ANALGESIC EFFICACY OF INTRAVENOUS VERSUS RECTAL ACETAMINOPHEN AFTER ADENO TONSILLECTOMY IN CHILDREN
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ABSTRACT: INTRODUCTION: Doses of acetaminophen 15mg/kg intravenous and 40 mg/kg rectally produce similar effect-site concentrations. However, the clinical effectiveness of these routes has not been compared. The aim of this study was to compare the efficacy of analgesia (in terms of duration of analgesia and effect on pain intensity) in children following adenotonsillectomy after acetaminophen either 15 mg/kg IV or 40 mg/kg rectally. METHODS: Fifty children, aged between 5 and 14 yrs., undergoing elective adenotonsillectomy were randomly allocated into two groups. Group IV received 15mg/kg intravenous acetaminophen and Group PR received 40mg/kg rectal acetaminophen. Blood pressure, heart rate, respiratory rate and oxygen saturation were continuously monitored. Postoperative pain was assessed by visual analogue scale (VAS) and rescue analgesia provided if scores were 4 or greater. The primary outcome measure was time to first rescue analgesia. RESULTS: The time to first rescue analgesia was significantly longer in children receiving rectal acetaminophen (8.96 ± 3.46) compared with those receiving IV acetaminophen (6.00 ± 1.63) (P-value 0.000). Only one child in IV Group required rescue analgesia within first 6 hours with differences between the groups being most prominent in the period from 6 to 10 hours. Vitals did not show any difference in both groups peri-operatively. Postoperative pain assessment by VAS at various time intervals showed no significant difference between the groups. CONCLUSIONS: Rectal acetaminophen 40 mg/kg provides longer analgesia for moderately painful procedures when compared with 15 mg/kg acetaminophen IV. However, efficacy of intravenous paracetamol has no superiority to rectal administration.

KEYWORDS: acetaminophen, analgesia, adenotonsillectomy.

INTRODUCTION: Adenoidectomy with or without tonsillectomy is among the most common surgical procedures carried out in children. Adenotonsillectomy is associated with an increased risk of respiratory adverse events, bleeding, pain after surgery, postoperative nausea and vomiting (PONV). Analgesia is often provided with a combination of small doses of opioids along with (NSAIDs) or acetaminophen, as acetaminophen and NSAIDs have an opioid-sparing effect. Various side effects including nausea, vomiting, respiratory depression, sedation, central nervous system depression restricts the use of opioids in post-operative pain management.

Many studies have been performed and a wide variety of medicines with topical and systemic effectiveness have been tried for this purpose. Paracetamol has the least side effect potential compared to other analgesics. The oral and rectal route of paracetamol produces an unpredictable plasma concentration and may not be accepted by all patients. Intravenous (IV) route provides less variability in plasma concentrations and can be used in children who are unable to take paracetamol orally.
The use of oral and IV paracetamol in post-operative pain management as a single drug or in combination with another drugs has been demonstrated in numerous studies.[11,12,13] However, the optimum route of administration of acetaminophen is unclear, there are few studies directly comparing routes of delivery for actual analgesic effectiveness.[4,14] We chose to compare single doses of acetaminophen 15 mg/kg IV and 40 mg/kg per rectal as these are the often used doses associated with similar plasma levels.[15,16]

MATERIAL AND METHODS: Informed written consent was taken from parents of all children after approval from ethical committee. This prospective, randomized, double blind study was performed on fifty children, age group of 5 to 14 years, ASA grade I and II, undergoing Adenoidectomy with or without tonsilslectomy under general anaesthesia. Patients were divided into groups of 25 each. Group IV received 15mg/kg intravenous acetaminophen and Group PR received 40mg/kg rectal acetaminophen immediately after intubation.

Exclusion criteria were: emergency surgery, known hypersensitivity to the drugs under study, a known history of active and severe renal, hepatic, respiratory, or cardiac disease, a history of seizures, neurological or neuromuscular disorders and history of chronic pain or analgesic drug use.

Anaesthetic Technique: All children were premedicated with syrup midazolam 0.5 mg/kg, 30 minutes before surgery and vascular access was secured. On arrival in the operating room, monitors were attached and baseline heart rate, blood pressure, respiratory rate and oxygen saturation were recorded. A crystalloid intravenous infusion of 6-8 ml/kg was started and children were premedicated with intravenous ranitidine (1mg/kg), metoclopramide (0.15 mg/kg), glycopyrrolate (0.01 mg/kg), dexamethasone 0.1 mg/kg and pentazocine (0.6 mg/kg). After pre-oxygenation for 3 min with 100% oxygen, anaesthesia was induced with propofol (2 mg/kg) or in a dose sufficient for loss of verbal commands. The direct laryngoscopy and intubation was facilitated with scoline 1.5 mg/kg and Anaesthesia was maintained with halothane (0.5% concentration) and nitrous oxide 50% in oxygen with vecuronium 0.08 mg/kg.

