Original Article

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Efficacy of Intravenous Infusion of Acetaminophen for Intrapartum Analgesia

Obstetrics and Gynaecology Section

VIJAY ZUTSHI[1], KUMARI USHA RANI[2], SHEEBA MARWAH[3*], MADHUMITA PATEL[4]

ABSTRACT

Introduction: The intensity of pain experienced by women in labour, has been found to affect the progress of labour, foetal well-being and maternal psychology. Adverse effects associated with commonly used opioids for providing intrapartum analgesia have created a need for an alternative non-opioid drug.

Aim: To evaluate the efficacy of an intravenous infusion of 1000 mg of acetaminophen as an intrapartum analgesic.

Materials and Methods: The present prospective single-centre, single blind, placebo-controlled randomized interventional study was conducted in Department of Obstetrics and Gynaecology in Vardhaman Mahavir Medical College & Safdarjung Hospital over a period of six months from September 2014 to March 2015. After receiving the ethical clearance and written informed consent. The first 200 consecutive parturients fulfilling the inclusion criteria were recruited into the study. Women were then randomised to receive either intravenous 1000 mg (100ml) of acetaminophen (Group A, n=100) or 100 ml normal saline (Group B, n=100). Primary outcome assessed was effectiveness of acetaminophen to provide an adequate amount of analgesia, as measured by a change in Visual Analogue Scale (VAS) pain intensity score at various times after drug administration. Secondary outcomes measured were duration of labour, need for additional rescue analgesia and presence of adverse maternal or foetal effect.

Results: There was pain reduction at 1 and 2 hours in both groups ($p<0.001$). However, it was more significant in the acetaminophen group, especially at 1 hour. Duration of labour was shortened in both the groups, without any maternal and foetal adverse effects.

Conclusion: Intravenous acetaminophen is an efficacious non-opioid drug for relieving labour pain without any significant maternal and foetal adverse effects.

Keywords: Labour, Paracetamol, Placebo, Opioids

INTRODUCTION

Child birth is allied with very severe pain for most women. Pain during labour is a complex, subjective and multi-faceted physiological phenomenon that varies in intensity among women and is subjected to many social and cultural modifiers. It encompasses both sensory component and the very vital emotional, motivational and cognitive facets [1,2]. Initially pain commences predominantly in cervix and lower uterine segment but later on, following descent, progressively grander pressure of foetus on vagina and perineum engender superfluous sources of pain. The intensity of pain felt during labour has a direct bearing on maternal psychology, labour progress and foetal well-being. Especially during the first stage, it evokes a generalized neuroendocrine stress response, instigating marked physiologic changes in oxygen consumption, acidemia and cardio-pulmonary functions, along with restraining uterine contractions [3]. Thus, it becomes imperative on the part of the modern day obstetrician to provide adequate analgesia to women in labour.

An ideal labour analgesic should have potent analgesic efficacy with negligible side-effects to be used for pain relief. Systemic opioids have been widely used for relief of labour pain. Of these are pethidine (meperidine), fentanyl, tramadol, butorphanol, remifentanil and ketamine [4]. However, systemic opioids are associated with maternal (dysphoria, sedation, respiratory depression, nausea and vomiting and delayed gastric emptying) and fetal adverse effects (fetal distress, early neonatal respiratory depression and behavioural and feeding problems) for up to six weeks post-delivery [5]. These concerns have led to an exploration of an alternative non-opioid for maternal pain relief in labour.

Acetaminophen is an effective non-narcotic analgesic and antipyretic drug with tolerable side-effects [6]. Acetaminophen is thought to exert its analgesic activity by inhibiting the synthesis of prostaglandins in the Central Nervous System (CNS) (central acting) and peripherally blocking pain impulse generation [7,8]. Also, it has a serotonergic (5-HT) mechanism and a cannabinoid agonism mechanism contributing to its analgesic effect [9]. When compared to other opioids, and nonsteroidal anti-inflammatory drugs, paracetamol has a favourable safety profile without any risk of congenital anomalies [8,10,11].

The use of IV formulation during labour for pain relief is advantageous with improved bioavailability and earlier onset of action with higher mean IV C max (maximum plasma concentration of drug) and an earlier time to maximum concentration (T-max), with less intra-subject variability, in contrast with other formulations.

Though its role in pre-emptive approach to management of postoperative pain has been adequately studied by various authors [12-14], there is paucity of work on utilization of paracetamol as an intrapartum analgesic drug. Thus, it appeared apposite to design a randomized trial to investigate the proposed use of acetaminophen. Hence, the purpose of the extant study was to appraise the effectiveness and unfavourable side effects (if any) of an intravenous infusion of 1000 mg of acetaminophen during the active phase of labour as a method of imparting pain reprieve to the parturients.

