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Randomised Trial on Intravenous Paracetamol versus Intramuscular Nalbuphine as Obstetrics Analgesia in First Stage of Labour

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ABSTRACT

Objectives: Labor pain is one of the most extreme pains ever described in the human experience, and different centers may have different standards and available pharmacologic options for managing labour pain. This study aimed to compare the efficacies of intravenous paracetamol and intramuscular nalbuphine for intrapartum analgesia.

Materials and Methods: We conducted a randomized controlled study from April 2019 to March 2020 in the Department of Obstetrics and Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan. This study involved 80 primigravidae who fulfilled the inclusion criteria and were randomly divided into two groups. The control group received 10 mg intramuscular nalbuphine, whereas the treatment group received 1,000 mg (100 mL vial) of intravenous paracetamol, infused over 15 minutes. Pain assessment before the administration of drugs and at 1 hour, 2 hours, and 3 hours post medication was recorded. Secondary outcomes, such as neonatal outcomes and maternal adverse events, were recorded.

Results: Demographic and clinical data between these two groups were similar. The mean pain score for the control and treatment groups before medication administration was 6.76 and 6.66, respectively. The mean pain score was 5.06 in the control group and 6.09 in the treatment group at 1-hour post medication, 6.19 and 6.89 at 2 hours post medication, and 7.51 and 7.57 at 3 hours post medication, respectively. No statistically significant difference in the mean pain score was found between the groups. However, more maternal adverse events were seen in the control group. No neonatal adverse events were reported in both groups.

Conclusion: Intravenous paracetamol showed no difference in intrapartum analgesic effect compared to intramuscular nalbuphine. However, in this study, we found out it has far fewer maternal adverse events.

Keywords: intravenous paracetamol, intramuscular nalbuphine, intrapartum analgesia, maternal adverse events, fetal adverse events.

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Introduction

Labour is the active process of delivering a fetus and is characterized by regular, painful uterine contractions that increase in frequency and intensity as parturition approaches. The intensity of labor pain faced by every woman has been found to affect the progress of labor, fetal outcome, and maternal physiological and psychological well-being.

Ideally, intrapartum analgesics should have high potency. However, the best choice of pain relief is determined by the available facilities and by a team of experts. Systemic opioids have been widely used for intrapartum analgesia; however, they are associated with maternal and fetal adverse events. These concerns have led to an exploration of alternative non-opioids for intrapartum analgesia.

Intravenous (IV) paracetamol is an effective antipyretic and non-opioid analgesic for treating moderate pain. Paracetamol has a central analgesic effect mediated through the activation of descending erotogenic pathways, inhibiting prostaglandin synthesis in the central nervous system and peripherally blocking pain impulse generation[1, 2]. Paracetamol has been used for a century, and its efficacy and tolerability are well established. However, there is a paucity of studies assessing its intrapartum use. Previous studies have shown that the analgesic effect of paracetamol is similar to that of a few types of opioids, and it has a favorable safety profile[3-6].

At our centre, we use intramuscular (IM) nalbuphine for intrapartum analgesia. Nalbuphine is a unique mixed agonist-antagonist in which a kappa-opioid receptor agonist as analgesia and a partial mu-opioid receptor antagonist which provides ceiling effect nausea, pruritus, and respiratory depression when compared to morphine[7]. It has been used as intrapartum analgesia and showed fewer side effects compare to other opioids[8-10]. Our extensive literature review revealed that no studies to date have compared IV paracetamol to IM nalbuphine. Hence, the current study aimed to compare the analgesic efficacy of IV paracetamol as intrapartum analgesia to that of IM nalbuphine and assess for maternal and neonatal adverse events.

Materials and Methods

This study was a randomized controlled trial performed from April 2019 to March 2020 in the Department of Obstetrics and Gynaecology, Hospital Raja Perempuan Zainab II Kota Bharu, Kelantan.

