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**Original Research Article**

# Paracetamol versus meperidine for relief of labour pain in primiparous women: a randomized controlled trial

**Sherif M. Habib[1], Mohamed H. Mostafa[1], Mohamed H. Salama[1]*, Hend G. Swilam[2]**

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2]Department of Obstetrics and Gynecology, Dar-Al-Welada (Maternitè Hospital), Alexandria, Egypt

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***Correspondence:**
Dr. Mohamed H. Salama,
E-mail: mhs_vagus2009@yahoo.com



## ABSTRACT

**Background:** Most parturient women request analgesia, of which, there are two types; opioids and non-opioids. Opioids include morphine and meperidine, while non-opioids, which are milder forms of painkillers, include acetaminophen (paracetamol) and non-steroid anti-inflammatory drugs. The major concerns associated with opioids are the risk of neonatal respiratory depression, the cost and availability.
**Methods:** The aim of this study was to compare the efficacy and safety of paracetamol versus meperidine for intra-partum pain relief. A total of 92 primiparous singleton term pregnant women were randomly allocated to receive intravenous paracetamol (1000 mg), or intramuscular meperidine (50 mg), at the beginning of the active phase of labor. The primary outcome was the labor pain perception, assessed using the visual analogue scale (VAS), at baseline, 15, 30, 60 and 120 minutes after administration of the drug.
**Results:** Women of both groups showed significant reduction of the VAS after administration of the medication. There were no differences between both groups regarding the mode of delivery and the durations of the first or second stages of labor. However, meperidine was associated with higher rates of dizziness and nausea/vomiting. The 1-min Apgar scores were significantly lower in meperidine group. However, there were no differences in the 5-min Apgar score, need for neonatal resuscitation or neonatal respiratory distress.
**Conclusions:** intravenous paracetamol as analgesia during labor is effective with no fetal or maternal adverse effects. Its use should have more chance for intrapartum pain relief. Additionally, it can be used as adjuvant with other types of analgesics.

**Keywords:** Intra-partum anaelgesia, Labour Pain, Meperidine, Paracetamol

## INTRODUCTION

The majority of women experience pain during labour, and for many women, it is the most significant pain they will experience in their lifetime. However, although it is associated with the same physiological process, not all women experience labour pain in the same way. Some women manage pain well, requiring minimal assistance, whereas others do not cope well and request interventions to alleviate the pain.[1] Stretch of the cervix, ischemia of the uterine wall, and stretch of the vagina and the perineum during the second stage of labour are causes of labour pain.[2]

Most labouring women request analgesia, whether pharmacological or non-pharmacological.[3] Non-pharmacological measures include continuous support, baths, touch and massage, maternal movements and re-

positioning, and transcutaneous elective nerve stimulation (TENS).[4]

Typically, analgesic regimens include opioids or non-opioid analgesics. Opioid analgesia, including Morphine, Meperidine, Fentanyl, Tramadol, Butorphanol, and Ketamine, are currently considered the gold standard for obstetric analgesia. However, there are a number of concerns regarding their us.[5]

Meperidine, as an example, has a number of side effects on the mother and the baby which makes it a less ideal choice for labour analgesia. It can cause nausea, vomiting, and dysphoria in women receiving it during labour, as well as neonatal respiratory distress.[6] High cost and difficult availability are additional limiting reasons for the use of these drugs as routine analgesic medications during labour.[7]

Paracetamol, as non-opioid analgesic, has an effective role as proposed by studies examining its analgesic potential in obstetric surgeries such as abortions, post-cesarean pain and pain associated with vaginal delivery.[8] At therapeutic doses, it is associated with fewer adverse effects, compared to both opioids and NSAID.[9] It crosses the placenta, but it is considered a non-teratogenic drug.[10]

Reviewing available literature, there is a sparsity of high-quality studies comparing analgesic actions of the opioid analgesic agent Meperidine to those of Paracetamol in intrapartum pain relief.

