

# Post Operative Analgesic Efficacy of Intravenous Versus Rectal Acetaminophen & Opioid Requirement after Cleft Lip Surgery in Children

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## ABSTRACT

**Objective:** To compare analgesic efficacy of intravenous versus rectal acetaminophen and postoperative opioids requirement with either route for pain management after cleft lip repair.

**Study Design:** Prospective interventional study.

**Place and duration:** Department of Anaesthesia, Peoples university of Medical and Health Sciences Nawabshah, from January 2011 to December 2012.

**Material & Methods:** 50 patients with American Society of Anesthesiologist physical status I (ASA I) of either sex, between 4 to 12 months of age further divided into two groups, 25 in each Group 1 (per rectal) and Group 2 (intravenous) scheduled for unilateral elective cleft lip repair at Paediatric surgery department received either intravenous or rectal acetaminophen after induction of anaesthesia. Intravenous group received 10mg/kg of acetaminophen and the rectal group received 30 mg/kg. After completion of surgery, patients were observed for pain at 10,30,60,90,120,150,180,210 and 240 minutes postoperatively. FLACC pain and behavioural Score was adopted to assess the postoperative pain

**Results:** Pain score of 4-6 requiring opioid supplement in Group 1 (per rectal) was observed twice in 6 (24%) patients and once only in 19 (76%) patients, while in Group 2 (intravenous) twice in 7 (28%) patients and once only in 18 (72%) patients up to 240 minutes postoperatively.

**Conclusion:** Both intravenous and rectal routes of administration of acetaminophen are equally effective in terms of analgesia and reduce opioid supplements for breakthrough pain control and there is no difference in duration of analgesia with either route.

**Key words:** Acetaminophen, Paediatric analgesia, Infant, Cleft lip.

## INTRODUCTION:

Cleft lip repair is among the most common surgical procedures carried out in children. Opioid analgesics are the mainstay of pain management in post operative periods in children. Opioid therapy has dose dependent

serious side effect of respiratory depression<sup>1</sup>. Acetaminophen is used for the management of mild-to-moderate postoperative pain in children and as an analgesic adjuvant, it reduces post operative opioid requirement for analgesia when given in dose of 40mg/kg and 60mg/kg rectally<sup>2</sup>. In children acetaminophen is often administered prophylactically, per rectum or intravenously, at anesthesia induction to provide postoperative analgesia and reduce supplementary opioid administration in the postoperative period<sup>3</sup>. However, the optimum route of administration of acetaminophen is unclear. With rectal route the plasma concentration of acetaminophen is unpredictable and therapeutic level may not be achieved in some cases<sup>3,5,6</sup>. One study, in a randomized controlled trial in 50 children of 2-5 years comparing 15mg/Kg intravenous and 40mg/Kg rectal administration of acetaminophen,

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have demonstrated to have longer analgesic effectiveness with rectal acetaminophen compared with intravenous. However both routes provided good analgesia for the first 6 hours<sup>4</sup>. In Bremrich DH et al study rectal acetaminophen up to 40 mg/Kg administered at anesthesia induction had no effect on early postoperative pain scores, no opioid-sparing effect in early postoperative period and did not result in analgesic plasma concentration<sup>3</sup>.

There is perception that i.v. acetaminophen works better than other route. Plasma concentration of acetaminophen is less variable after i.v. administration<sup>7,8</sup>. Recently in a prospective cohort study in elderly hip fracture patients it has been shown that intravenous acetaminophen significantly reduced the doses of morphine for pain management postoperatively<sup>9</sup>. Although plasma levels are more predictable with i.v. acetaminophen, to our knowledge there is no local study comparing the clinical efficacy of i.v. acetaminophen with rectal route in children. This study was designed to compare the analgesic efficacy of acetaminophen, intravenous versus rectal route, and to compare postoperative opioid requirement with both routes.

#### **MATERIAL & METHODS:**

This prospective comparative study was carried out by department of Anaesthesiology, PUMHSW Nawabshah from January 2011 to December 2012. After approval of ethical committee and informed written consent of parents of children aged from 4 months to 12 months of both sexes with unilateral cleft lip, American Society of Anesthesiologist physical status I, undergoing cleft lip repair surgery in routine elective list of paediatric surgery department were included in the study. Children were selected at the preoperative anaesthetic evaluation the day before surgery. Exclusion criteria were: age below 4 months; hypersensitivity to the drug under study; a history of active renal, hepatic, respiratory, or cardiac disease; a history of seizures; neurological or neuromuscular disorders; chronic pain or analgesic drug use; taking of acetaminophen in the last 72 hours and refusal by parents.