Approval to conduct this study was obtained from the Human Medical Research and Ethics Committee of Universiti Sains Malaysia (Ethics Approval Number: USM/JEPeM/18110756) and the Medical Research and Ethics Committee of the Ministry of Health, Malaysia (Ethics Approval Number: NMRR-18-3168-44683). This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki by the World Medical Association, the Malaysian Guideline for Good Clinical Practice, and other applicable regulatory requirements.

Written informed consent was obtained from primigravidae in labor who fulfilled the inclusion criteria. The inclusion criteria were singleton pregnancy at term in spontaneous labor without any risk factors (e.g. diabetes mellitus, hypertension, heart disease, blood-borne infectious diseases like hepatitis B/C or human immunodeficiency virus (HIV), liver disease or renal impairment) and a body mass index (BMI) of 18 - 30 kg/m^2. Women with a history of a scarred uterus, medical disorders, use of any analgesic before

recruitment, fetal distress or hypersensitivity to paracetamol or nalbuphine, and those who did not complete 4 hours in the study were excluded.

After enrolment, each participant was allocated the next available number in a concealed sequence of a computer-generated randomization plan that determined which drug was to be administered. The participants were randomly allocated into two groups. In the paracetamol (intervention) group, patients received an IV infusion of 1,000 mg paracetamol contained in a 100-mL vial over 15 minutes. In the nalbuphine (control) group, patients received 10 mg IM nalbuphine (1 ampoule, 1 mL = 10 mg). The recommended dose for IV paracetamol is 15 mg/kg, whereas that of nalbuphine is 10 - 20 mg 3 - 6 hourly with a maximum dose of 160 mg[11].

The drugs were immediately given after the artificial rupture of membranes (ARM) or the lack of membranes and when cardiotocography (CTG) was normal. The study drugs were prepared and administered by a staff nurse who was not involved in the assessment of outcome measures. Both medications were available in the labor room. Participants reported pain intensity by scoring on a visual analogue ccale (VAS; 0 = no pain; 10 = worst pain). Pain assessment was performed by a medical officer in the labor room who had no role in participant enrolment. Pain assessment before administering drugs and at 1 hour, 2 hours, and 3 hours post medication was recorded. Participants who had not delivered within 4 hours and still needed analgesics were given another dose of treatment (a minimum interval between each administration is 4 hours). A participant who requested rescue analgesics before the expected time (before 4 hours of labor) received Entonox® inhalation.

Labour was managed actively, using a partogram to monitor the maternal well-being (vital signs; blood pressure, pulse, temperature, pain score, urine output, hydration, and drug administered), fetal well-being (liquor, fetal heart rate, formation of caput or molding) and progress of labor (cervical dilatation, descend of fetal presentation, and uterine contraction). Duration of the first stage of labor, CTG, mode of delivery, and any intrapartum complication and maternal adverse events were recorded. Following delivery, birth weight, Apgar scores at 1 minute and 5 minutes, and any neonatal complications such as immediate neonatal respiratory problems and neonatal intensive care unit (NICU) admission were recorded.

Sample size calculation

The sample size of the study was calculated using the Power and Sample size (PS) software.

Significance level = 0.05, power = 80%, m = 1:1. The primary outcome VAS score measure was used to calculate the sample size. The parameters used in this sample size determination were the mean difference = 1.0, SD for paracetamol = 1.35[12] and p value of comparing analgesic effects of group paracetamol and placebo = 0.007. It was calculated that a minimum sample size of 30 women in each group would be needed to observe this difference at a similar or narrower confidence interval. Assuming a dropout rate of 20%, the sample size was set to 40 in each group. Thus, the total sample size is 80.