MATERIALS AND METHODS

The present single-centre, single blind, randomized parallel assessment trial was conducted in Department of Obstetrics and

Gynaecology in Vardhaman Mahavir Medical College & Safdarjung hospital over a period of six months from September 2014 to March 2015 after getting ethical clearance. Subsequently, after taking a written informed consent, the first 200 consecutive women in labour presenting for delivery at the institute, fulfilling the following inclusion criteria were recruited into the study: a) primiparous low-risk parturients; b) aged 18–35years; c) spontaneous onset of labour at term (37–42 weeks gestation); d) First stage of labour with cervical dilatation of 3–6 cm; e) single viable fetus; f) cephalic presentation; g) patient seeking analgesia. The exclusion criteria were: a) clinical evidence of cephalo-pelvic disproportion; b) malpresentation; c) any medical disorder during pregnancy; d) induction of labour; e) use of any other kind of analgesia before recruitment to the study; f) scarred uterus; g) fetal distress; h) Antepartum Haemorrhage (APH); i) Intrapartum bleeding; j) Polyhydraminos; k) Prelabour rupture of membranes(PROM); l) Intrauterine infection; m) Postpartum Haemorrhage (PPH); n) Previous history of hypersensitivity to paracetamol.

Among 960 women scrutinized, 200 fulfilling the inclusion criteria were enrolled in the study after excluding 760 females. Cervical dilatation and demographic data, including age, gestational age, and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), were recorded.

The sample size was calculated using the latest available via Epi Info version to obtain a power (β) of 80% and a significance level (α) of 0.05. Analysing the body of work on labour analgesia, a minimal sample size of 100 women in each group was needed to observe the optimal confidence interval. After conscription, each participant was randomly allocated to either of the two Groups A or B by a concealed sequence of a computer-generated randomization plan.

The participants in Group A (Cases, n=100) received a 100-mL intravenous infusion containing 1000 mg of acetaminophen (Paraglan-IV, Gland pharma limited, Hyderabad, India) over 15 minutes; in group B (Controls, n=100), women received an intravenous infusion of 100 mL of normal saline (NS, Albert David limited, Ghaziabad, UP, India) over 15 minutes. Labour was followed up according to the hospital's protocols with artificial rupture of membranes and subsequent augmentation with an oxytocin infusion (if there were fewer than 3 contractions in 10 minutes, each lasting less than 40 seconds). Parturients described pain intensity on a 100-mm VAS, delimited by "no pain" and "the worst pain", just before having obtained the study drug and subsequently at 15 minutes, 1 hour, 2 hours, 3 hours and 4 hours after drug administration. Pain assessment was performed by intern (who had no role in patient enrolment and was blind to the drug administration). Women who did not deliver within 4 hours and still needed analgesia were given an additional injection of tramadol intramuscularly 50mg (Pentazen, Ind Swift Limited, Najabgarh, India) in both the groups. All the drugs used were available free in hospital supply. Pain was not assessed after 4 hours because, despite the possibility of repeated drug intake, by then more than 50% of participants had delivered—either vaginally or by caesarean. This would lower the participant numbers and shorten the interval to delivery, making the comparison non-informative.

The primary outcome measured were efficacy of the drug to supply adequate analgesia, as measured by a change in the VAS pain intensity score at 15 minutes, 1 hour, 2 hours, 3 hours and 4 hours after drug administration. Secondary outcome measures included duration of labour, need for rescue or additional analgesia, and presence of maternal uneasiness or adverse effect (dizziness, tachycardia, dyspnoea, vomiting, blurred vision, dryness of mouth, and significant changes in blood pressure {≥30 mm Hg systolic or ≥15 mm Hg diastolic}) and fetal/ neonatal adverse events (non-reassuring cardiotocography including foetal tachycardia, low Apgar scores at 1 and 5 minutes, and need for admission to the intensive care unit).

STATISTICAL ANALYSIS

Data was recorded on a predesigned proforma and deciphered at end of study using relevant statistical tests. Excel 2010 (Microsoft, Redmond, WA, USA) and SPSS version 18.0 (IBM, Armonk, NY, USA) were used for data presentation and statistical analysis.