All patients were fasted for 4-6 hours. Standard monitoring was applied, including electrocardiogram, pulse oximetry and noninvasive arterial pressure. After IV cannulation, 5 microgram/kg glycopyrolate and 0.1mg/kg nalbuphine were administered. Anaesthesia was induced by using propofol 3-4mg/kg. Succinylcholine 1-1.5mg/kg was given to facilitate endotracheal intubation. Patients were ventilated to maintain normocapnia with 100% oxygen. Anaesthesia was maintained with 2-2.5% isoflurane. All children received dextrose containing Ringer's lactate solution intraoperatively according to their weight. Blood pressure (BP), heart rate (HR), and oxygen saturation were continuously monitored. The surgery was done at paediatric surgery department. After the anaesthesia induction, patients received either acetaminophen 10 mg/kg intravenously (II group) or 30mg/kg rectally (I group). Combinations of different dose suppositories were used to deliver total amount in group I.

After completion of surgery patients were observed for pain at 10,30,60,90,120,150,180,210 and 240 minutes postoperatively. FLACC pain and behavioral Score was adopted to assess the postoperative pain. Patients were not allowed to go beyond 4-6 Score. The opioid (nalbuphine 0.1mg/kg) bolus was given at the score of 4-6 to relieve pain.

#### **Interpretation of the Behavioral score:**

- 0 - Relaxed and comfortable
- 1-3 - Mild discomfort
- 4-6 - Moderate Pain
- 7-10 - Severe discomfort or pain or both.

#### **RESULTS:**

In our study there were total 50 patients (25 in each group). There were 37 males (18 in group I and 19 in group II) and 13 females (7 in group I and 6 in group II), male female ratio of 2.84:1. Age of patients ranged from 4 months to 12 months with an average age of 7.46 months. The number of patients having pain score of 4-6 and requiring opioid (nalbuphine 0.1mg/kg) supplement at different time intervals is shown in table I.

From group I, 19 (76%) patients required opioid supplement once only and 6 (24%) patients required twice postoperatively. From group II, 18 (72%) required opioid supplement once only, while 7 (28%) patients required twice. No one patient from either group needed 3 or >3 opioid supplement within 240 minutes after surgery.

Table 1. No. of Patients experiencing pain score of 4-6 & requiring opioid supplement at different time intervals postoperatively

Time (in min) post op	Group I (per rectal) n (%)	Group II (intravenous) n (%)
10 min	6 (24%)	7 (28%)
90 min	9 (36%)	8 (32%)
120 min	9 (36%)	9 (36%)
150 min	7 (28%)	8 (32%)
> 150-240 min	00	00

#### DISCUSSION:

Acetaminophen (Paracetamol) is now available in oral, rectal and intravenous formulations<sup>10</sup>. However; optimum route of administration is unclear. Intravenous acetaminophen formulation is the new method to deliver the drug, which has the theoretical advantage of greater predictability and acceptability compared with other routes of delivery.

We demonstrated in this study that both rectal acetaminophen 30 mg/kg and intravenous acetaminophen 10mg/kg were equally effective in controlling pain, both routes decreased the opioid requirement and there was no difference in duration of analgesia following unilateral cleft lip repair. One study, in a randomized controlled trial in 50 children of 2-5 years undergoing elective adenoidectomy or adenotonsillectomy, comparing 15mg intravenous and 40mg rectal administration of acetaminophen, have demonstrated to have longer analgesic effective with rectal acetaminophen compared with intravenous. However both routes provided good analgesia for the first 6 hours<sup>4</sup>. Another study demonstrated in infants and small children under going elective cleft palate repair that rectal

acetaminophen up to 40mg/kg administered at anesthesia induction had no effect on early postoperative pain scores and no opioid-sparing effect in early postoperative period<sup>3</sup>. The ideal effect-site concentration of acetaminophen for adequate analgesia remains unclear. An effect-site concentration of around 10mg/litre has been suggested to provide effective analgesia for mild to moderate pain<sup>7,11</sup>. Few studies have suggested that a single rectal dose of 45mg/kg provide plasma concentration of 10-20mg/litre<sup>12,13</sup>, and therefore this is often used as the appropriate leading dose of acetaminophen given rectally. There are some data in i.v. acetaminophen<sup>7-9,14</sup>, however, much of them pertain to paracetamol. One gram of paracetamol is hydrolysed to 0.5 g acetaminophen and therefore 15mg/kg of acetaminophen is equivalent to 30mg/kg of paracetamol<sup>15</sup>. The dose of i.v. acetaminophen usually is 15mg/kg<sup>4,8,16</sup>. We choose to compare single doses of 30 mg/kg rectally and 10 mg/kg i.v. As the dose of rectal acetaminophen at which 50% of the children did not require a rescue opioid (ED50) in the day-care setting has been shown to be 35.4mg/kg<sup>2</sup> and clearance of i.v. acetaminophen has been reported to be reduced in children less than 1 year of age<sup>7</sup>. Estimation of plasma level of acetaminophen was not performed as such facility is not available at our institute; moreover primary question of this study was clinical analgesic efficacy and opioid requirement postoperatively with two routes of administration with doses of acetaminophen under study.

