**Pethidine versus nitrous oxide for pain relief during labor among multiparous. A randomized controlled trial**

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**Condensation**

Intravenous pethidine and inhaled nitrous oxide have similar intrapartum analgesic effect among multiparous 20-30 min after administration. Maternal and neonatal side effects are also comparable.

**Short Title:** Intrapartum pethidine *vs* nitrous oxide among multiparous

**AJOG at a Glance**

**Why was this study conducted?**

Several parous women elect not to have epidural analgesia, particularly multiparous who are expected to have a shorter delivery duration compared to primiparous, and parous women who have any contraindication or preference not to have. This trial was conducted to examine the efficacy and adverse effects of intravenous pethidine compared to inhaled nitrous oxide for intrapartum analgesia among multiparous women as an epidural alternative.

**Key findings**

The results of the present randomized trial indicate that the severity of pain as measured by the VAS score after 20-30 minutes of intravenous pethidine or inhaled nitrous oxide administration is similar. The prevalence of maternal and neonatal side effects, were also comparable. The proportion of women who established breastfeeding immediately at delivery tended to be higher among women who used nitrous oxide.

**What does this add to what is known?**

Inhaled nitrous oxide has similar efficacy to intravenous pethidine but tended to be associated with increase breastfeeding rate immediately after birth. These observations enable parous women and providers to avoid intrapartum opioid use when epidural analgesia is not an option, and by that, probably lessen the concern related to postpartum opioid chronic use.

**Keywords:** intrapartum analgesia; multiparous; nitrous oxide; pethidine.

**Abstract**

**Objective**

Multiparous, who are expected to have a shorter labor compared to primiparous women, prefer at times to avoid intrapartum invasive pain relief such as neuraxial analgesia. Additionally, in a number of medical centers, neuraxial analgesia may not be available immediately upon request or contraindicated. In these cases, the drug of choice to begin with among laboring multiparous is unknown. We aimed to examine the efficacy and adverse effects of intravenous (IV) pethidine (meperidine) compared to inhaled nitrous oxide (NO) for intrapartum analgesia among multiparous women.

**Methods**

Randomized controlled trial conducted at Emek medical center, Afula, Israel, between August 2016 and May 2019. Term, singleton, multiparous women in labor were randomized in a 1:1 ratio to 50mg IV pethidine or inhaled NO. Primary outcome was pain intensity 20-30 min. after analgesia administration measured by visual analog scale (VAS) from 0 to 10 cm. Secondary outcomes included need for additional analgesia, labor length, delivery mode, adverse maternal and neonatal effects. In order to detect 1±2.6 difference in VAS score between the groups, 214 women (107 in each group), were needed to achieve 80% power with alpha of 0.05.

**Results**

Of 214 women enrolled, 14 were excluded after randomization. Of the 200 analyzed, 102 received NO and 98 IV pethidine. Demographic and obstetric variables were comparable between the two groups. VAS score at 20-30 min after analgesia administration did not differ between the groups (7.6 ±2.7 and 7.7±2.3, in the pethidine and NO groups respectively, p=0.89). There were no significant differences between the groups in the rate of additional analgesia use, labor length, delivery mode, Agar score, rate of breastfeeding, women satisfaction or in maternal and neonatal side effects.

**Conclusion**

Pain intensity 20-30 min after administration of pethidine and NO was comparable among multiparous women. Side effects were comparable as well.

