

Postoperative analgesic efficacy of single high dose and low dose rectal acetaminophen in pediatric ophthalmic surgery

Ranju Gandhi, Rani Sunder

Department of Anaesthesia and Intensive Care, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background: Analgesic efficacy of rectal acetaminophen is variable in different surgical procedures. Little data is available on its efficacy in ophthalmic surgeries. We conducted this prospective, randomized, double blind study to evaluate and compare the efficacy of single high dose and low dose rectal acetaminophen in pediatric ophthalmic surgery over a 24 hour period.

Materials and Methods: 135 children scheduled for elective ophthalmic surgery were randomly allocated to one of the three groups, high, low, or control (H, L, or N) and received rectal acetaminophen 40 mg/kg, 20 mg/kg or no rectal drug respectively after induction of general anesthesia. Postoperative observations included recovery score, hourly observational pain score (OPS) up to 8 hours, time to first analgesic demand, and requirement of rescue analgesics and antiemetics over a 24 hour period.

Results: Nineteen of 30 (63%) of children in group N required postoperative rescue analgesic versus 5/48 (10%) of group H ($P < 0.0001$) and 10/47 (23%) of group L ($P = 0.0005$) during 24 hour period. Mean time to requirement of first analgesic was 206 ± 185 min in group H, 189 ± 203 min in group L, and 196 ± 170 min in group N ($P = 0.985$). OPS was significantly lower in group H and L compared to group N during first 8 hours. Requirement of rescue antiemetic was 18.7% in group H as compared to 23% each in group L and group N ($P > 0.5$).

Conclusions: Single dose rectal acetaminophen can provide effective postoperative analgesia for pediatric ophthalmic surgery at both high dose (40 mg/kg) and low dose (20 mg/kg) both in early postoperative and over a 24 hour period.

Key words: Postoperative analgesia, rectal acetaminophen, pediatric ophthalmic surgery

Introduction

Acetaminophen or paracetamol is one of the most commonly administered analgesic in the pediatric age group. Acetaminophen is a centrally acting inhibitor of cyclooxygenases and is also recently demonstrated to have weak peripheral effects. Its central analgesic effect is mediated through activation of descending serotonergic pathway as well.^[1] As an analgesic adjuvant, it reduces postoperative opioid requirements and is devoid of side effects commonly observed with the use of opioids (drowsiness, nausea, vomiting, respiratory depression, pruritus) and non-steroidal

anti-inflammatory drugs (increased bleeding). It can be administered by oral, rectal, intramuscular, and intravenous routes. Rectal acetaminophen can be given after induction of anesthesia for prophylaxis and treatment of mild to moderate postoperative pain in children. Evidence points toward dose related analgesic efficacy of rectal acetaminophen.^[2] Various doses, ranging from 10 to 70 mg/kg, have been studied but there is no consensus regarding its therapeutic efficacy.^[2-5] Pediatric pharmacokinetic models using rectal acetaminophen in the dose range of 20–40 mg/kg have reported blood levels between 10 and 20 mg/l with varying results in early postoperative pain scores.^[6]

The value of good early postoperative pain scores in good surgical outcome and early discharge of day care patients has been proven without doubt. General anesthesia with short acting opioid like fentanyl suffices intraoperatively for pediatric ophthalmic surgery, but postoperative pain can be a troublesome problem as crying can increase venous pressure and intraocular pressure. Acetaminophen may have doubtful efficacy in severe pain intensity procedures as a sole agent. Ophthalmic surgeries are low and moderate pain intensity procedures with greater incidence of postoperative nausea and vomiting (PONV) which may benefit by an opioid sparing intervention.

Address for correspondence: Dr. Ranju Gandhi,
C-1/1065, Vasant Kunj, New Delhi - 110 070, India.
E-mail: icu_era@yahoo.co.in

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.101906

There is scarce data available on efficacy of rectal acetaminophen in ophthalmic procedures. We conducted this prospective randomized, double-blind, placebo controlled study to evaluate the efficacy of single dose of rectal acetaminophen in pediatric ophthalmic surgery and to compare the analgesic efficacy of high dose (40 mg/kg) and low dose (20 mg/kg) rectal acetaminophen over the 24 hour period.