## METHODS

This was a randomized controlled study assessing the use of IV paracetamol for intrapartum pain relief, in comparison to IM Meperidine. The study recruited 92 primiparous women attending at Ain Shams University Maternity Hospital over 12 months, from July 2017 till July 2018. The eligibility criteria were term, singleton primiparous women at the beginning of the active phase of labor, seeking analgesia. Malpresentations, high-risk or complicated pregnancies, and known hypersensitivity to paracetamol or meperidine were the exclusion criteria.

### *Interventions*

Eligible women were randomized to receive either:

- Group I: intravenous infusion of 1000-mg paracetamol (Perfalgan®, Bristol-Mayers Squibb Pharmaceuticals, France). A second dose was given at least 4 hours after the initial dose, when needed
- Group II: intramuscular 50 mg of meperidine HCl (Pethidine®, Misr Company for Pharmaceuticals, Egypt). Further doses of intramuscular meperidine were upon woman's request with a maximum dose of 200 mg (i.e. 4 doses). Before administering each dose, delivery should not be anticipated at less than 2 hours (roughly estimated to correspond to a cervical dilatation of <8 cm).

For both groups, the treatment was administered at the beginning of the active phase of labor (defined as a cervical dilatation of 3-4 cm and a cervical effacement ≥50%).

Randomization was performed using a computer-generated randomization system, with allocation concealment using serially numbered opaque envelops that were only released after recruitment.

### *Outcomes*

The primary outcome was the reduction of the intensity of perceived labor pain, while the secondary outcomes included:

*Maternal outcomes*

- Duration of the active phase of the first stage of labor
- Duration of the second stage of labor
- Need for further analgesia
- Maternal dizziness, nausea and/or vomiting.

*Neonatal outcomes*

- The 1 and 5 minutes Apgar scores
- Need for neonatal resuscitation
- Neonatal respiratory distress or depression.

*Assessment of pain*

Labor pain was semi-objectively assessed using the visual analogue scale (VAS) (Figure 1), with the 0 denoting no pain, while 10 denoting the worst possible pain. An average of two observers' pain assessments was taken to minimize personal bias.

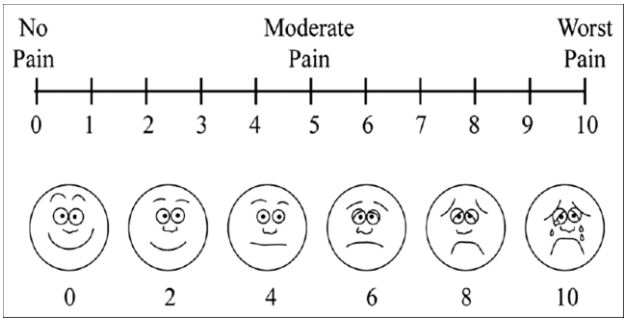



**Figure 1: Visual analogue scale (VAS).**

### *Ethical considerations*

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Before admission to the study, each patient signed an informed consent to participate, after the nature, scope and possible consequences of the clinical study had been explained.

All participants' data were kept confidential.