**Clinical Trial Registration:** clinicaltrials.gov Identifier: NCT02783508

**Introduction**

Pain relief during childbirth is an essential part of good medical care (1). The intensity of pain during childbirth and its management influence the course of labor, maternal and fetal outcomes, and satisfaction with the entire birth process (1). A good painkiller should be strong enough to reduce pain perception on the one hand and has as few side effects as possible on the other hand (2). Several women, particularly multiparous who are expected to have a shorter delivery duration compared to primiparous and who are interested in pain relief, might prefer to avoid using invasive approaches such as neuraxial analgesia. Additionally, even in institutions where there is a full availability of anesthesia for the obstetric team, there may be a situation where neuraxial analgesia will not be available immediately or will fail for technical reasons or a contraindication exist as in the case of thrombocytopenia (1)

Both inhaled analgesics and intravenous opioids are known pharmacological means of analgesia during childbirth (2,3). Inhaled nitrous oxide has been used for pain relief during childbirth since the late 19th century (3). Nitrous oxide in combination with oxygen at a concentration of 50:50 is the most common dose to use during childbirth. Its onset of effect is rapid (within 30 to 60 seconds) and so is the evacuation (3 to 4 exhalations) (1). It has an effect on the mother's pain sensation as well as an anti-anxiety effect (3). Various side effects associated with nitrous oxide as nausea, dizziness, and drowsiness have been reported (1).

Opioids are widely used for pain relief during childbirth. Their advantage is that they are inexpensive, easy to use and have high availability (4). Pethidine (meperidine) is one of the most widely used opioids. It can be given by intravenous (or intramuscular) administration when the effect begins within a few minutes and lasts 2 to 4 hours (3). Opioids have known side effects on the mother that include nausea, vomiting, discomfort and risk of chronic use postpartum. In the newborn, the drug may lead to postpartum respiratory depression, difficulty in breastfeeding and restlessness due to transfer across the placenta (5).

Data that compares these two drugs are scarce, and in the present there is no first-line painkiller in women who are not interested in having neuraxial analgesia. Accordingly, the aim of the present trial was to compare between these two agents in order to try to determine the superior painkiller. Since most primiparous elect to have neuraxial analgesia (6) the study population selected for this trial included only multiparous women.

**Patients and methods**

This was a randomized controlled trial that took place in the delivery ward of Emek Medical Center, Afula, Israel between August 2016 and May 2018. The study population included term singleton pregnant women (37 to 41 weeks) who were admitted to the delivery ward in labor and expressed their desire for analgesic. Criteria for exclusion included women who expressed their desire for neuraxial analgesia in advance, women who received pethidine 24 hours before entering the delivery room, any contraindication to vaginal birth, known susceptibility to pethidine or nitrous oxide, history of drug use, and women who had a previous cesarean section. The recruitment for the trial took place in the delivery ward. Consented women received upon request one of the study drugs. The use of each of the study drugs was according to the usual protocols in the delivery room. Group 1; intravenous pethidine at a dose of 50 mg diluted in 100 mL of 0.9% sodium chloride solution infused over 10 minutes. Repeated doses of pethidine, if required, were given in the same dose at intervals of at least two hours between doses, and up to a maximum of 4 doses. Group 2; inhaled nitrous oxide combined with oxygen at a concentration of 50:50. The mask attached to the device was adapted to adhere to the woman face. The mask was connected to the device using a tube with a valve for gas emissions. The women were instructed and trained by midwifes to press the mask forward and breathe through it once the contraction is felt to reach. The goal was to achieve at least three deep inhalations through the mask and exhale through it. Between contractions the woman was instructed not to breathe through the mask.

Prior to administration of the analgesic, women were asked regarding the severity of the pain according to the Visual Analogue Scale (VAS) from 0 to 10, where score 10 indicates unbearable pain.

At analgesia request, baseline VAS score was recorded by midwifes just before study drugs were administered. At 20 to 30 minutes of experiencing one of the study drugs, midwifes repeated the recorded of pain severity according to the VAS score. Maximal VAS during the last contraction was recorded. In cases where at 20 to 30 minutes the VAS did not decrease, a crossover between the drugs or an epidural were offered.

Data collection was performed from the hospital's computerized sheets. The basic demographic and obstetric characteristics of the women were collected from the admission sheets. Data on the course of labor, use of labor induction, time from administration of the painkiller to delivery, use of additional painkillers and mode of delivery, were collected from the delivery ward computerized sheets. Neonatal outcomes were collected from the computerized admission sheets to the nursery. Data on the severity of pain and side effects were documented in a dedicated study sheet. Repeated pethidine use, transition from one group to another, or use of an epidural were documented in the designated sheet.