Materials and Methods

An institutional review board approval was obtained and the study was conducted over a 4 month period. After an informed parental consent 135 children with ASA physical status I or 2, between ages of 6 months and 12 years, of either sex, scheduled for elective ophthalmic surgery (squint, lid repair, orbitotomy, vitreo-retinal, glaucoma or lens aspiration), under general anesthesia, were randomly allocated to one of the three groups [H, L, or N] using the opaque sealed envelope method. Exclusion criteria included allergy or previous reaction to acetaminophen, history of liver or kidney disease, bleeding diathesis, inflammatory lesion of rectum or anus, recent history of rectal or anal bleeding or if they had received acetaminophen within 24 hours prior to the time of surgery. No premedication was given. Anesthesia was induced by inhalation of sevoflurane or intravenously (IV) with propofol, depending on acceptability of the technique. As soon as IV access was established, 2 mcg/kg of fentanyl was administered. Vecuronium 0.08 mg/kg was used for muscle relaxation and the airway secured with appropriate sized endotracheal tube (ETT) or laryngeal mask airway (LMA) (at the discretion of anesthesiologist). After induction of anesthesia, group H received 40 mg/kg of rectal acetaminophen and group L received 20 mg/kg rectal acetaminophen by a nurse not involved in the study by opening the opaque sealed envelope, while the Group N did not receive any rectal drug. The rectal suppositories were acetaminophen slurry contained in polyethylene glycol polymer (hydrophilic base) available in three sizes (80, 170, 250 mg) [Anamol, Elder Pharmaceuticals]. A total rectal dose, as close as possible to either 20 mg/kg or 40 mg/kg, was administered by placing one or a combination of two, three, or four suppositories. The monitoring and interventions thereafter were performed by an anesthesiologist blinded to the rectal drug administered. None of the children received local anesthetic eye drops or any nerve blocks.

Anesthesia was maintained with isoflurane at 1 MAC in 50% nitrous oxide in oxygen with controlled ventilation. Normocarbia and normothermia were maintained. Rescue analgesia with fentanyl 0.5 mcg/kg was administered when there was greater than 20% increase in heart rate or mean

arterial blood pressure (MAP). At the end of procedure, residual neuromuscular block was reversed with neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg and airway device removed once the child was awake. The patient was shifted to the postanesthesia care unit (PACU), where heart rate, oxygen saturation, and respiratory rate were monitored.

In the PACU, the following parameters were observed—type of recovery (Recovery score); hourly observational pain score (OPS) up to 8 hours; time to first postoperative analgesic (in minutes); and postoperative nausea and vomiting (PONV). Pain was assessed at hourly intervals for 8 hours postoperatively using Observational Pain Score (OPS) based on 5 behavioral objective parameters modified from pain/discomfort scale used by Hannallah *et al.*^[7] by an independent observer blinded to the treatment group. This scale has been validated in infants and children and has been used previously to score pain after ENT surgery.^[8] Each variable was scored on a three point scale (1 = none, 2 = moderate, and 3 = severe) to give a cumulative score of 5–15 (Table 1: score of 5 indicating excellent analgesia while score of 15 indicating ineffective analgesia). Rescue analgesia was given if OPS > 10 with fentanyl 0.5 mcg/kg IV up to 2 hours or ibuprofen syrup 0.5 mg/kg after 2 hours.

After 8 hours, rescue analgesic was given if parent or nurse observed that the child had pain or if they requested for analgesia (in case of children >6 years). Children were followed for postoperative rescue analgesic demands till 24 hours for the study period.

Recovery was assessed in the PACU after parental union using a four-point Recovery Score (1 = crying, thrashing, need for restraint, 2 = constant crying, 3 = occasional crying, 4 = quiet) modified from the four-point agitation/discomfort scale described by Watcha *et al.*^[9] PONV was assessed at 0, 2, 4, 6, and 24 hours postoperatively using PONV score [0 = no nausea or vomiting, 1 = nausea or retching but no vomiting, 2 = vomiting once, 3 = persistent nausea (>30 min) or two or more episodes of vomiting in 30 minutes]. Rescue antiemetic ondansetron 0.1 mg/kg was given if PONV score was ≥ 2 . In the absence of PONV, oral fluids were started 2–3 hours after surgery.

Table 1: Observational pain score (OPS)

Behavioral objectives	None	Moderate	Severe
Crying	1	2	3
Facial expression	1	2	3
Position of legs	1	2	3
Position of torso	1	2	3
Motor restlessness	1	2	3

A minimum of 35 patients were required in each group to distinguish with 80% power and at a significance level of 0.05 an average difference of OPS of 2 between treatment groups and control group. All the data was compiled and statistically analyzed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean \pm SD. Categorical variables were expressed as frequencies. Differences between groups were assessed with chi-square or Fisher's exact test for categorical variables. Analysis of variance (ANOVA) test was used for comparison of continuous variables among the groups and *post hoc* analysis was done using Bonferroni correction. All tests were considered significant if $P \leq 0.05$.