Data were analyzed using SPSS version 24 for Windows. A probability value of < 0.05 was considered to be statistically significant with a 95% confidence interval (CI). Descriptive data were expressed as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. The median and interquartile range were used to express skewed data. Demographic data, baseline characteristics, and primary and secondary outcome measures of both the groups were compared using an independent t-test and chi-squared/Fisher's exact test. Repeated-measures analysis of variance (ANOVA) was conducted to study the efficacy of IV paracetamol (intervention group) and IM nalbuphine (control group) based on pain scores using VAS. First, within-group analysis was performed to determine the individual effects within each group based on the VAS score. Second, between-group analysis was performed to compare the effects of each group treatment based on VAS score regardless of time. Lastly, within-between group analysis was used to compare the treatment effects between the two groups based on time. Multivariate analysis was performed for the VAS -

treatment interaction results based on the F-test. We used (two-way) repeated-measures ANOVA to test the hypothesis and determine the mean difference between groups (independent group and within group) at three repeated time points and also an interaction between each group and time.

The association between maternal adverse events and the study groups was tested using Pearson's chi-squared test. An independent t-test was used to compare fetal adverse events and Apgar scores at 1 minute and 5 minutes between the two groups. The association between fetal adverse events and CTG and the study groups was tested using Fisher's exact test.

Results

A total of 80 pregnant women were recruited and completed the study. Forty women were randomly included in the intervention group and 40 were designated as controls. The flow chart for patient recruitment is shown in Fig. 1.