Women were monitored in the in the labor and delivery ward. Vital signs were examined before the analgesic was given, 20-30 minutes after receiving the drug trials and continued hourly until delivery. Assessment of maternal sedation, occurrence of nausea, vomiting, headache and dry mouth was recorded during the first hour following the administration of the analgesic. Midwifes assessed maternal sedation on a 4-point scale where 0 equal to alert; 1, mildly drowsy; 2, moderately drowsy and 3, asleep (7).

Maternal satisfaction and desire to use the same analgesic in future delivery were assessed by a questionnaire delivered to the mother within 48 hours of birth. Respondents express their satisfaction on a five-point scale where 1 is very dissatisfied, and 5 is very satisfied.

**Randomization**

Women were randomly assigned to the study group or the control group at a 1:1 ratio. A researcher (RS), not otherwise involved in enrolling women into the trial, prepared the random allocation in blocks of 10 using computer-generated random allocation. Eligible women were assigned the next available sequence in the randomization list. The list was concealed and investigators and participants enrolled were unaware of the upcoming group assignments until the moment of assignment. Placebo was not used, and the details of the research drug were unmasked to the midwife and medical staff.

**Primary outcome**

Severity of pain measured at 20 to 30 minutes by VAS score after administration of one of the study drugs.

**Sample size**

In order to demonstrate a difference of 1 in VAS (on a scale from 0 to 10cm) with a standard deviation of 2.6 (7,8), 20 to 30 minutes from the administration of the analgesic, 214 women in total were needed to achieve a power of 80% and a two-sided alpha of 0.05.

**Ethics**

The institutional review board at Emek Medical Center, Afula, Israel approved the trial protocol on June 21, 2016 (#0072-16-EMC). All individual participants provided informed consent. The trial was registered on [www.Clinical](http://www.clinical)Trials.gov (Identifier: NCT02783508). A local data monitoring committee implemented quality control of screening, and verification of compliance to protocol.

**Statistical analysis**

Continuous variables were presented using standard distribution indices (mean, standard deviation, median, and range). Categorical variables were presented using frequency and relative frequency. The relationship between the study groups (group 1, pethidine; group 2, nitrous oxide) and categorical variables was examined using Chi -square test (or Fisher's exact test), and the difference between the different levels of these variables was represented by the odds ratio (OR). For continuous variables the relationship was examined using the Student's test (or Wilcoxon test). The processing was performed using SAS 9.4 software. A significant result was obtained if *P* <0.05. An intention to treat analysis was employed.

**Results**

During the study period, 214 women were recruited to participate in the study; 106 in the pethidine group and 108 in the nitrous oxide group. Of all recruited women, 14 were excluded from the final analysis; 8 from the pethidine group (4 were excluded since at the time of data collection after delivery it became clear that they had received pethidine in 24 hours before recruitment, 3 progressed rapidly in labor before receiving the study drug, and in 1 woman, the primary and several secondary outcomes were not collected), and 6 from the nitrous oxide (4 progressed rapidly in labor before receiving the study drug, 1 was 35 weeks after accurate dating was performed again, and in 1 woman the primary outcome and several secondary outcomes were not collected). Overall data of 200 women, 102 in the nitrous oxide group and 98 in the pethidine group were analyzed (Figure 1).

