

# Effects of high dose orally administered paracetamol for heel prick pain in premature infants

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## ABSTRACT

**الأهداف:** تم تصميم هذه الدراسة من أجل تقييم الجرعة العالية من عقار باراسيتامول (40mg/kg عبر الفم) من أجل تخفيف الألم لدى الرضع الخدج.

**الطريقة:** كانت هذه الدراسة العشوائية عبارة عن تجربة تحليلية على تأثير الجرعة العالية من عقار باراسيتامول عبر الفم على الاستجابة للألم لدى 72 رضيع خديج تلقوا المعالجة في وحدة العناية المركزة للأطفال حديثي الولادة -مستشفى الزهراء الجامعي -مدينة أصفهان -إيران خلال الفترة من أبريل 2007 إلى أغسطس 2007م. تلقى المرضى قبل 90 دقيقة عقار باراسيتامول عبر الفم بجرعة مقدارها (40mg/kg) للمجموعة الأولى وعلى نفس المقدار تلقت المجموعة الثانية عقار بلاسيبو. قمنا بتقييم الألم باستعمال نقاط ملف الألم للرضع الخدج (PIPP).

**النتائج:** كانت مدة الحمل لدى المجموعتين متشابهة mean±SD: 31.7± 1.7 مقابل 32.6±1.5 والوزن عند الولادة (mean±SD: 1530±292 مقابل 1739±369). المتوسط نقاط mean±SD PIPP كانت 11.1±3.8 مقابل 9.7±4.2،  $p=0.15$ .

**خاتمة:** لا يبدو على جرعة عالية مفردة من الباراسيتامول أنها توفر تسكين دقيق للألم الحاد لدى الأطفال الخدج حديثي الولادة.

**Objectives:** To evaluate whether high dose paracetamol (40mg/kg orally) relieves pain in premature infants.

**Methods:** This study was a randomized controlled trial analyzing the effect of high dose oral paracetamol on pain response due to heel prick in 72 premature infants treated in the neonatal intensive care unit of Alzahra University Hospital, Isfahan, Iran during the period of April 2007 to August 2007. Ninety minutes before the heel prick, neonates received paracetamol orally in a dose of 40 mg/kg (Group 1) or an equal volume of placebo (Group 2). We assessed the pain using the premature infant pain profile (PIPP) score.

**Results:** Infants in the paracetamol and placebo groups had similar gestational ages (mean±SD: 31.7±1.7 versus 32.6±1.5) and birth weights (mean±SD: 1530±292 versus 1739±369). The mean±SD PIPP scores in Group 1 was 11.1±3.8 and in Group 2 was 9.7±4.2, ( $p=0.15$ ).

**Conclusion:** Single high dose paracetamol does not appear to provide adequate analgesia for the acute pain caused by heel prick in premature neonates.

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Because of advancement in perinatal care, survival of preterm infants in neonatal intensive care units (NICUs) is increasing.<sup>1</sup> These newborns need many diagnostic and therapeutic procedures such as heel lancing and endotracheal intubation.<sup>1-3</sup> In contrast to ancient ideas, newborn infants even premature ones, feel pain.<sup>4</sup> Experience of pain in this period could induce both acute and permanent functional and structural changes.<sup>5,6</sup> For this reason, it is important to find effective and safe methods of pain reduction in these newborns. Opioids are powerful analgesics even for serious pain, but have the major problem of respiratory depression, which is more obvious in newborn infants.<sup>7</sup> The analgesic effects of sucrose have been approved in procedural pain in newborn infants but the effects of repeated doses of sucrose should be identified.<sup>4</sup> A recent study showed that using sucrose for repeated painful procedures could not prevent processing of remote hyperalgesia in neonates.<sup>4</sup> Paracetamol is an antipyretic

and analgesic medication that is readily available. Although paracetamol potency is less than opioids, this drug may have fewer side effects. It is the most frequently used drug for treatment of mild to moderate pain in infants, including newborns. It can be prescribed by the rectal, oral or intravenous way.<sup>8</sup> To our knowledge there has not been any study on the efficacy of high dose paracetamol for acute pain relief for procedures such as heel prick. The objective of this study was to evaluate the efficacy of high dose oral paracetamol as an analgesic in preterm neonates subjected to heel prick.