***Statistical analysis***

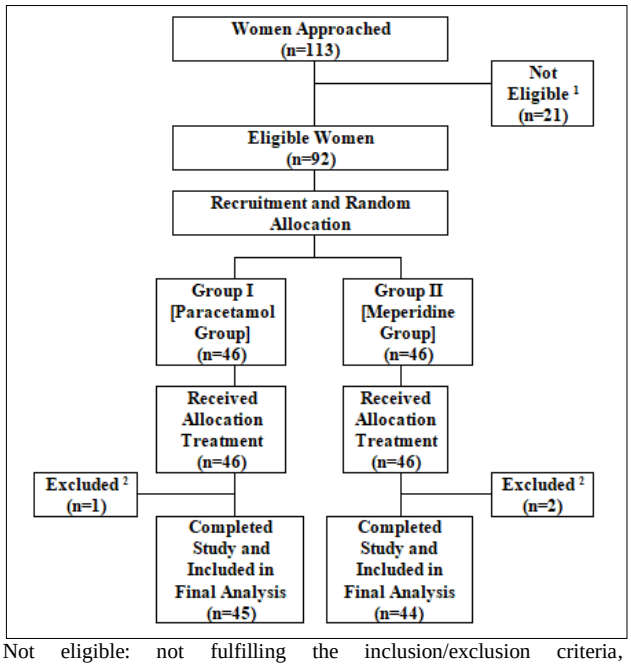
It was estimated that a sample size of 92 patients randomized into either study group (n=46 patients per group), would achieve a power of 91% (type II error, 0.09) to detect a difference of 22% between the 2 groups as regards the percentage of women requiring rescue analgesia. The percentage of women requiring rescue analgesia is assumed to be identical in both groups and to equal 22% under the null hypothesis, according to a previous published study.[11]

## RESULTS

A total of 92 primiparous women were recruited in the current study, according to the study flow-chart (Figure 2). A total of 113 women were approached, of whom, 21 were deemed ineligible for the study. The remaining eligible 92 were then randomly allocated to receive either paracetamol (Group I), or meperidine (Group II). Three women were further excluded due to either having an emergency CS within 2 hours after receiving the treatment, declining to complete the study or refusal to respond to the investigator. Eventually, 45 and 44 women completed the3 study, and their data statistically analysed in Group I and II, respectively.

The baseline characteristics of the study population are demonstrated in Table 1, showing no significant differences between the 2 groups. The age of the participants in Group I ranged from 20-34 years (26.6±4.06), and in Group II from 20-34 years (26.6±4.1).

The gestational age at deliver in Group I ranged from 37-41.86 weeks (39.67±1.39), and in Group II from 37-41.86 weeks (39.3±1.5). The maternal weight in Group I ranged from 55-94 kg (73.4±11.7), and in Group II from 56-93 kg (74.7±11.7). Finally, the maternal BMI in Group I ranged from 19.38-39.91 (27.4±4.9), and in Group II from 20.9-37.95 (27.8±4.5). The differences in all these baseline characteristics were all statistically insignificant.




Not eligible: not fulfilling the inclusion/exclusion criteria, Excluded after allocation and receiving treatment (emergency CS within 2 hours after receiving the treatment, or decline to complete the study and refused responding to the investigator).

**Figure 2: Flow chart of the study course.**

**Table 1: Baseline characteristics of the study population.**

| | Group I (Paracetamol) (n=46) | Group II (Meperidine) (n=46) | MD (95% CI) | *P* [1] |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Range | 20-34 | 20-34 | 1.5 | 0.075 |
| Mean±SD | 26.6±4.06 | 26.06±4.1 | (-0.2 to 3.2) | NS |
| **Gestational Age (weeks)** | | | | |
| Range | 37-41.86 | 37-41.86 | 0.3 | 0.289 |
| Mean±SD | 39.67±1.39 | 39.3±1.5 | (-0.3 to 0.9) | NS |
| **Maternal Weight (kg)** | | | | |
| Range | 55-94 | 56-93 | -1.3 | 0.59 |
| Mean±SD | 73.4±11.7 | 74.7±11.7 | (-6.2 to 3.5) | NS |
| **Maternal BMI (kg/m$^2$)** | | | | |
| Range | 19.38-39.91 | 20.9-37.95 | -0.4 | 0.651 |
| Mean±SD | 27.4±4.9 | 27.8±4.5 | (-2.4 to 1.5) | NS |

SD standard deviation; BMI body mass index [calculated as weight (kg) divided by squared height (m$^2$)]; MD (95% CI) mean difference and its 95% confidence interval; 1 Analysis using independent student's t-test; NS non-significant

The number of doses of the allocated medication was significantly higher in women receiving meperidine (Group II), 15 (34.1%) of whom received 3 doses, in contrast to none among those receiving paracetamol (Group I) (Figure 3).