Demographic and intrapartum variables of the trial groups are presented in Table 1. There were no significant differences between the two groups including in cervical conditions (dilatation and effacement) when requiring analgesia. The severity of pain according to the VAS score at the time of analgesic requirement was 7.9±1.9 and 7.8±2.2 in nitrous oxide and the pethidine groups, respectively (*P* = 0.69). In 76.5% and 68.4% of women in the nitrous oxide and the pethidine groups, respectively had VAS score 7.0 cm or more (*P*=0.21) at analgesic request. Mean VAS score after 20–30 min from administration of the analgesic, i.e., the primary outcome, was 7.7±2.3 and 7.6±2.7 in the nitrous oxide and the pethidine groups, respectively (*P* = 0.89), (Table 2). VAS score at 60 min was significantly lower in the pethidine group than in the nitrous oxide group (7.7±2.3 vs 8.6 ±1.9 respectively; *P*=0.03), though the difference did not exceed 1.0 cm. At 120 and 180 min the VAS did not differ significantly between the groups (Table 2). Additionally, there was no significant difference between the groups in the need for an additional analgesic including epidural. There was no significant difference between the groups in terms of the mother's satisfaction with the pain relief or the willingness to use the same painkiller in future deliveries.

Time from analgesia request to delivery as well as mode of delivery did not differ significantly between the groups. In the nitrous oxide group all women had spontaneous vaginal delivery and in the pethidine group there were 4 (4.1%) cases of vacuum deliveries. None delivered by a cesarean section in both groups (Table 3). There was no significant difference between the groups in the incidence of side effects that could be attributed to the analgesic drug used (Table 3).

Neonatal outcomes are presented in Table 4. There was no significant difference between the groups in terms of Apgar score, cord artery pH or need for oxygen supplementation immediately after delivery. The rate of neonates who breastfeed immediately after delivery was 95.1% in the nitrous oxide group compared to 87.8% in the pethidine group (*P*=0.06). The rates of breastfeeding at 24 hours postpartum, were similar (*P*=0.71). Other neonatal outcomes examined were comparable between the two groups.

**Discussion**

The results of the present study indicate that the severity of pain as measured by the VAS score after 20 to 30 minutes of intravenous pethidine or nitrous oxide administration among laboring multiparous women is similar. The effect on labor duration and mode of delivery was also comparable. The prevalence of maternal side effects, including the degree of drowsiness, was similar between the groups. There was also no difference in the outcomes of the newborns. The proportion of women who established breastfeeding immediately at delivery tended to be lower among women who used pethidine.

Intravenous opioids and inhaled nitrous oxide are two widely used medications for pain relief during childbirth. Nevertheless, there are scarce data that present head-to-head intravenous pethidine and nitrous oxide in multiparous women only. Chantrasiri et al reported in a small trial that both agents have comparable effectiveness. Women who received nitrous oxide were more satisfied. The trial was composed of both primi- and multiparous women (9). Mobaraki et al randomized a total of 100 mothers to intramuscularly pethidine or inhaled nitrous oxide and found contrary to the present trial that nitrous oxide was more effective in relieving pain compared to pethidine at 30 minutes after administration (10). The difference in the results is probably related to the fact that in the present study the administration of pethidine was intravenous compared to the intramuscular administration in Mobaraki trial (10). In intravenous administration, the effect of pethidine is faster and reaches a peak within 5 to 7 minutes compared to intramuscular administration where the peak is 30 to 50 minutes after administration. Hence, at 30 minutes the maximal effect may not be achieved (11).

It is remarkable that both study drugs had low effect on decreasing analgesia perception from baseline as demonstrated at 30, 60, 120 and 180 minutes of administration. It has been reported that the analgesia these agents provided is less effective than epidural when pain scores are the outcome of interest (12). Still, the reduction in VAS score was less than 1 cm compared to baseline in both groups. On the other hand, in both groups more than 30% of the women had any sedative effect related to the study drugs. This effect is probably the main effect related to these agents during childbirth. Olofsson, reported that opioids provide sedation and a sense of euphoria, but their analgesic effect in labor is limited, and their primary mechanism of action is sedation (13). In the case of nitrous oxide, the minor effect on analgesia perception may be related to several reasons. Women receiving nitrous oxide may start using the mask too late and not once the contraction is felt despite adequate instruction and training by the midwifes. Additionally, the method of administration during childbirth, i.e. on demand and not in a continuous manner, may also influence the efficiency. In the field of gastroenterology, Løberg et al reported that the conflicting finding that nitrous oxide is comparable to intravenous medication in colonoscopy but hardly favorable to placebo in flexible sigmoidoscopy might be explained by the continuous use during colonoscopy and on demand during flexible sigmoidoscopy (14). Furthermore, concentration other than 50:50 with oxygen, may also determine the level of effect on pain.

