1 (95% confidence interval 1.7-2.3, $P < 0.0001$), and continued to decrease significantly over the study period ($P < 0.0001$). The RASS scores continuously improved after each cycle ($P < 0.0001$). Only 1 parturient from the cohort became lightly sedated (RASS = −1). Two parturients vomited, and no significant changes in maternal hemodynamics or fetal heart rate changes were identified during treatment. 67% of the parturients reported very good or excellent satisfaction with treatment. **Conclusion:** Penthrox™ provides rapid, robust, and satisfactory therapy to control pain and restlessness during epidural placement in laboring parturient.

Key words: *Epidural analgesia, labor pain, methoxyflurane inhalation*

INTRODUCTION

Pain during the advanced stage of labor is often severe.[1] An epidural is the most effective method of relieving labor pain.[2] However, its safe placement requires the women to be cooperative and in a stable position. Establishing an epidural in a distressed and restless woman is a technical challenge for the anesthesiologist and one of the major causes of failure. Strict aseptic precautions may be breached, and complications of epidural placement (such as unintentional dural puncture) are more likely to happen if the mothers cannot maintain a steady posture during the procedure.

Methoxyflurane is an inhalational anesthetic, which in lower (sub-anesthetic) concentrations has analgesic properties.[3,4] We hypothesized that it might be useful to provide short lived analgesia during epidural placement. Inhalational methoxyflurane labor analgesia (Penthrane™ - Abbott Laboratories) was practiced in late 1960s and 1970s.[5] Concern about its nephrotoxic metabolites at general anesthetic concentrations and the concomitant emerging popularity of epidural analgesia during this period caused the decline of the methoxyflurane analgesia for the labor pain.[6] However, many studies have shown that the nephrotoxic effect of methoxyflurane is relevant only at higher anesthetic concentrations when used for many hours.[7,8] Whereas, for a relatively short period, it is thought to be safe and has been recently released for short term pain treatment in Australia.[9]

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Methoxyflurane is self-administered under observation (and assisted if necessary) using the hand-held Penthrox™ Inhaler (Medical Development International limited, Victoria, Australia).[10] Effective methoxyflurane analgesia has been used for various painful procedures, such as during minor surgery,[11] burn dressings,[12] bone fracture,[13] dental procedures,[14] and for management of acute pain in the prehospital,[15] military,[16] emergency search and rescue and industrial setting[17] in Australia.

Because of its good past safety record, simplicity and ease of administration of Penthrox™ device, we hypothesized that the use of self-administered methoxyflurane during placement of an epidural catheter would be useful to attenuate the parturient's pain and resulting restlessness, which in turn would help the anesthesiologist placing the epidural. Therefore, we conducted a prospective observational study to evaluate efficacy in comforting the laboring mother while anesthesiologist is performing her epidural.

MATERIALS AND METHODS

After Institutional Review Board approval (# 325/2007) and parturient written consent, we conducted a prospective observational study in Prince Sultan Military Medical City, Riyadh, Saudi Arabia. Sixty-four consecutive laboring women with full term pregnancies, who requested for epidural analgesia for painful labor (with visual analogue pain score ≥7) and have not had parenteral analgesia for labor pain, were included in this study. Parturients were excluded from the study if they did not understand or were unable to use the methoxyflurane inhaler, or had an absolute contraindication to the epidural. Parturients with preeclampsia, renal disease or a history of recent drug intake of antibiotics, diuretic or enzyme inducer or with premature or growth restricted fetus' were also excluded from the study.

Methoxyflurane administration

Penthrox™ is a prepared analgesic system that consists of a hand-held inhaler, which is a small, lightweight, disposable, cylindrical polyethylene device with distinctive green color, which looks like a whistle. From inside, the device contains a wick, which absorbs the liquid methoxyflurane. At one end is a mouthpiece [Figure 1]. A one-way valve internally allows air and methoxyflurane to be inhaled through the wick. The valve closes with respiratory expiration to prevent exhalations passing back through the wick and into the atmosphere. Through the other end of the device, 3.0 ml of methoxyflurane liquid is poured in, which is absorbed by the wick. The delivered methoxyflurane concentrations are 0.2-0.4% when the diluter hole open and 0.5-0.7% when it is covered.[10] The patients were instructed to occlude the devise hole.