Women of both groups showed significant reduction in the VAS for intrapartum pain at 15, 30, 60 and 120 minutes after administration of either medication.

The median VAS for intrapartum pain was only significantly different between both groups at 15 minutes after administration in favour of meperidine (Table 2).

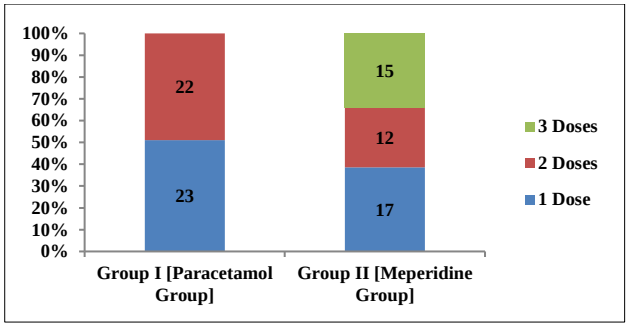



**Figure 3: Comparison of the study groups regarding the number of doses of allocated medications.**

**Table 2: Differences between groups as to the VAS for intrapartum pain.**

| VAS for intrapartum pain | Group I (Paracetamol) (n=45) | Group II (Meperidine) (n=44) | MD (95% CI) | *P* [1] |
|---|---|---|---|---|
| **Initial VAS** | | | | |
| Range | 6-9 | 6-9 | 0.2 | 0.235 |
| Median (IQR) | 7 (7-8) | 7 (7-7) | (-0.2 to 0.6) | NS |
| **VAS after 15 min** | | | | |
| Range | 4-9 | 2-9 | 0.9 | 0.012 |
| Median (IQR) | 7 (6-8) | 6 (4-7) | (0.3 to 1.6) | S |
| **VAS after 30 min** | | | | |
| Range | 2-9 | 2-9 | 0.4 | 0.351 |
| Median (IQR) | 5 (4-7) | 5 (4-6) | (-0.3 to 1.1) | NS |
| **VAS after 60 min** | | | | |
| Range | 2-9 | 1-9 | 0.5 | 0.253 |
| Median (IQR) | 5 (4-6) | 5 (3-6) | (-0.3 to 1.2) | NS |
| **VAS after 120 min** | | | | |
| Range | 6-8 | 6-8 | 0.08 | 0.630 |
| Median (IQR) | 8 (7-8) | 8 (7-8) | (-0.3 to 0.4) | NS |

**Table 3: Differences between groups regarding mode of delivery and duration of labor.**

| | Group I (Paracetamol) (n=45) | Group II (Meperidine) (n=44) | RR/MD (95% CI) | *P* |
|---|---|---|---|---|
| **Mode of delivery** | | | | |
| Vaginal delivery | 37 (82.2%) | 35 (79.5%) | 1.03 | 0.748 [1] |
| Cesarean section | 8 (17.8%) | 9 (20.5%) | (0.8 to 1.3) | Ns |
| **Duration of first stage of labor (min)** | | | | |
| Range | 270 - 480 | 270 - 480 | -4.1 | 0.774 [2] |
| Median (IQR) | 420 (300 - 450) | 390 (330 - 450) | (-36.9 to 28.8) | NS |
| **Duration of second stage of labor (min)** | | | | |
| Range | 30 - 120 | 30 - 120 | 2.8 | 0.719 [2] |
| Median (IQR) | 90 (45 - 105) | 75 (60 - 105) | (-11.5 to 17.03) | NS |

Data presented as number (percentage); or range, median (IQR); IQR interquartile range; RR (95% CI) risk ratio and its 95% confidence interval; MD (95% CI) mean difference and its 95% confidence interval; 1 Analysis using chi-squared test; 2 Analysis using Mann-Whitney's U-test; NS non-significant.