According to the results of this study, the incidence of maternal side effects was relatively low in the two study groups compared to other reports (7,8). Additionally incidence of side effects was also comparable, as compared to previous publications that showed higher rates with intravenous opioids use (15,16). In terms of effects on the newborn, there was no difference between the groups in the incidence of neonatal outcomes that were examined. The rate of neonatal adverse events was generally low in both study groups and in accordance with others particularly related to the occurrence of neonatal respiratory depression (9).

The nitrous oxide group tended to have a higher rate of breastfeeding immediately after birth than in the pethidine group. It can be thought that this difference is related to the degree of sleepiness of the mother after birth and her ability to breastfeed. Nevertheless, there was no difference between the groups in sleepiness rate. Administration of pethidine intravenously cross the placenta and can accumulate in the fetal blood system and affect newborn behavior including suckling ability after birth (17-19). This is in contrast to nitrous oxide which is released rapidly from the blood system (20). In this study we did not examine the levels of pethidine and its metabolites in the newborns' blood, but it is possible that this explanation underlies the difference in the rate of immediate breastfeeding between groups.

Satisfaction is a complex measure associated with several personal and environmental characteristics and is difficult to assess thoroughly. During childbirth many factors affect the mother's satisfaction, including the mother's expectations, her involvement in the birth process and the relationship with the care team (21,22). In this trial, mother's satisfaction and willingness to use the same painkiller in the future were comparable between the groups.

**Strength and limitations**

The different form of administration of the two study drugs led to difficulty in using a placebo and conducting a double blind trial. The strengths of the study stem from being a randomized trial, focusing on multiparous women only, i.e., a group of parous women that use intrapartum analgesia other than epidural in higher percentage compared to primiparous women. In addition, the fact that the study was conducted in a single institution, with identical intrapartum management reinforces the results.

**Conclusion**

The best painkiller is one that will have a beneficial effect on the pain with minimal side effects for the mother and the newborn. There are many years of experience in using both nitrous oxide and pethidine in the delivery ward. Both are easy to use and associated with low costs. The results of the present trial show that nitrous oxide has similar efficacy to pethidine and might be associated with increase breastfeeding rate immediately after birth. Use of nitrous oxide for the purpose of reducing opioid use peripartum is probably another goal since chronic postpartum use of opioid stands as a great concern. These observations enable to provide informed and reliable counsel to mothers, particularly multiparous, on the various options for pain relief during childbirth.

**References**

1. Klomp T, van Poppel M, Jones L, Lazet J, Di Nisio M, Lagro-Janssen ALM. Inhaled analgesia for pain management in labour (Review). The Cochrane Collaboration. Cochrane Database Syst Rev 2012;9:CD009351.

2. Keskina HL, Aktepe Keskina E, Avsara AF, Tabukb M, Caglara GS. Pethidine versus tramadol for pain relief during labor. Int J Gynaecol Obstet 2003;82:11–6.

3. Likis FE, Andrews JC, Collins MR, et al. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg 2014;118:153–67.

4. Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, Jordan S, Lavender T, Neilson JP. Pain management for women in labour: an overview of systematic reviews. Cochrane Database Syst Rev 2012;2012:CD009234.

5. Wee MY, Tuckey JP, Thomas PW, Burnard S. A comparison of intramuscular diamorphine and intramuscular pethidine for labour analgesia: a two-centre randomised blinded controlled trial. BJOG 2014;121:447–56.