Patients were mechanically ventilated to maintain the normocapnia (CO₂ between 35 and 40 mmHg). After intubation, patients were randomized to receive either acetaminophen 15 mg/kg IV (IV group) or 40 mg/kg rectally (PR group). Blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation were continuously monitored. After completion of surgery, residual neuromuscular block was antagonized with appropriate doses of neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg), and extubation was performed when respiration and airway reflexes were adequate.

Postoperative pain was assessed by visual analogue Scale at 0, 1, 2, 4, 6, 8, 10 and 12 hours interval and rescue analgesia provided if scores were 4 or greater. In both groups Injection diclofenac 1 mg/kg was started eight hourly in postoperative ward as per routine analgesic protocol being followed in our institution by surgeons, starting from the time when patient has arrived in postsurgical ward from operation theatre. At any point of time if VAS was >4, injection tramadol 1 mg/kg body weight 8 hourly was planned to be added.

STATISTICAL ANALYSIS: Data was analyzed on computer software SPSS 21. Study population was calculated by power analysis (power 80% & α error 0.05). Characteristics of the patients between two groups were compared with student t- tests and chi-square test as appropriate. Duration to first
rescue analgesia and pain intensity (VAS) between the two groups were compared with student t-tests. P-value < 0.05 was considered significant.

RESULTS: It was found that the two study groups were comparable with respect to age, sex, weight, operative time and ASA status (Table 1). The vital findings were comparable in both the groups.

It was noted that time to first analgesic request was longer in children receiving rectal acetaminophen (8.96± 3.46) compared with those receiving IV acetaminophen (6.00±1.63, P=0.000) (table 2). Only one child needed rescue analgesia in first 6 hours in IV group and none in PR group (P=0.322), with differences between the groups being most prominent in the period from 6 to 10 h (24 children in IV group and 18 children in PR group, P =0.043) (table 3). Postoperative pain assessed by VAS at various time interval showed no significant difference between the groups at 0 hour, IV vs PR (0.92 ± 0.86 vs 1.08±0.86, P= 0.515), 1 hr (1.00±0.763 vs 1.12±0.781, P=0.585), 2 hr (1.60±1.25 vs 1.64±0.90, P=0.898), 4 hr (2.64±1.18 vs 2.60±1.11, P=.903), 6 hr (4.20 ± 1.63 vs 3.72 ± 0.61, P=0.175), 8 hr (3.56 ± 0.91 vs 3.52 ± 0.82, P=0.872), 10 hr (3.92 ±0.40 vs 4.36 ±1.18, P=0.085), 12 hr (2.32 ± 1.18 vs 2.12 ±1.39, P=0.587) (table 4).
### DISCUSSION

Pain control is an important part of post-operative patient care. Non-steroid anti-inflammatory medication and paracetamol are agents used in post-operative pain management. Many studies have reported oral paracetamol as an agent that is effective and well tolerated in different surgical procedures.\(^{[17]}\) However, the post-operative use of oral paracetamol is limited. In addition, parenteral administration of paracetamol has been reported a more rapid onset of effect and longer activity compared to administration by the oral route. Intravenous administration of paracetamol is preferred in cases where the oral use is difficult or rapid analgesic activity is required.\(^{[3]}\)

In our study, we compared the IV and PR use of paracetamol in the management of post-operative analgesia after adenotonsillectomy operations in the pediatric age group. Although, a placebo control was usually recommended in analgesic studies to validate the efficacy of methods, it would be unethical to use a placebo group in children where the analgesic effect of paracetamol has been already demonstrated.\(^{[18,5]}\)

In this study, we demonstrated longer analgesic effectiveness with rectal acetaminophen 40 mg/kg compared with IV acetaminophen 15 mg/kg. IV acetaminophen is a new method to deliver acetaminophen, which has the theoretical advantage of greater predictability and acceptability compared with oral or rectal routes of delivery. However there are few, if any studies directly comparing routes of delivery for actual analgesic effectiveness.