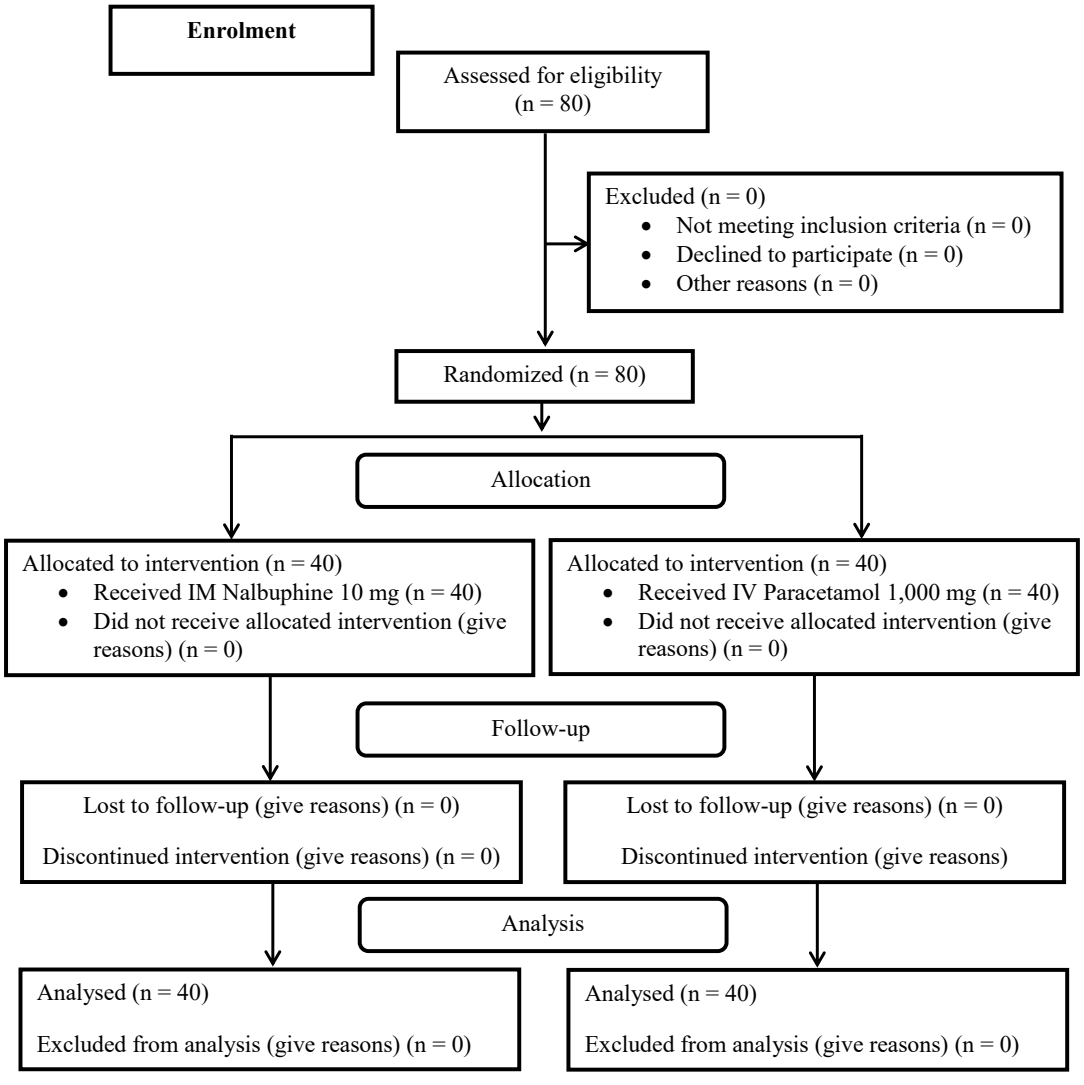

Fig. 1. Trial profile of this randomized controlled trial on IV paracetamol versus IM nalbuphine as intrapartum analgesia.

IM: intramuscular, IV: intravenous.

The mean age of the control group was 24.70 ± 3.65 years, and the mean age of the intervention group was 25.00 ± 2.84 years. All participants belonged to the Malay ethnic group. All participants were at term. Sixty-eight (85.0%) participants had ARM, whereas 12 (15.0%) had spontaneous rupture of membranes.

Meanwhile, 49 (61.3%) participants were on oxytocin so that all patients achieved four strong contractions in 10 minutes, of which, 45 (56.2%) presented with 4 cm cervical dilation, whereas 23 (28.8%) and 12 (15.0%) presented with 5 cm and 6 cm dilations, respectively. Only 2 (2.5%) patients required rescue analgesia in the control group and 3(3.75%) in the treatment group. A total of 60 (75.0%) participants delivered by spontaneous vaginal delivery, whereas 8 (10.0%) and 12 (15.0%) participants delivered by instrumental delivery and lower segment Cesarean section, respectively. The mean duration of labor for participants in the control and intervention groups was 4.47 (1.49) and 5.23 (2.34) hours, respectively. The maternal and labor characteristics are described in Table 1.

Table 1. Maternal and labor characteristics of enrolled patients.

Maternal characteristics	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	p value
Age	24.70 (3.65)†	25.00 (2.84)†	0.683*
Weight	55.00 (9.00)†	56.00 (10.00)†	0.849*
Height	154.85 (5.46)†	154.75 (4.98)†	0.932*
BMI	24.47 (3.89)†	24.39 (2.81)†	0.918*
Gestation on admission			0.304**
37 - 38^{+6}	19 (23.8)	14 (17.5)	
39 - 40^{+6}	18 (22.5)	19 (23.8)	
41 - 41^{+6}	3 (3.8)	7 (8.8)	
Oxytocin augmentation			0.251**
No	18 (22.5)	13 (16.3)	
Yes	22 (27.5)	27 (33.8)	
Rescue analgesia			0.644**
No	38 (47.5)	37 (46.3)	
Yes	2 (2.5)	3 (3.8)	
Dilatation of cervix			0.295**
4	22 (27.5)	23 (28.8)	
5	14 (17.5)	9 (11.3)	
6	4 (5.0)	8 (10.0)	
Mode of delivery			0.659**
Spontaneous vaginal delivery	30 (37.5)	30 (37.5)	
Caesarean section	7 (8.8)	5 (6.3)	
Instrumental delivery	3 (3.8)	5 (6.3)	
Duration of labour			0.091*
First stage (hours)	4.47 (1.49)†	5.23 (2.34)†	
Second stage (minute)	30.52 (16.40)†	28.78 (13.70)†	
Third stage (minute)	11.15 (6.51)†	10.74 (5.45)†	

† mean and standard deviation (SD). Otherwise, all values are in frequency and percentage. * Independent t-test. Otherwise, **Pearson Chi-square. BMI: body mass index

The distribution of outcomes in this study was described based on the primary and secondary outcomes. The primary outcome observed was the pain assessment after the administration of IV paracetamol (intervention group) and IM nalbuphine (control group). The primary outcomes are described in Table 2.