**Methods.** This prospective, randomized, double blind, placebo controlled study was designed to include 72 preterm neonates treated in the NICU of Alzahra University Hospital, Isfahan, Iran during the period of April 2007 - August 2007. The hospital committee for research ethics approved the study and informed consent was obtained from the parents of each neonate before the infant participated in the study procedure. The inclusion criteria were as follows: neonates born  $\leq 34$  week gestation; age  $\geq 24$  hours; no feeding for at least 30 minutes; Apgar scores  $>3$  at 5 minutes and availability of one investigator who performed all pain evaluations. Exclusion criteria were assisted ventilation, oxygen treatment, infant medical instability and administration of a sedative or a major analgesic during the last 48 hours. The heel prick procedure comprised 4 phases: baseline; heel picking; squeezing the heel; and return to baseline. Videotaping begun just before heel lancing and continued until 3 minutes after the procedure. The research pharmacist randomized newborns to the treatment and placebo groups by a computer generated block randomization. Before the heel prick, the treatment group received oral paracetamol (25 mg/ml) in a dose of 40 mg/kg and placebo group received equal volume of sterile water. The exact dose of paracetamol or sterile water was measured using a 2 ml syringe. The study drug was administered 90 minutes before the heel lancing. Each newborn had continuous monitoring of heart rate and oxygen saturation throughout the study. We assessed the pain response using the premature infant pain profile (PIPP) and the length of crying time. The PIPP is a 7-indicator scoring system including 2 indicators for gestational age and behavioral state, 3 indicators for the occurrence of facial actions (brow bulge, eye squeeze, nasolabial furrow), one for heart rate and one for oxygen saturation.<sup>9</sup> Neither the observers nor the nurse who carried out the heel

lancing was aware of which treatment had been given to the neonate. Four independent observers, who knew the observation protocol and trained in the PIPP technique, performed the observations. Ordinarily, a total score of 6 or less signify minimal or no pain. The highest PIPP score for premature infants is 21. Demographic characteristics, including gestational age, birth weight, postnatal age, gender and type of delivery were allocated on a standardized data collection form. We calculated the sample size using these assumptions: a minimal clinical important difference of 2.3 on PIPP, an standard deviation of 3.5 units on the PIPP with a statistical power of 80%.

All data were analyzed using SPSS version 11 (SPSS Inc., Chicago, USA), and p-values  $<0.05$  were considered statistically significant. Demographic characteristics and pain assessments were compared between groups using chi square analysis or Fischer's exact test for categorical data and student's t test for continuous date. Means, standard deviations, and/or confidence intervals were measured for continues data. The effect of infant characteristics on pain scores was assessed using linear regression.

**Results.** Seventy-two newborns were enrolled; 36 in the paracetamol (group 1) and 36 in the placebo (group 2) group. There were no substantial differences between the groups with respect to demographic characteristics (Table 1). There was no statistically significant difference in PIPP scores between the paracetamol group and the placebo group. The duration of the crying did not differ between the groups. There was an increase in heart rate in both groups, indicating a physiologic response. The mean heart rate for the paracetamol group before the test was  $138.6 \pm 16.2$  beats per minute, and that immediately after the test was  $154.6 \pm 18.2$  beats per minute. The corresponding figures for the placebo group were  $136.2 \pm 14.8$  and  $150.3 \pm 15.6$  beats per minute. There were no significant differences between the 2 groups ( $p=0.51$ ,  $p=0.28$ ). The mean saturation of peripheral oxygen (SPO<sub>2</sub>) for the paracetamol group before the test was  $93.1 \pm 4.1$  and the minimum SPO<sub>2</sub> during 3 minutes after the test was  $88.5 \pm 7.8$ . The corresponding figures for the placebo group were  $94.1 \pm 2.2$  and  $90.2 \pm 5.2$  ( $p=0.24$ ,  $p=0.22$ ). The PIPP scores, duration of crying during the first 3 minutes, decreases in SPO<sub>2</sub> and increases in heart rate between baseline and heel-lancing period are shown in Table 2. Infants' birth weight and gestational age did not affect PIPP score or crying time. We did not check liver function tests or bilirubin for enrolled patients but clinically no adverse effects were observed for any of the participants.

**Discussion.** Preterm infants have to face minor procedures during their stay in NICU. As a result,

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**Table 1** - Demographic characteristics of study subjects.

Demographic characteristics	Group 1 (n=36)	Group 2 (n=36)	P-value
Gestational age (weeks) (mean±SD)	31.7 ± 1.7	32.6 ± 1.5	0.26
Birth weight (gram) (mean±SD)	1530 ± 292	1739 ± 369	0.17
Vaginal delivery (n)	19	23	0.8
Apgar score at one minute (mean±SD)	7.1 ± 1.1	7.8 ± 0.8	0.35
Apgar score at 5 minutes (mean±SD)	8.8 ± 0.9	8.9 ± 0.6	0.7
Boy/girls	10/26	10/26	>0.9
Age (day) (mean ±SD)	3.1 ± 0.8	2.9 ± 1.1	0.8

**Table 2** - Mean ± standard deviation of the PIPP scores, duration of crying during the first 3 minutes, decreases in SPO<sub>2</sub>, and increases in heart rate between baseline and heel prick period.