RESULTS

Parturients in both the groups were primigravidae in active stage of labour and were comparable to one another in their demographic characteristics [Table/Fig-1]. Women in both the groups had comparable VAS scores before the initiation of treatment (6.82-7.34 in Group A and 6.76-7.28 in group B) [Table/Fig-2]. In contrast to the pretreatment score, the mean VAS score was lower at 15 minutes, 1 hour, 2 hour, 3 hours and 4 hours after treatment in both groups. The lowest scores were observed at 2 hours of drug administration. Comparing the change in VAS score from the initial score between the two groups, the reduction in pain was significantly greater in Group A at all times except at 15 minutes. [Table/Fig-2]. No variation in mean drug-to-delivery interval was noted (paracetamol group, 3.6 hours; placebo 3.5 hours) [Table/Fig-3] in both the groups. No variance in the percentage of vaginal deliveries (94% each) was observed in either of the groups [Table/Fig-4]. Lower Segment Caesarean Section was performed in six subjects each in both the groups due to non-reassuring fetal heart rate patterns. No adverse maternal or neonatal effects were witnessed in either groups. There were no differences in the occurrence of intrapartum fetal distress or lowered neonatal Apgar scores between both groups [Table/Fig-5].

Baseline characteristics	Cases (Group A) (n=100)	Controls (Group B) (n=100)	p-value
Age (years)			
<20	40	28	0.063
20-25	44	66	
26-30	16	6	
>30	0	0	
Gestational age (weeks)			
37-40weeks	86	84	0.790
40-42 weeks	14	16	
Religion			
Hindu	72	86	0.134
Muslim	24	12	
Sikh	4	2	
Christian	0	0	
Others	0	0	
Residence			
Urban	22	10	0.102
Rural	78	90	
SE_a status (Modified Kuppuswami)			
i)	0	0	0.248
ii)	0	0	
iii)	10	4	
iv)	34	48	
v)	56	48	
BMI (Kg/m^2)			
Underweight	38	30	0.396
Normal	60	70	
Overweight	2	0	
Obese	0	0	
Cervical dilation at admission			
3-4cm	60	60	1.00
5-6cm	40	40	

[Table/Fig-1]: Baseline demographic and maternal characteristics.
[a] Socioeconomic Status.
[b] Body Mass Index.

Pain assessment VAS score	Group A Mean [95% CI]	p-value[a]	Group B Mean [95% CI]	p-value[b]	p-value[c]
At injection	7.08 [6.82-7.34]	-----	7.02 [6.76-7.28]	-----	0.742
After 15 minutes	6.92 [6.66-7.18]	0.393	6.90 [6.64-7.16]	0.532	0.881
After I hour	5.94 [5.68-6.20]	<0.0001	6.42 [6.16-6.68]	0.006	0.089
After 2 hours	5.125 [4.86-5.39]	<0.0001	5.86 [5.61-6.14]	<0.0001	0.007
After 3 hours	5.66 [5.38-5.94]	<0.0001	6.11 [5.83-6.39]	<0.0001	0.011
After 4 hours	6.0 [5.61-6.39]	<0.0001	6.0 [5.61-6.39]	<0.0001	0.013

[Table/Fig-2]: Pain Assessment by VAS Scoring.
[a] p-value describing analgesic effect of Intravenous Acetaminophen in women in Group A
[b] p-value describing analgesic effect of Intravenous Normal Saline in women in Group B
[c]p-value comparing analgesic effects of Group A and B (Acetaminophen and Normal saline)

Duration of labour	Cases (Group A) (mean)	Controls (Group B) (mean)	p-value
	3.60 hours	3.59 hours	0.995

[Table/Fig-3]: Duration of labour.

Mode of delivery	Cases (Group A) (n=100)	Controls (Group B) (n=100)	p-value
Vaginal delivery	94	94	1.00
LSCS[a]	6	6	

[Table/Fig-4]: Mode of delivery.
[a]Lower segment Caesarean Section

Fetal side effects	Group A (Acetaminophen) n	Group B (Placebo) n	P-value
NRFHR	2	2	1.00
Low apgar 1min	4	4	1.00
Low apgar 5min	2	2	1.00
NICU admission	0	0	

[Table/Fig-5]: Fetal adverse events
[a] Non Reassuring Fetal Heart rate.
[b] Neonatal Intensive Care Unit.

DISCUSSION

Pain relief during labour has been exemplified to have a positive bearing on its course [15]. During the last two decades, obstetric analgesia and anaesthesia have evolved from an ambiguous probability to actuality. Amongst pharmacological approaches, although central neuraxial analgesia is considered the criterion standard, a number of parturients may still be reluctant to have regional analgesia [4]. Also, it entails participation of skilled anaesthesiologist, expensive paraphernalia and incessant monitoring amenities that cannot be made routinely accessible in developing countries like India, where a major chunk of obstetric services is still rendered by midwives, trained nurses and non-specialist doctors at grassroots levels. An effective substitute may be the utilization of parenteral opioids with a relative ease of administration [16]. But marked side effects restrict their liberal use for the same. This propelled exploration for role of IV acetaminophen as intrapartum analgesic.