There were no significant differences between women of both groups regarding the mode of delivery and durations of the first or second stages of labor (Table 3). Thirty-seven (82.2%) of the ladies in Group I, and 35 (79.5%) in Group II delivered vaginally, while 8 (17.8%), and 9 (20.5%) delivered by CS in each group, respectively. The mean duration of the first stage of labour ranged from 270-480 min in both groups, with a median of 420 min,

and inter-quartile range of 300-450 min in Group I, while the median was 420 min, and the inter-quartile range 300-450 min in Group II. Similarly, the mean duration of the second stage of labour ranged from 30-120 min in both groups, with a median of 90 min, and inter-quartile range of 45-105 min in Group I, while the median was 75 min and the inter-quartile range 60-105 min in Group II. All these differences between the 2 groups were statistically non-significant.

Administration of meperidine was significantly associated with higher rates of maternal dizziness and nausea/vomiting compared to paracetamol [RR 0.08, 95% CI (0.01 to 0.6), p<0.001, RR 0.1, 95% CI (0.01 to 0.73), p=0.003; respectively].

There were no significant differences between both groups regarding the neonatal birth weight. As to the Apgar score, the 1-min score was significantly lower in women of Group II. Additionally, the proportion of neonates who had a 1-min Apgar score < 7 was higher among neonates of Group II; the difference was, however, not statistically significant. On the other hand, there were no significant differences between both groups regarding 5-min Apgar score, need for neonatal resuscitation or neonatal respiratory distress (Table 4).

**Table 4: Comparison of the neonatal outcomes of the study groups.**

| | Group I (Paracetamol) (n=45) | Group II (Meperidine) (n=44) | MD/RR (95% CI) | *P* | NNH |
|---|---|---|---|---|---|
| **Birth weight (g)** | | | | | |
| Range | 2250-3700 | 2300-3900 | -48.9 (-237.3 to 139.4) | 0.607[1] NS | - |
| Mean±SD | 3053.3±433.9 | 3102.3±460.02 | | | |
| **1-min Apgar score** | | | | | |
| Range | 6-9 | 4-9 | 0.7 (0.2 to 1.1) | 0.023[2] S | - |
| Median (IQR) | 8 (7-9) | 8 (7-8) | | | |
| **1-min Apgar score < 7** | 1 (2.2%) | 5 (11.4%) | 0.2 (0.02 to 1.6) | 0.195[3] NS | 11 |
| **5-min Apgar score** | | | | | |
| Range | 6-9 | 6-9 | 0.09 (-0.2 to 0.4) | 0.591[2] NS | - |
| Median (IQR) | 8 (7-9) | 8 (7-9) | | | |
| **5-min Apgar score < 7** | 1 (2.2%) | 1 (2.3%) | 0.98 (0.06 to 15.2) | 0.484[3] NS | 1980 |
| **Need for neonatal resuscitation** | 1 (2.2%) | 4 (9.1%) | 0.2 (0.03 to 2.1) | 0.344[3] NS | 15 |
| **Neonatal respiratory distress** | 1 (2.2%) | 2 (4.5%) | 0.5 (0.05 to 5.2) | 0.984[3] NS | 43 |

Data presented as range, mean±SD; range, median (IQR); or number (percentage); SD standard deviation; IQR interquartile range; MD (95% CI) mean difference and its 95% confidence interval; RR (95% CI) risk ratio and its 95% confidence interval; 1 Analysis using independent student's t-test; 2 Analysis using Mann-Whitney's U-test; 3 Analysis using chi-squared test; NS non-significant-S significant; NNH number to needed to harm.