Variables	Group 1 (n=36)	Group 2 (n=36)	P-value	95% CI
PIPP score (mean ±SD)	11.1 ± 3.8	9.7 ± 4.2	0.15	-2.82 - 4.29
Duration of crying (seconds) (mean ±SD)	61.5 ± 58.9	53.4 ± 58.8	0.56	-29.96 - 51.88
Decrease in spo <sub>2</sub> (%) (mean ±SD)	6.6 ± 7.9	4.0 ± 5.7	0.11	-1.90 - 5.90
Increase in heart rate (mean ±SD)	15.9 ± 15.8	14.0 ± 12.8	0.57	-9.35 - 14.09

PIPP - premature infant pain profile, SPO<sub>2</sub> - saturation of peripheral oxygen, CI - confidence interval

they need effective analgesia for pain management. For management of pain during short lasting procedures, commonly used drugs are not suitable for these infants. We assessed analgesic effects of paracetamol because it is a safe drug in neonatal period.<sup>10</sup> Heel lancing is the standard method of taking blood for screening tests and measurement of serum bilirubin.<sup>11</sup> Most previous trials on the prevention and treatment of pain in neonates proved that heel prick is a painful procedure. Vertanen et al<sup>12</sup> used a mechanical device lancet for heel pricking and found that this device is less traumatic than manual heel lance. Ogawa et al<sup>13</sup> found that heel lancing is more painful than venipuncture for blood sampling in newborn infants. They also showed that oral sucrose significantly reduce the pain score in newborns undergoing heel lancing.<sup>13</sup> A Cochrane systematic review showed that pain from single procedures could be effectively manage by sucrose but they found that for repeated painful procedures, the efficacy, and safety of sucrose should be assessed in other studies.<sup>14</sup> van der Marel et al<sup>15</sup> showed that paracetamol, as an adjuvant to continuous morphine infusion, does not have an additional analgesic effect and should not to be considered as a standard of care in young infants after major thoracic or abdominal surgery. Bonetto et al<sup>16</sup> compared the analgesic effects of oral glucose, EMLA cream and oral paracetamol in 76 term newborn. They found that EMLA cream (a topical anesthetic) and oral paracetamol (20 mg/kg) could not reduce pain from heel

lancing in newborn infants. Van Lingen et al<sup>17</sup> found that one dose of paracetamol 20 mg/kg given rectally to neonates delivered by vacuum extraction did not result in a significant change in objective pain scores. The efficacy of oral paracetamol (20 mg/kg) as an analgesic has also been studied in 75 term neonates undergoing heel prick and was found to be ineffective for decreasing the pain from heel prick.<sup>10</sup> They assumed that patients may not achieve therapeutic plasma paracetamol concentration.<sup>10</sup> Anderson<sup>18</sup> suggested that neonates may have altered pharmacokinetics of paracetamol compared with older children. He supposed that the given 20 mg/kg dose of paracetamol might have been too small to show differences between paracetamol and the placebo group and suggested higher starting dose of 30 mg/kg in term infants on the first day of life.<sup>18</sup> Allegaert et al<sup>8</sup> looked at intravenous paracetamol in term and preterm infants. They demonstrated that a mean steady state through concentration of 10 mg/l can be achieved with a loading dose of 20 mg/kg followed by a maintenance dose based on the gestational age.<sup>8</sup> Anderson et al<sup>19</sup> studied the pharmacokinetics of different formulations of paracetamol and found that a mean steady state target concentration of 10 mg/l at trough can be achieved by an oral dose of 25 mg/kg/day in premature neonates at 30 weeks post-conception, 45 mg/kg/day at 34 weeks gestation and 60 mg/kg/day at term. We did not measure the plasma concentrations of paracetamol, but administered a dose of 40 mg/kg, 90 minutes before heel prick. Our results indicated that

higher doses of paracetamol have not analgesic effect on heel prick in preterm neonates. Thus, the lack of efficacy of paracetamol is not possibly due to its low plasma concentration. A possible explanation for the lack of efficacy of paracetamol is that the pain of heel prick may be profound and paracetamol is believed to have only mild to moderate analgesic activity. Van Lingen et al<sup>20</sup> studied pharmacokinetics after rectal administration of paracetamol in 28 preterm newborns in the first day of life. The mean time to reach maximal serum concentration was 3.9 hours in the 28-32 weeks gestational age group and 5.1 hours in 28-32 weeks gestational age group. They concluded that gestational age must be taken into account.<sup>20</sup> Another study showed that the maximum serum paracetamol concentration in term infants reached between 30 and 180 minutes after a rectal dose of 20 mg/kg.<sup>21</sup> Another possible explanation for the lack of efficacy of paracetamol in our study is that the PIPP score performed 90 minutes after the administration of paracetamol might have been too early to show pain effects. Therefore, the maximum serum concentration of oral paracetamol might reach later than 90 minutes.

The limitation of this study is that we did not measure the bilirubin or liver enzyme tests for assessment of paracetamol intoxication. However, none of the enrolled newborn infants demonstrated significant hyperbilirubinemia.

On the basis of our results, we conclude that single high dose orally administered paracetamol given 90 minutes before heel stick does not provide adequate analgesia for premature infants who are exposed to acute pain resulting from heel stick. Why paracetamol have not enough analgesic activity for heel prick is open to supposition. Paracetamol may have only mild to moderate analgesic activity that cannot alleviate severe pain resulting from heel prick.

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