To our knowledge there is no study comparing the efficacy of intravenous versus rectal administration of acetaminophen for pain management after cleft lip repair surgery in infants. However the results of study with relatively low doses of both intravenous and rectal acetaminophen are comparable with the results of Capici et al<sup>14</sup>, who have compared duration and efficacy of analgesia in children aged 2-5 years following adenotonsillectomy after acetaminophen either 40mg/kg rectally or 15mg/kg intravenously, showing that both routes provided good analgesia for the first 6 hours. This can be explained by different analgesic requirement with different surgical procedures. The weakness of study was

that it was patient blinded but not observer, so bias could not be excluded.

### CONCLUSION:

We conclude that both intravenous and rectal routes of administration of acetaminophen are equally effective in terms of analgesia and decrease opioid supplements as rescue analgesia and there is no difference in duration of analgesia with either route. Thus in our opinion the only advantage of intravenous route of acetaminophen over per rectal route is ease in administration.

Furthermore we recommend large scale study, with maximum upper safe limits of the doses of Acetaminophen for both routes for authenticated results.

### REFERENCES:

1. Landsman IS, Hays SR, Karsanac CJ and Frankilin A. Pediatric Anesthesia. In Coran AG, Adzick NS, Krummel TM, Laberge JM, Shamberger RC, Caldamone A eds: Pediatric Surgery 7th Edition Philadelphia: Elsevier Saunders Inc. 2012; 1:201-26.
2. Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in pediatric day-case surgery. *Anesthesiology*. 1999; 91: 442-7.
3. Bremerich DH, Neidhart G, Heimann K, Kessler P and Behne M. Prophylactically-Administered Rectal Acetaminophen does not reduce postoperative Opioid requirement in infants and small children undergoing elective cleft palate repair. *Anesth Analg*. 2001; 92:907-12.
4. Capici F, Ingelmo PM, Davidson A, Sacchi CA, Milan B, Sperti LR et al. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. *Br J Anaesth*. 2008; 100(2):251-5.
5. Anderson BJ, Holford NH, Woollard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. *Anesthesiology*. 1999; 90:411-21.
6. Birmingham PK, Tobin MJ, Fisher DM, Henthorn TK, Hall SC, Cote CJ. Initial and subsequent dosing of rectal acetaminophen in children: a 24 hour pharmacokinetic study of new dose recommendations. *Anesthesiology*. 2001; 94:385-9.
7. Andeson BJ, Pons G, Autret-Leca E, Allegaert K, Boccard E. Pediatric Intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Paediatr Anaes* 2005; 15:282-92.
8. Palmer GM, Atkins M, Anderson BJ et al. I. V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesthesia* 2008; 101 (4): 523-30.
9. Tsang KS, Page J, Mackenney P. Can intravenous Paracetamol reduce opioid use in preoperative hip fracture patients? *Orthopedics* 2013; 36 (2): 20-24.
10. Speed EK. Three Routes of Acetaminophen: Three ways to achieve the same result. *Drugs and Therapy Bulletin*. January 2012; volume 26, number 1: Shands University of Florida.
11. Anderson BJ. Comparing the efficacy on NSAIDs and Paracetamol in children. *Paediatr Anaesth*. 2004; 14:201-17.
12. Howell TK, Patel D. Plasma Paracetamol concentrations after different doses of rectal Paracetamol in older children. A comparison of 1g vs 40mg/kg, *Anaesthesia*. 2003; 58:69-73.
13. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45mg/kg) rectal acetaminophen in children. *Can J Anaesth*. 1995; 42:982-6.
14. Khan ZU, Iqbal J, Saleh H, El Deek AM. Intravenous Paracetamol is as effective as Morphine in Knee Arthroscopic Day Surgery Procedures. *Pak J Med Sci*. 2007; 23(6):851-3.
15. Duhamel JF, Le Gall E, Dalphin ML, Payen-Champenois C. Antipyretic efficacy and safety of single intravenous administration of 15mg/kg Paracetamol versus 30mg/kg proparacetamol in children with acute fever due to infection. *Int J Clin Pharmacol Ther*. 2007; 45:221-9.
16. Alhashemi JA, Daghistani MF. Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration. *Eur J Anaesthesiol*. 2007; 24(2): 128-33.