Table 2. Distribution of pain assessment based on the visual analogue scale scores and mean pain scores.

Pain	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	Mean difference (95% CI)	p value
Before injection	6.76 (1.91)	6.66 (1.86)	- 0.44 (- 1.34, 0.47)	0.339
After 1 hour of injection	5.06 (1.75)	6.09 (2.09)	- 0.69 (- 1.61, 0.21)	0.131
After 2 hours of injection	6.19 (1.84)	6.89 (2.03)	- 0.06 (- 0.89, 0.78)	0.891
After 3 hours of injection	7.51 (1.84)	7.57 (1.74)	- 1.19 (- 3.63, 1.25)	0.334

Repeated-measures ANOVA for within-between group analyses based on time was applied. Assumptions of normality, homogeneity of variances, and compound symmetry were checked and fulfilled. A p-value of < 0.005 indicated statistical significance.
CI: confidence interval

No significant difference was observed in the mean pain score between patients in the intervention and control groups based on VAS scores, regardless of the time in labor. As shown in Table 3, repeated-measures ANOVA was conducted to identify the within-group effects of each study drug based on time showing that there was a significant mean difference in each measurement time comparison within each group.

The secondary outcomes were maternal adverse effects during the medication period (Table 4).

Table 3. Comparison of within-group pain scores based on time (time effect).

Time	Control group (n = 40)		Intervention group (n = 40)	
	MD (95% CI)	p value	MD (95% CI)	p value
1 - 2 hours post injection	- 0.54 (- 0.94, - 0.14)	0.005	- 0.80 (- 1.26, - 0.34)	< 0.001
1 - 3 hours post injection	- 1.87 (- 2.52, - 1.21)	< 0.001	- 1.49 (- 2.13, - 0.85)	< 0.001
2 - 3 hours post injection	- 1.32 (- 1.93, - 0.72)	< 0.001	- 0.69 (- 1.08, - 0.29)	< 0.001

Repeated-measures ANOVA for within-group analyses was applied followed by multiple comparisons. Bonferroni correction was applied. A p value of < 0.05 indicated statistical significance. MD: mean difference, CI: confidence interval

Table 4. Distribution and association between maternal adverse effects and study group.

Maternal adverse effects	Control group (n = 40) n (%)	Intervention group (n = 40) n (%)	p value
Dizziness	8 (10.0)	1 (1.2)	0.001*
Nausea and vomiting	4 (5.0)	0 (0.0)	0.001*

* Fisher's exact test.

Twelve out of 40 patients in the control group experienced dizziness, nausea, and vomiting, whereas, in the intervention group, only 1 out of 40 patients complained of dizziness.

Fetal adverse events are shown in Table 5. The Apgar scores at 1 minute and 5 minutes between the control and intervention groups were found not significantly different (p = 0.233 and 0.323, respectively) with a 95% CI of mean difference (- 0.13, 0.53; - 0.10, 0.30, respectively).

Table 5. Distribution and association between fetal adverse effects and study group.