## DISCUSSION

Tools of obstetric analgesia and anesthesia include both non-pharmacological and pharmacological techniques. There are two primary types of analgesic drugs: opioids and non-opioids.[12]

Non-opioid analgesics have antipyretic and analgesic properties. They do not bind to opioid receptors and are, therefore, milder forms of painkiller. Paracetamol has been considered as the most common over-the-counter analgesic used.[12]

Opioids agents bind to opioid receptors, principally existing in the central and peripheral nervous system and the gastrointestinal tract.[13] The major concerns are associated with the use of opioid analgesia are the risk of fetal/neonatal respiratory depression, and the cost and availability.[14]

Therefore, there is a call to find a readily-available, low-cost and quite safe analgesic for labor pain relief.

A total of 92 primiparous singleton term pregnant women were recruited in the current randomized controlled trial. Women were randomly allocated to receive either intravenous infusion of paracetamol (1000 mg), or intramuscular meperidine (50 mg), at the beginning of the active phase of labor. Repeat doses were given upon women's requests.

Women of both groups showed significant reduction of the VAS measured 15, 30 and 60 minutes after administration of the allocated medication. The difference between both groups regarding the analgesic

effect was only significant at 15 minutes after administration, in favor of meperidine groups (indicating a more rapid onset of action).

The significantly higher efficacy of meperidine shortly after administration is explained by the short time-to-peak-onset-of-action that is known with all opioid analgesics. In triple-blind randomized trial on 120 primiparous women, randomized into receiving either 1000 mg of paracetamol infusion, meperidine (50 mg), or placebo, there were significantly lower pain scores 15 and 30 min after administration of the medication.[14]

Similarly, in a recent randomized trial on 38 women by Ankumah and colleagues, the pain scores were comparable in both groups of women up to 120 min after administration of the analgesic.[15]

Regarding the maternal adverse effects, the administration of meperidine was associated with a 12-fold risk of dizziness and nausea/vomiting compared to paracetamol.

In agreement with our results, Elbohoty et al, found a nil rate of adverse effects among women who received paracetamol in contrast to 64% of women who received pethidine.[6] The adverse effects included nausea, vomiting, dizziness and drowsiness.

About 51% of women of group I needed one dose of paracetamol, and 49% needed two doses. On the contrary, 39% of women of group II needed one dose of meperidine, 27% needed two doses, and 34% needed three doses.

Despite the relatively longer half-life of meperidine (8-12 hours) in comparison to paracetamol (1-3 hours), the significantly higher number of doses observed with the former in comparison to the latter might be explained by the finding that meperidine is rapidly hydrolyzed in the liver into pethidinic acid and is also demthylated into norpethidine, which almost has half the analgesic potency of meperidine.[16]

There were no significant differences between women of both groups regarding the mode of delivery and the durations of the first or second stages of labor.

In partial disagreement with the results of the current trial, Makkar et al, found a significantly shorter duration of the first stage of labor in women who received paracetamol when compared to those who received tramadol (248±98.17 min versus 340.53±111.59 min, respectively, p=0.003), and comparable durations of the second stage of labor in both groups.[17] This might be explained by the fact that in our study, meperidine was withheld when the patients reached 8 cm of cervical dilatation, or that the used doses in their study was higher (1mg/kg).

The 1-min Apgar scores were significantly lower in women who received meperidine. However, the proportion of neonates with a 1-min Apgar score < 7 was not different between both groups. There were no significant differences between both groups regarding the 5-min Apgar score, the need for neonatal resuscitation or the incidence of neonatal respiratory distress.

Meperidine is known to cross the placenta, and the birth of a newborn between 1 and 4 hours following its administration was shown to be associated with neonatal respiratory depression, with maximal respiratory depression occurring 2-3 hours after administration 18. This may explain the reason for lower 1-min Apgar scores in neonates of women who received meperidine. However, this effect is probably temporary, as the 5-min Apgar scores were comparable in both groups.

## CONCLUSION

The present study shows that the use of IV paracetamol as analgesia during labor appeared to be effective, safe, with no fetal or maternal adverse effects. Using paracetamol for labor analgesia needs to have more chance in comparison with other forms and routes. Additionally, it can be used as an adjuvant with other types of analgesics.

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*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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