The new formulation of acetaminophen, IV paracetamol, might improve prediction of concentration compared to enteral formulations, by eliminating of plasma variability due to absorption.\(^{[19]}\) It has been also suggested that oral and rectal paracetamols may not achieve therapeutic levels in some cases.\(^{[19,20]}\) Although plasma levels are more predictable in IV paracetamol, studies comparing the clinical efficacy of IV paracetamol with other routes are limited.\(^{[10]}\)

Rectal route can be used after induction of anesthesia with a mean analgesic duration of 4-6 hours.\(^{[21]}\) In rectal route, single dose of acetaminophen 40 mg/kg is used as loading dose and provides plasma concentrations of 10-20 mg/litre.\(^{[15]}\) Pharmacokinetic studies on IV paracetamol suggest that initial dose of IV paracetamol is 15 mg/kg for children. This dose provides a plasma concentration of 10 mg/litre for 6 hours.\(^{[19]}\) Therefore, we chose to compare the single dose of acetaminophen 40

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**Table 4: Postoperative pain score**

| VAS SCORE | GROUP IV (n = 25) (Mean ± S.D.) | GROUP PR (n = 25) (Mean ± S.D.) | P-Value |
|-----------|---------------------------------|---------------------------------|---------|
| 0 hr.     | 0.92 ± 0.86                     | 1.08 ± 0.86                     | 0.515   |
| 1 hr.     | 1.00 ± 0.763                    | 1.12 ± 0.781                    | 0.585   |
| 2 hr.     | 1.60 ± 1.25                     | 1.64 ± 0.90                     | 0.898   |
| 4 hr.     | 2.64 ± 1.18                     | 2.60 ± 1.11                     | 0.903   |
| 6 hr.     | 4.20 ± 1.63                     | 3.72 ± 0.61                     | 0.175   |
| 8 hr.     | 3.56 ± 0.91                     | 3.52 ± 0.82                     | 0.872   |
| 10 hr.    | 3.92 ± 0.40                     | 4.36 ± 1.18                     | 0.085   |
| 12 hr.    | 2.32 ± 1.18                     | 2.12 ± 1.39                     | 0.587   |

*Significant (p<0.05), ** Highly Significant (p<0.01)
mg/kg rectally and 15 mg/kg intravenously. These doses are associated with similar plasma levels and have been chosen according to previously published studies and pharmacokinetic data.\textsuperscript{10,19}

Contrary to our findings, previous studies have found rectal acetaminophen to provide erratic and inconsistent analgesia after tonsillectomy.\textsuperscript{22–24} This variation may be explained by differing analgesic requirements with different surgical techniques, different doses of acetaminophen or the concurrent use of other analgesic agents. The observation that rectal acetaminophen provided good analgesia in spite of previously described erratic absorption might indicate that either the effect-site concentration needed to provide effective analgesia in this population is low or the relationship between effect-site concentration and analgesia is more complex than expected.\textsuperscript{19}

In a previous study paracetamol, propacetamole and placebo in pain management during the post dental surgery period was compared.\textsuperscript{6} Their study involved 175 subjects who were administered for post-op analgesia, 2 min bolus injection of 1 gm IV, 15 min infusion and 1 gm oral paracetamol versus placebo. Although paracetamol IV bolus and infusion had significant analgesic effect compared to placebo, the study found no significant difference in terms of analgesic activity between both drugs. In addition, the authors also reported that local reaction development was frequent in the route of administration in the use of IV bolus propacetamole.\textsuperscript{6}

In a clinical trial, comparing the analgesic efficacy of IV paracetamol after inguinal hernia repair in children.\textsuperscript{13} Similar to our results, they found that no clinically significant abnormality in vital signs were observed with this new solution of paracetamol. Also, we did not observe any adverse effect of drug during IV administration.

Similar to our results, previous study reported that rectal paracetamol provided a longer analgesia (for a period of more than 6 hours) when compared to IV paracetamol in children with adenotonsillectomy. They suggested that rectal paracetamol had a slower onset analgesic effect which lasts longer.\textsuperscript{10,25} According to their data, children receiving rectal acetaminophen needed rescue analgesia after a longer period when compared with those receiving IV acetaminophen.\textsuperscript{10} In our study, we performed rescue analgesia in 24 children in IV group, however only 18 children received rescue analgesia in PR group between 6-10 hours.

Our study suggests that the duration of analgesia was prolonged with 40 mg/kg per rectal paracetamol than with 15 mg/kg IV paracetamol. Both routes provided good analgesia for the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h. Presumably, the effect-site concentration is maintained for a longer period with the larger rectal dose in spite of lower bioavailability.