Foetal adverse effects	Control group (n = 40) mean (SD)	Intervention group (n = 40) mean (SD)	p value
Apgar scores at 1 minute	8.88 (0.56)	8.68 (0.89)	0.233
Apgar scores at 5 minutes	10.00 (0.00)	9.90 (0.63)	0.323
CTG			0.675[a]
Suspicious/abnormal	28 (35.0)*	39 (48.8)	
Normal	12 (15.0)*	1 (1.2)	
Birth weight (kg)	3.05 (0.41)	3.18 (0.38)	0.160[b]
Respiratory problem immediate post delivery	0 (0.0)*	0 (0.0)*	
Admission to NICU	0 (0.0)*	0 (0.0)*	

* Frequency and percentage. Otherwise, all values are in mean and standard deviation (SD). Fischer's exact test. b Independent t-test.
CTG: cardiotocography, NICU: neonatal intensive care unit

Discussion

We conducted a single-center randomized clinical study to compare IV paracetamol with IM nalbuphine for pain relief in labor on a group of primigravidae and found no significant difference in pain scores. Interestingly, adverse maternal events were significantly lower in the IV paracetamol-treated group. Every birth experience is different, and the degree of pain may vary between individual pregnancies. Labour pain is complex and subjective and can vary greatly. It is a multifactorial physiological phenomenon that varies in intensity among women and is subject to social and cultural modifiers. Multiple pharmacological options are available to help women manage labor pain. The optimal analgesic effect is still regional anesthesia; however, with limited skilled staff, limited equipment, and high economic cost, it cannot be made routinely accessible to all. While opioids are effective substitutes, they cause marked side effects in both mother and fetus, including maternal nausea, vomiting, and drowsiness[8-11, 13, 14]. Pethidine is the most commonly used opioid worldwide[13, 14].

The in-hospital labour analgesic at Raja Perempuan Zainab II is IM nalbuphine (10 mg). A previous study showed that the analgesic efficacy of nalbuphine is comparable to that of pethidine; however, the side effects may also be similar, i.e. nalbuphine also induces nausea and vomiting[8, 10, 13-15]. Concerns regarding the side effects on women and babies suppress the usage of opioid medication for labor analgesia.

In this study, the patient sociodemographic characteristics were comparable between the control and treatment groups (Table 1). All our patients were primigravidae and had no previous experience of labor pain. This is an important factor to prevent biased results. Other factors influencing labor pain and delivery include maternal psychological state, mental preparation, family support, cultural background, and size and presentation of the fetus[16]. However, these other factors were not specifically considered in this study. Of particular note, since all patients belonged to the same

on oxytocin augmentation, with comparable prevalence between the two groups. The comparison is shown in Table 2, in which the number of patients on oxytocin augmentation in the control and treatment groups was 22 and 27, respectively. This is important in view of the aggravated pain usually caused by oxytocin in labor.

The mean duration of labor in the control and intervention groups was 4.47 and 5.23 hours, respectively. This finding contradicted that of previous studies, which demonstrated a remarkably shorter mean drug-to-delivery interval with paracetamol than with either tramadol or pethidine[3, 5]. The overall duration of labor between the two groups in our study did not differ significantly. Furthermore, cervical dilation before analgesic administration was also comparable between the groups (Table 1). Thus, the clinical presentation and handling of participants in both groups were also similar.

We successfully demonstrated that IV paracetamol for intrapartum analgesia was as effective as IM nalbuphine. The analgesic effect of paracetamol peaks at 1 hour following administration. This was demonstrable with a reduction in the mean pain score at 1 hour compared with the pre-treatment pain score (Table 2). The mean VAS score at 1 hour in the nalbuphine group was 5.06 and 6.09 in the paracetamol group. Both groups showed similar patterns in the rise and fall of VAS scores. The high pre-treatment pain scores amongst the patients in our study were likely due to the patient recruitment coinciding with the active phase of labor during which analgesia is deemed most needed. However, at 3 hours, the mean score increased even higher than the pre-treatment score. The onset of action of paracetamol occurs within 5 - 10 minutes of administration for a total duration of approximately 4 - 6 hours[17]. The increased mean score at 3 hours of treatment may be contributed by labor progress, which would be accompanied by increasing contraction pain intensity and frequency.