6. Howell CJ, Kidd C, Roberts W, et al. A randomised controlled trial of epidural compared with non-epidural analgesia in labour. BJOG 2001;108:27–33.

7. Fairlie FM, Marshall L, Walker JJ, Elbourne D. Intramuscular opioids for maternal pain relief in labour: a randomised controlled trial comparing pethidine with diamorphine. Br J Obstet Gynaecol 1999;106:1181–7.

8. The IDvIP trial: a two-centre randomised double-blind controlled trial comparing intramuscular diamorphine and intramuscular pethidine for labour analgesia. BMC Pregnancy Childbirth 2011;11:51.

9. Chantrasiri R, Wanapirak C, Tongsong T. Entonox® versus Pethidine in Labor Pain Relief: A Randomized Controlled Trial. Int J Environ Res Public Health 2021;18:12571.

10. Mobaraki N, Yousefian M, Seifi S, Sakaki M. A Randomized Controlled Trial Comparing Use of Enthonox With Pethidine for Pain Relief in Primigravid Women During the Active Phase of Labor. Anesth Pain Med 2016;24;6:e37420.

11. <https://www.uptodate.com/contents/meperidine-pethidine-drug-information>.

12. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 209: Obstetric Analgesia and Anesthesia. Obstet Gynecol 2019;133:e208–e225

13. Olofsson C, Ekblom A, Ekman-Ordeberg G, Hjelm A, Irestedt L. Lack of analgesic effect of systemically administered morphine or pethidine on labour pain. *Br J Obstet Gynaecol* 1996;103:968.

14. Løberg M, Furholm S, Hoff I, Aabakken L, Hoff G, Bretthauer M. Nitrous oxide for analgesia in colonoscopy without sedation. Gastrointest Endosc 2011;74:1347–53.

15. Volmanen P, Akural E, Raudaskoski T, Ohtonen P, Alahuhta S. Comparison of remifentanil and nitrous oxide in labour analgesia. Acta Anaesthesiol Scand 2005;49:453–8.

16. Tsui MH, Ngan Kee WD, Ng FF, Lau TK. A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. BJOG 2004;111:648–55.

17. Belsey EM, Rosenblatt DB, Lieberman BA, et al. The influence of maternal analgesia on neonatal behaviour: I. Pethidine. Br J Obstet Gynaecol 1981;88:398–406.

18. Belfrage P, Boreus LO, Hartvig P, Irestedt L, Raabe N. Neonatal depression after obstetrical analgesia with pethidine. The role of the injection-delivery time interval and of the plasma concentrations of pethidine and norpethidine. Acta Obstet Gynecol Scand 1981;60:43–9.

19. Nissen E, Widstrom AM, Lilja G, et al. Effects of routinely given pethidine during labour on infants’ developing breastfeeding behaviour. Effects of dose-delivery time interval and various concentrations of pethidine/norpethidine in cord plasma. Acta Paediatr 1997;86:201–8.

20. Einarsson S, Stenqvist O, Bengtsson A, Norén H, Bengtson JP. Gas kinetics during nitrous oxide analgesia for labour. Anaesthesia 1996;51:449–52.

21. Berkowitz B. The patient experience and patient satisfaction: measurement of a complex dynamic. Online J Issues Nurs 2016;21:1.

22. Hodnett ED. Pain and women’s satisfaction with the experience of childbirth: a systematic review. Am J Obstet Gynecol 2002;186:S160–S172.