Observations of the present study lucidly demonstrate that use of IV acetaminophen injection for intrapartum analgesia is superior to placebo, as determined by the considerable drop in VAS score from 15 minutes and one hour and a statistically significant reduction in pain at 2 hours, 3 hours and 4 hours in comparison to the pretreatment VAS pain score. These results were better than the research of Lallar et al., and Elbohoty et al., involving IV acetaminophen, thus establishing it as a feasible option for labour analgesia [17,18]. However, the high pre-treatment pain scores amongst the participants in our study may be explained by recruitment of women in active labour who were deemed in need of analgesia.

Unlike the past pollsters [18], the mean VAS in the concurrent study after 2 hours was always lower than the pre-treatment scores, and this effect lasted for 4 hour giving us reassuring data about the duration of effectiveness of acetaminophen.

Akin to the research done there was no difference in the mean drug to delivery interval between the two groups, although there was some shortening effect than the usual anticipated duration of 4 to 6 hours [19]. This could be attributed to the positive influence of analgesia on maternal bearing down efforts and progress of labour. However, these results were different from those obtained by few recent studies [17,20]. The possible reasons could be the non-recording of dose and mean duration of administration of oxytocin by those investigators, besides lack of adequate power in those studies. Nevertheless, this role of acetaminophen in shortening the drug delivery interval needs to be reconnoitred in future on a larger scale.

In our study, only 16% women required rescue shot of analgesia, further reinforcing the efficacy of acetaminophen as intrapartum analgesic.

Analyzing mode of delivery, no variance in the percentage of vaginal deliveries (94% each) was observed, with 6 subjects in each group undergoing LSCS due to non-reassuring fetal heart rate patterns [Table/Fig-4]. There was no instrumental vaginal delivery in either group. These findings corroborated those witnessed by most of the canvassers [17,18,21].

Absence of any maternal adverse effects (sedation, respiratory depression, delayed gastric emptying, nausea and vomiting) or neonatal adverse effects (respiratory depression and decreased Apgar scores) associated with opioids in the current study further bolstered liberal use of acetaminophen to alleviate labour pain [18-21]. Passable assessment of pain, utilizing authenticated tools apposite to the study population is an indispensable prerequisite of successful analgesia. A Numeric Rating Scale (NRS) with numbers from 0 to 10 ('no pain' to 'worst pain imaginable') has off late emerged as more practical and easier to understand than a VAS, in assessing pain relief in women especially with difficult communication or patients suffering from cognitive impairment [22,23].

All the aforementioned findings thus validate IV acetaminophen to be an effectual and innocuous intrapartum analgesic, of equitable cost and requiring no proficiency in dispensation.

LIMITATION

There are certain limitations of this study. Firstly, having been drawn from a moderately small study populace of 200 women over a short span of six months, the aforesaid results may not be representative of the initial promising results in other settings. Thus, larger powered studies with larger size of study population are recommended to precisely elucidate the analgesic profile of intravenous acetaminophen in labour. Secondly, in the present study, there was no statistically significant shortening on the duration of labour caused by acetaminophen. This could be ascribed to women enrolled into the study with a relatively wide range of cervical dilatation of 3-6 cm. A further breakup of this parameter to compare the effect of drug on labour duration between ≤4cm and ≥5cm dilatation of cervix on administration could cause enhanced enrichment of the investigators with respect to it in order to justify its use for this purpose. Thirdly use of NRS might have enhanced our results even further in favour of acetaminophen.

CONCLUSION

Intravenous acetaminophen is an efficacious non-opioid drug for relieving labour pain without any maternal and fetal adverse effects. It shortens the duration of labour. However, further larger studies comparing acetaminophen infusion with opioid analgesics are recommended to confirm these findings. Also, the effect of acetaminophen in reducing duration of labour is beguiling and necessitates future research, with potential benefits being, a) a lower incidence of complications associated with prolonged labour (neonatal sepsis or maternal infection such as chorioamnionitis or puerperal sepsis); b) advantageous in diminished foeto-placental reserve, reducing the incidence of abdominal delivery; c) Reducing the time of parturition would be welcomed by women and by health authorities with limited medical resources especially in low-income countries.

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PARTICULARS OF CONTRIBUTORS:
1. Consultant and Professor, Department of Obstetrics and Gynaecology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
2. Senior Specialist, Department of Obstetrics and Gynaecology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
3. Senior Resident, Department of Obstetrics and Gynaecology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
4. Senior Resident, Department of Obstetrics and Gynaecology, Vardhaman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sheeba Marwah,
Senior Resident, Department of Obstetrics and Gynecology, Vardhaman Mahavir Medical College and Safdarjung Hospital,
New Delhi-110029, India.
E-mail: sheebamarwah@yahoo.co.in

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