Study protocol

A standard intravenous infusion (NaCl 0.9%) and patient monitoring (heart rate, blood pressure and pulse oximeter) were established. The patient was sitting for the epidural procedure. The first sets of observations (pain, restlessness, drowsiness, nausea, and vomiting) were made 30 s after the cessation of contraction that precedes the first methoxyflurane inhalation. Parturients were provided with one inhaler containing 3 ml methoxyflurane and with practice inhaler and shown how to self-administer methoxyflurane with the device. She was told that, on the instruction from the midwife, she should start and stop the methoxyflurane inhalation, and that this might make her feel dizzy. The midwife (who has had tutorial about Penthrox™ inhaler) instructed the patient to start methoxyflurane 30-40 s before the onset of anticipated uterine contraction and stop after the peak of the contraction is over. Meanwhile the anesthesiologist, standing at the back of the patient, started the epidural procedure. Under full aseptic precautions, the skin was cleaned (with chlorhexidine 0.5% + alcohol 70%), the spine is palpated to identify suitable lumbar inter-spinous space and the skin, and deeper tissues were infiltrated with 1.0% lidocaine The Touhy epidural needle was inserted through the anaesthetized skin into the inter-spinous ligament until loss of resistance to saline or air was identified. During the contraction, advancement of the needle was stopped till the contraction was over. Verbal contact with the mother is maintained throughout the procedure.

Outcome measurements

The primary outcome was the change in pain intensity (during uterine contraction) after Penthrox™ administration which was measured with numerical rating score (NRS) scale, with 0 meaning no pain and 10 meaning the worst pain the patient could imagine.

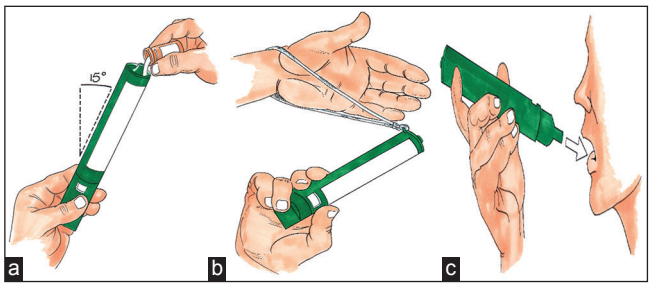

Figure 1: Manufacture illustration for the devise use. (a) Tilt Penthrox™ Inhaler and slowly pour contents of 3 ml Penthrox™ bottle into base while rotating then shake it lightly. (b) Place wrist loop around patient's wrist. (c) Patient self-administers by placing mouthpiece into mouth

Secondary outcomes:

- Parturient restlessness and consciousness levels throughout the treatment period, using the Richmond Agitation Sedation Scale (RASS)[18] as: +4 = Combative, +3 = very agitated, +2 = agitated, +1 = restless, 0 = alert and calm, −1 = drowsy, −2 = light sedation, −3 = moderate sedation, −4 = deep sedation, and −5 = unarousable.
- Nausea and vomiting scored as: 0 = No nausea, no vomiting, 1 = nausea without vomiting, 2 = nausea with vomiting, <3 times, and 3 = nausea with vomiting, >3 times.[19]
- Maternal hemodynamics and oxygen saturation recorded using the noninvasive blood pressure cuff and oximeter. Before the procedure, three readings were taken and averaged to determine the baseline. 10% drop from the baseline was considered clinically significant, and 20% mandated vasopressor treatment.
- Fetal heart rate was recorded before commencing and after the last contraction cycle with the methoxyflurane analgesia.
- After establishing the epidural labor analgesia, parturients were asked to give a score for satisfaction with Penthrox™ administration as 1 = Poor, 2 = Fair, 3 = Good, 4 = Very Good, and 5 = Excellent.

The first set of observations was taken before the commencement of the methoxyflurane inhalation while subsequent sets were completed, 30 s after cessation of each uterine contraction and methoxyflurane inhalation. Cyclic methoxyflurane inhalations and observations were continued till the epidural catheter is inserted, and epidural needle is withdrawn. The attending midwife, who was unaware of the purpose of data collection made the observations.

Statistical analysis

An interim analysis after 20 parturients was made to determine the appropriate sample size. The mean difference and its standard deviation were found to be 1.65 ± 1 in NRS units after the first use of the Penthrox™ inhaler. A sample size of 45 patients was deemed adequate to identify this effect size with 90% power and with alpha 0.05, using two-sided, paired *t*-test. To compensate for any possible drop out and missing data, we intended to recruit 30% more patients.

Data were first assessed for distribution normality by the Shapiro-Wilk test and Q-Q plots. Normally distributed data were presented as mean and standard deviation. Otherwise they were presented as median and 25th and 75th interquartile range. Categorical variables were compared with Chi-square tests or Fisher exact tests, as appropriate. Comparison between two points (i.e., before and after Penthrox™ inhalation) was evaluated with a paired *t*-test. One-way ANOVA was also used to assess the significance of the intervention throughout the study period. A $P < 0.05$ was considered as statistically significant. SPSS 21 software (SPSS, Chicago, IL, USA) was used for the analysis.