This study found no significant difference in the mean pain scores between patients in the intervention and control groups. Furthermore, the comparison revealed no statistically significant difference in pain scores at 1, 2, and 3 hours post-injection between the two groups ($p = 0.312$, 0.223, and 0.891, respectively). This was similar to previous findings in which the onset of analgesia after IV paracetamol occurred within 5 minutes, peaking at 40 - 60 minutes and lasting 4 - 6 hours[18]. The increase in the mean VAS score at 2 - 3 hours may indicate diminished clinical effect or accelerated pain because of labor progress.

The numbers of patients who required rescue analgesia were similar in both the groups, two in the control group and three in the treatment group. We gave Entonox to patients who had intolerable pain despite receiving analgesic treatment. This is the finding that supports the usage of these drugs as intrapartum analgesia as less than 10% of patients in each group required rescue analgesia. The pain is subjective and the accelerated pain because of Pitocin usage and progress of labor make the use of pain scoring cannot be used as the only indicator of the drug effect intrapartum. Most comparative studies involved IV paracetamol pitted against opioids such as tramadol and pethidine[3-6]. Although these trials used different opioids, they consistently showed reduced pain scores in the paracetamol group, thus indicating similar pain relief effects.

Common side effects of nalbuphine include drowsiness, dizziness, headache, nausea and vomiting, whereas the most commonly reported side effects of IV paracetamol are nausea and vomiting. In this study, more adverse events were observed in the nalbuphine group, whereas in the paracetamol group, only one patient experienced dizziness, indicating a favorable side effect profile for paracetamol (Table 4). This finding was consistent with that of other studies[1-21].

Neonatal outcomes were favorable in both groups. Most of our patients delivered babies with good Apgar scores who did not require NICU admission. Four cases of suspicious fetal heart tracing were reported in the nalbuphine group and two cases in the paracetamol group. However, at the time of delivery, the babies obtained good Apgar scores (Table 5). These findings confirm the absence of any clinically significant adverse neonatal effects with the use of the either drug. None

of the neonates required narcain post-delivery. All pharmacologic relief for intrapartum analgesia has side effects, either for the mother or the fetus. The placental transfer of nalbuphine is high, rapid, and variable, with a mother-to-fetus ratio ranging from 1:0.37 to 1:6.00. Foetal and neonatal adverse events have been reported, including fetal bradycardia, respiratory depression at birth, apnoea, cyanosis and hypotonia[23]. One study reported fetal heart rate flattening in 54% of cases and one neonate with a low Apgar score[25]. Paracetamol is considered safe for use in pregnancy, although a small amount of active drug may cross the placenta[6]. Paracetamol also has a non-selective inhibitory action on peripheral and central cyclooxygenase (COXs) and they may also contribute to explaining more recent proposed positive effects of paracetamol such as the closure of a patent ductus arteriosus (PDA) in the preterm, and other unwanted effects of paracetamol such as issues related to atopy, fertility and/or neurobehavioral following perinatal exposure during the first and second trimester[22]. The short-term safety has been documented and it is safe to use as intrapartum analgesia in term gestation[12, 22].

The outcome of this study gave an additional option of intrapartum analgesia available at our hospital, and the cost implication should be considered in the usage of this analgesia.

Limitations

VAS scoring was a subjective tool in this study. It was also impossible to blind the subjects, trial coordinator, and assessor because the drugs were dispensed without any camouflage.

Future equivalent and non-inferior trials should be conducted to show that intravenous paracetamol is recommended as intrapartum analgesia as it may have an equivalent effect with fewer side effects.

Conclusion

Intravenous paracetamol showed no difference in intrapartum analgesic effect compared to intramuscular nalbuphine. However, in this study, we found out it has far fewer maternal adverse events.

Acknowledgement

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Potential conflicts of interest

The authors declare no conflicts of interest.

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