REFERENCES:
1. Anderson BJ. Comparing the efficacy of NSAIDs and paracetamol in children. Paediatr Anaesth 2004; 14: 201–17.
2. Pendeville PE, Von Montiqny S, Dort JP, Veyckemans F. Douleblind randomized study of tramadol vs. paracetamol in analgesia after daycare tonsillectomy in children. Eur J Anaesthesiol 2000; 17: 576-86.
3. Lui CM, Su CY. Postoperative pain control with topical steroid injection after hot dissection tonsillectomy. J Laryngol and Otol 1996; 110: 1038-40.
4. Oktem F, Korkut N, Oz F, Ozdogan A, Toprak M, Ada M et al. Effect of sukralfate on morbidity of posttonsillectomy. Turk Arch ORL 1998; 36: 37-40.
5. Kehlet H, Holte K. Effect of postoperative analgesia and surgical outcome. Br J Anaesth 2001; 87: 62-70.
6. Moller PL, Juhl GD, Payen-Champenois C. Intravenous acetaminophen (Paracetamol): Comparable analgesic efficacy, but better local safety than its prodrug (propacetamol) for postoperative pain after third molar surgery. Anesth Analg 2005; 101: 90-96.
7. Aghamir K, Mojtahedzahed M, Alizahed F, Khalili Pharm H, Sadeghi M, Najafi A et al. Propacetamol vs tramadol for postoperative pain management after urologic surgery: The Internet Journal of Pharmacology 2006;4:2.
8. Hernandez-Palazon J, Tortosa JA, Martinez-Lage JF, Perez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. Anesth Analg 2001; 92: 1473-6.
9. Granry JC, Rod B, Monrigal JP, Merckx J, Berniere J, Jean N et al. The analgesic efficacy of an injectable prodrug of acetaminophen in children after orthopaedic surgery. Pediatr Anaesth 1997; 7: 445-9.
10. F. Capici, P. M. Ingelmo, A. Davidson. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children British Journal of Anaesthesia.2008; 100 (2): 251-5.
11. Jarde O, Boccard E. Parenteral versus oral route increases paracetamol efficiency. Clin Drug Invest 1997; 14: 474-7.
12. Pettersson Holmer P, Owall A, Jakobsson J. Early bioavailability of paracetamol after oral or intravenous administration. Acta Anaesthesiol Scand 2004; 48: 867-70.
13. Murat I, Baudard C, Foussat C, et al. Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair. Paediatr Anaesth 2005; 15: 663-70.
14. Anderson BJ, Woolard GA, Holford NH. Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatric Anaesth 1995; 5: 237-42.
15. Howell TK, Patel D. Plasma paracetamol concentrations after different doses of rectal paracetamol in older children. A comparison of 1 g vs. 40 mg x kg (-1). Anaesthesia 2003; 58: 69–73.
16. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mg.kg-1) rectal acetaminophen in children. Can J Anaesth 1995; 42: 982-6.
17. Lechat P, Kisch R. Paracetamol. Present status of knowledge in 1989. Therapie1989; 44: 337-44.
18. Howard CR, Howard FM, Weitzman ML. Acetaminophen analgesia in neonatal circumcision: The effect on pain. Pediatrics 1994; 93: 641-646.
19. Anderson BJ, Pons G, Autret-Leca e, Allegaert K, Boccard E. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. Pediatric Anesthesia 2005; 15: 282-292.
20. Andersen BJ, Holford NH, Woolard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anesthesiology 1999; 90: 411-21.
21. Remy C, Marret E, Bonnet F. State of the art of paracetamol in acute pain therapy. Curr Opin Anaesthesiol 2006; 19: 562-5.
22. Gaudreault P, Guay J, Nicol O, Dupuis C. Pharmacokinetics and clinical efficacy of intrarectal solution of acetaminophen. Can J Anaesth. 1988; 35: 149–52.
23. Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. Anaesth Intensive Care 1996; 24: 669–73.

24. Viitanen H, Tuominen N, Vaaraniemi H, Nikanne E, Annila P. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. Br J Anaesth. 2003; 91: 363–7.

25. Neil K. Singlaa, Cherri Parulana, Roselle Samsona Plasma and Cerebrospinal Fluid Pharmacokinetic Parameters after Single-Dose Administration of Intravenous, Oral or Rectal Acetaminophen. proceedings and abstracts of the 10th annual American society of regional anaesthesia and pain medicine meeting and workshops. New Orleans, Loulsiana, November 17-20, 2011.

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