RESULTS

A total of 64 parturients were enrolled in the study. Eight of them were excluded for the following reasons; 4 were unable to use the Penthrox™ inhaler, either due to its smell ($n = 1$), because overwhelming labor pain ($n = 2$) or inability to understand how to breathe through the inhaler ($n = 1$). In three patients, the second stage of labor started before epidural placement. One woman unable to express her pain in numbers was also excluded from the analysis. The data from the remaining 56 patients were analyzed. The demographic and labor characteristics are shown in Table 1. The duration between uterine contraction cycles ranged between 2 and 5 min.

Primary outcome

The severity of pain decreased significantly after the use of Penthrox™ over the study period (i.e., before the epidural attempt until placing the catheter) ($P < 0.0001$; ANOVA) [Figure 2]. The mean baseline (before) pain scores was 8.2 ± 1.5 and was decreased to 6.2 ± 2.0 after the first cycle (i.e., after the first uterine contraction and the concomitant use of Penthrox™), the mean difference is 2.0 ± 1.1 (95% confidence interval [CI] 1.7-2.3, $P < 0.0001$; paired *t*-test). This pain score reduction continued throughout the study period. It reached 4.8 ± 2.0 after the second cycle with a mean difference from the baseline 3.4 ± 1.4 (95% CI 3.0-3.8, $P < 0.0001$; paired *t*-test), and reached a mean of 3.7 ± 1.5 after the third cycle, with a mean difference from the baseline of 4.5 ± 1.5 (95% CI 4.0-5.0, $P < 0.0001$; paired *t*-test).

Secondary outcomes

Clinically and statistically significant reductions in pain intensity were also reflected in the parturient restlessness

Table 1: Demographic and clinical characteristics of the cohort

Characteristics	Descriptive statistics
Age (years)	27±5*
Para	1 (0, 2)**
Maternal weight (kg)	79±11*
Duration of first stage of labor at the time of epidural placement (hours)	5 (4, 8)**
Cervical dilatation at the time of epidural placement (cm)	5 (5, 5)**

*Data presented as mean and SD; **Data presented as median and first and third quartile. SD: Standard deviation

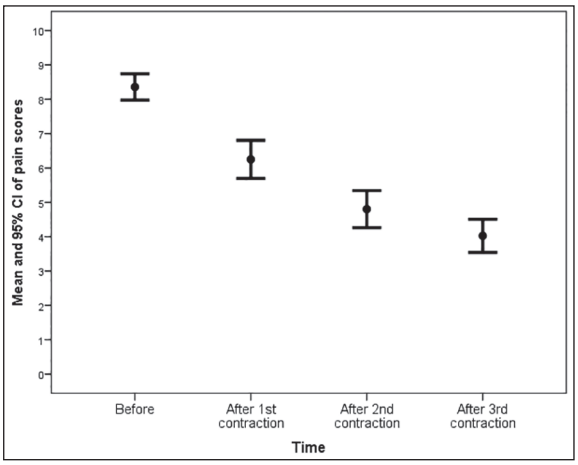

Figure 2: Mean and 95% confidence interval of pain scores before and after the parturient using Penthrox™

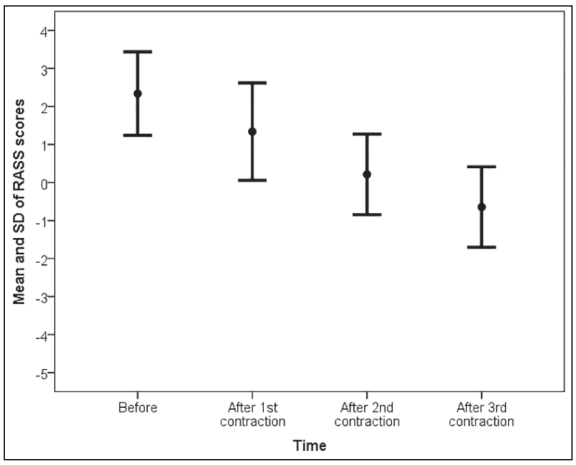

Figure 3: Mean and standard deviation of Richmond Agitation Sedation Scale scores

during the procedure. The RASS scores were continuously improved after each cycle ($P < 0.0001$; ANOVA) [Figure 3]. Only 1 parturient from the cohort became lightly sedated (RASS = −1).