**Table 1. Maternal demographic and intrapartum variables of the trial groups**

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | **Nitrous oxide** **N=102** | **Pethidine** **N=98** | ***P*-value\*** |
| Maternal age, years | 29.7±4.7[29.5; 26.0-33.0] | 29.5±5.4[28; 25.0-33.0] | 0.50 |
| Ethnicity Jews Arabs  | 35 (34.3)67 (65.7) | 23 (23.5)75 (76.5) | 0.09 |
| Pre-gestational body mass index, kg/m2 | 25±4.7[24.4; 21.9-28.2] | 25±4.5[24.9; 21.4-28.0] | 0.81 |
| Parity  | 3±1.2[3; 2-4] | 3.1±1.2[3; 2-4] | 0.68 |
| Gestational age at delivery  | 39.4±1.1[39.3; 38.6-40.2] | 39.1±1.1[39.2; 38.2-40.1] | 0.07 |
| Induction of labor | 15 (14.7) | 16 (16.3) | 0.75 |
| Oxytocin augmentation | 45 (44.1) | 34 (34.7) | 0.17 |
| Cervical dilatation at analgesic request | 3.5±1.2[3.5; 2.5-4.5] | 3.3±1.2[3; 2.5-4] | 0.24 |
| Cervical effacement at analgesic request | 83±8.3[80; 80-90] | 82.9±9.0[80; 80-90] | 0.96 |
| VAS at analgesic request  | 7.9±1.9[8.0; 7.0-10.0] | 7.8±2.2[8.0; 6.0-10.0] | 0.69 |
| VAS >7 at analgesic request | 78 (76.5) | 67 (68.4) | 0.21 |

Data are mean ± standard deviation, [median, IQR], or n (%).

VAS; visual analog scale from 0 (no pain) to 10 cm (worst pain).

**Table 2. Response to pain after nitrous oxide versus pethidine administration.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Response** | **Nitrous oxide** **N=102** | **Pethidine** **N=98** | ***P*-value\*** | **OR(95%CI)** |
| VAS 20-30 min. after analgesic request | 7.7±2.3[8.0; 6.0-10.0] | 7.6±2.7[8.0; 6.0-10.0] | 0.89 | -- |
| VAS at 60 min.  | 8.6±1.9[9.3; 8.0-10.0] | 7.7±2.3[8.0; 7.0-10.0] | 0.03 | -- |
| VAS at 120 min. | 8.5±2.1[9.5; 8.0-10.0] | 9.0±1.4[10.0; 8.0-10.0] | 0.63 | -- |
| VAS at 180 min. | 8.5±2.0[9.0; 8.0-10.0] | 8.5±1.9[9.0; 8.0-10.0] | 0.94 | -- |
| Analgesic crossover  | 34 (33.3) | 24 (24.5) | 0.17 | 1.54 (0.83- 2.86) |
| Epidural use  | 7 (6.9) | 9 (9.2) | 0.54 | 0.73 (0.26- 2.04) |
| VAS before second line use | 9.0±1.6[10.0; 9.0-10.0] | 8.8±1.7[10.0; 8.0-10.0] | 0.85 | -- |
| VAS at complete dilatation  | 9.4±1.9[10.0; 10.0-10.0] | 9.4±1.8[10.0; 10.0-10.0] | 0.76 | -- |
| Efficacy of analgesia from 1 to 5 (most efficient)  | 3.4±1.4[3; 2-5] | 3.1±1.3[3; 2-4] | 0.1 | -- |
| Maternal satisfaction from 1 to 5 (most satisfied)  | 4.0±1.0[4; 4-5] | 4.1±0.9[4; 4-5] | 0.98 | -- |
| Future use of the same analgesic | 66 (64.7) | 65 (66.3) | 0.81 | 0.93 (0.52- 1.67) |

Data are mean ± standard deviation, [median, IQR], or n (%).