The use of Penthrox™ was not associated with a statistically significant increase in nausea and vomiting compared to the baseline period ($P = 0.831$). Four parturients reported nausea, and two vomited after the second cycle. No statistically significant changes were found in the maternal and fetal hemodynamics. Baseline maternal heart rate was 99 ± 10 bpm and systolic blood pressure was 126 ± 10 mmHg, while heart rate was 94 ± 9 bpm and systolic blood pressure was 120 ± 10 mmHg at the end of Penthrox™ administration. No parturient had >10% reduction in heart rate or 20% systolic blood pressure and none required treatment. Baseline mean fetal heart rate was 141 ± 10 bpm before and 137 ± 10 bpm at the end of Penthrox™ administration. No fetus had >10% or 20% reduction in the average heart rate.

Parturient satisfaction was high; 36.4% ($n = 20$) reported excellent satisfaction, 31% ($n = 17$) very good, 23.6% ($n = 13$) good, 7% ($n = 4$) fair, and 2% ($n = 1$) poor.

DISCUSSION

Intermittent inhalation of 0.25% methoxyflurane using the penthox™ device as a bridging analgesic technique for labor pain and accompanying restless during epidural placement was markedly effective. Our results are congruent with a very recent study by Coffey *et al*.[20] Their results suggest that a methoxyflurane administered via the Penthrox inhaler is an efficacious, safe, and rapidly acting analgesic, when used for the treatment of acute pain in pediatric patients presenting to the emergency department with minor trauma. The magnitude, the gradual decrease of pain and the peak effects that we found with the second and third contraction cycle were similar to other studies findings, where they found rapid reduction of acute pain at 5 and 10 min.[11,21]

While the epidural procedure is performed, the patient must assume an immobile posture. This is important both for the success of the procedure and avoidance of inadvertent dural puncture. Uterine pain like other visceral pain such as gall bladder and renal colic is often accompanied by restlessness. Both the drug and its mode of administration should have the characteristic, which addresses the intermittent nature of pain and restlessness. Intermittent use of Entonox™ (mixture of 50% nitrous oxide with 50% oxygen), an inhalational PCA, has been popular since 1967. However, this requires nitrous oxide filled cylinder, tubing and a facemask for self-administration. Methoxyflurane was found to be more effective and associated with less drowsiness compared to nitrous oxide when self-administered as an intermittently inhaled analgesic technique for the treatment of labor pain.[22]

Jones and Rosen, demonstrated that the methoxyflurane was not only good analgesic for labor pain but that their patients were more cooperative and alert.[23] In addition to the analgesic effect, methoxyflurane has been shown to decrease the anxiety and modify mood.[24] A study in healthy volunteers, the pain threshold remained significantly greater than controlled value for 20 min after the administration of methoxyflurane was ceased.[25]

Desirable analgesic and anxiolytic effects of 0.25% methoxyflurane coupled with a low incidence of undesirable effects (drowsiness, nausea and vomiting) make this a potentially useful self-administered inhalational analgesic technique to facilitate epidural placement in laboring

women. Moreover, there are certain features, which favor its use. Penthorax™ analgesia system device looks like a "green whistle." It is small, simple and lightweight, and when compared to Entonox™ and is devoid of bulky equipment. The vast majority of women (91%) in our study accepted Penthrox™ administration and graded its ease of administration as good to excellent. The main objection against Penthrox™ was its fruity smell which some (12%) of them did not like.

Methoxyflurane is a colorless volatile fluorinated hydrocarbon anesthetic agent with a fruity odor.[26] Because of its high blood gas partition coefficient of 13, it has the potential benefit of providing analgesic effects after cessation of inhalation.[26] Because of the anecdotal reports of dose-dependent renal toxicity with anesthetic doses of methoxyflurane,[27] the manufacturer has recommended a maximum number of doses per day (6 ml) and per week (15 ml) to avoid possible renal complications.[10] In our study, all patients used considerably less than the recommended number of doses. Furthermore, recently Spruyt *et al*.[28] using the same device, studied that safety and efficacy of methoxyflurane for procedural pain of a bone marrow biopsy. They measured the urea, creatinine and creatinine clearance before and after the drug administrations. None of their measurements showed a difference, which would set the likelihood of developing nephrotoxicity with such doses very unlikely.

Despite the growing concern about possible adverse effects in the fetal developing nervous system from long term use of general anesthetics in rodent and nonhuman primate models, clinical relevance has not been identified. The dose and time course of methoxyflurane used in this study does not approach those that have been concerning in animal models.

A potential limitation of this study is the lack of a double-blinded randomized comparator.

Blinding would be difficult in this instance as even if a device were available to provide placebo inhalation, the distinct smell of methoxyflurane would be difficult to mimic. Furthermore, it was unknown if the effect size in labor pain would merit constructing a device and conduct of such a study before completion of this observational trial.

In conclusion, we found that Penthrox™ provides rapid, potent, and highly patient satisfied, bridging pain management in a laboring parturient, which can be used during the establishment of more long lasting and efficacious technique for labor analgesia.

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