VAS; visual analog scale from 0 (no pain) to 10 cm (worst pain).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **OR(95%CI)** | ***P*-value** | **Pethidine** **N=98** | **Nitrous oxide** **N=102** | Outcomes  |
| -- | 0.8 | 2.3±2.19[1.58; 0.74-3.14] | 2.1±2.14[1.67; 0.83-2.50] | Time from analgesia use to complete dilatation, hours |
| -- | 0.83 | 0.007±0.007[0.005; 0.003-0.009] | 0.009±0.01[0.005; 0.003-0.01] | Length of second stage, hours |
| -- | 0.77 | 2.50±2.28[1.77; 0.85-3.31] | 2.22±1.86[1.76; 1.02-2.75] | Time from analgesia use to delivery  |
| -- | 0.13 | 0.01±0.005[0.009; 0.006-0.01] | 0.009±0.006[0.007; 0.006-0.01] | Length of third stage, hours |
| Ref.---- | 0.13 | 94 (95.9)4 (4.1)0 (0.0) | 102 (100)0 (0.0)0 (0.0) | Mode of deliverySpontaneous Vaginal Vacuum extractionCesarean  |
| 0.63 (0.10 – 3.87) | 0.67 | 3 (3.1) | 2 (2.0) | Postpartum hemorrhage  |
| 0.48 (0.04-5.33) | 0.61 | 2 (2.0) | 1 (1.0) | Blood transfusion  |
| -- | --- | 0 (0.0) | 0 )0.0) | Saturation <95% |
| 0.96 (0.06-15.57) | >0.99 | 1 (1.0) | 1 (1.0) | Pulse rate >110 |
| 0.84 (0.31-2.28) | 0.80 | 9 (9.2) | 8 (7.8) | Nausea |
| 1.29 (0.28-5.92) | >0.99 | 3 (3.1) | 4 (3.9) | Vomiting  |
| -- |  | 0 (0.0) | 0 (0.0) | Itching |
| 0.96 (0.30-3.01) | 0.92 | 6 (6.1) | 6 (5.9) | Headache  |
| 1.26 (0.54-2.92) | 0.59 | 11 (11.2) | 14 (13.7) | Dry mouth |
| 1.16 (0.62- 2.17) | 0.64 | 25 (25.5) | 29 (28.4) | Any side effect |
| 1.13 (0.62 – 2.05) | 0.68 | 30 (30.6) | 34 (33.3) | Any sedative effect  |

**Table 3. Intrapartum outcomes and maternal side effects according to the trial groups.**

Data are mean ± standard deviation, [median, IQR], or n (%).

Table 4. Neonatal outcomes according to the trial groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **OR(95%CI)** | ***P*-value\*** | **Pethidine** **N=98** | **Nitrous oxide** **N=102** | **Outcomes** |
| -- | 0.16 | 3669.7±332.6[2802; 3071.5-3581] | 3401.4±373.6[3399; 3128-3695] | Neonatal birthweight, gr |
| Ref 1.51 (0.86-2.65) | 0.14 | 59 (60.2)39 (39.8) | 51 (50.0)51 (50.0) | Neonatal genderMales Females  |
| 1.44 (0.59-3.55) | 0.42 | 9 (9.2) | 13 (12.7) | Meconium  |
| 0.96 (0.06-15.57) | >0.99 |  1 (1.0) | 1 (1.0) | Apgar score <7 at 1 min |
| -- | 0.49 | 1 (1.0) | 0 (0.0) | Apgar score <7 at 5 min |
| 0.31 (0.03-3.07) | 0.36 | 3 (3.1) | 1 (1.0) | Cord artery pH < 7.1 |
| 0.96 (0.06-15.57) | >0.99 | 1 (1.0) | 1 (1.0) | Oxygen use  |
| -- | 0.49 | 1 (1.0) | 0 (0.0) | Artificial ventilation  |
| -- | 0.11 | 3 (3.1) | 0 (0.0) | NICU admission  |
| 2.71 (0.92-7.99) | 0.06 | 86 (87.8) | 97 (95.1) | Breastfeed immediately after birth  |
| 1.23 (0.40-3.8) | 0.71 | 91 (92.9) | 96 (94.1) | Breastfeed at 24h after delivery |
| 1.00 (0.54-1.87) | 0.99 | 71 (72.4) | 74 (72.5) | Formula use  |

Data are mean ± standard deviation, [median, IQR], or n (%).