Results

One hundred and thirty-five children included in the study were randomly distributed to three groups (50 in Group H, 50 in Group L, and 35 in Group N). Ten children were excluded from the study due to protocol violations as they received intraoperative pethidine (2 in group H, 3 in group L, and 5 in group N). The age, weight, sex distribution, duration of anesthesia, and surgery were comparable in all the three groups [Table 2]. Type of induction (IV or inhalational) and airway device used (LMA or endotracheal tube) was comparable in all the three groups. There was no significant difference in distribution of surgical procedures in different groups [Table 3].

Nineteen out of 30 patients of group N (63%) required postoperative rescue analgesic versus 5/48 (10%) of group H ($P < 0.0001$) and 11/47 (23%) of group L ($P = 0.0005$) during 24 hour period. The difference was not statistically significant between group H and L ($P = 0.091$).

In the first hour, maximum rescue analgesia was demanded by group N (8/30) compared to 1/48 for group H ($P = 0.0009$) and 4/47 for group L ($P = 0.032$). The difference was not statistically significant between group H and L ($P = 0.161$). For group L, maximum demand for rescue analgesia was in the first hour (4/47) though it was not significantly greater than the second hour demand (3/47). The second peak for group L came at the 6–7 hour period (3/47) while for group N it was in the 5–6 hour period (11/30). There was no peak in demand for

rescue analgesia with group H though 3 out of 5 patients who demanded rescue analgesic needed it before 4 hours.

Five out of 30 patients of group N required second postoperative rescue analgesic versus 2/48 ($P = 0.050$) of group H and 2/47 of group L ($P = 0.020$). The difference was not significant between group H and L ($P = 0.570$). The mean time to requirement of first analgesic was 206 ± 185 min in group H, 189 ± 203 min in group L, and 196 ± 170 min in group N ($P = 0.965$). The mean time to requirement of second analgesic was 630 ± 382 min in group H, 600 ± 85 min in group L, and 576 ± 197 min in group N ($P = 0.960$). Three patients in group N required third rescue analgesic while none of the children in group H and L required third rescue analgesic. Mean time to requirement of third analgesic was 960 ± 416 min in group N.

Intraoperative fentanyl top-ups were not required in H and L groups, while five patients in group N (16.6%) required fentanyl top-up once. The difference was statistically significant between group H and N ($P = 0.004$) as well as L and N ($P = 0.004$). Recovery score and pain scores did not vary significantly with type of surgery in the three groups. Recovery of children in H and L groups was better than in group N. Number of patients with recovery score 4 were significantly more in group H (28/48) and L (28/47) as compared to group N (2/30) ($P < 0.0001$) [Table 4]. The difference between group H and L was not significant ($P = 0.902$). Hourly mean OPS was lower in group H and L compared to group N during first 8 hours [Table 5]. It was significant in second, fifth, sixth, and eighth hour postoperatively. The difference between group H and L was not significant at any time interval. Requirement of rescue anti-emetic was 18.7% in group H as compared to 23% each in group L and Group N but the difference among groups was not statistically significant.

Discussion

We undertook this study to investigate the efficacy of single low and high dose rectal acetaminophen. Our study shows that single dose rectal acetaminophen can provide effective postoperative analgesia for pediatric ophthalmic surgery at both low and high doses. Although fewer children in group H

Table 2: Patient characteristics

	Group H (n= 48)	Group L (n=47)	Group N (n=30)	P value
Age (years)	5.62 \pm 3.40	7.40 \pm 3.36	6.635 \pm 4.15	0.056
Weight (kg)	18.06 \pm 7.09	21.56 \pm 9.34	19.73 \pm 11.75	0.185
Sex (M/F)	35/13	36/11	21/9	0.185
ASA(1/2)	44/4	45/2	29/1	0.568
Duration of anesthesia (min)	68.23 \pm 24.65	69.79 \pm 22.36	70.83 \pm 16.97	0.872
Duration of surgery (min)	50.83 \pm 21.09	52.02 \pm 19.411	52.50 \pm 14.36	0.921

Table 3: Surgical procedure

	Group H (n = 48)	Group L (n=47)	Group N (n=30)	P value
Lid surgery	7	4	3	0.064
Corneoscleral/lens aspiration	18	21	19	
Glaucoma surgery	6	6	0	
Squint surgery	11	9	4	
Vitreoretinal surgery	1	6	4	
Enucleation	5	1	0	

Table 4: Recovery score

Recovery score	Group H (n=48)	Group L (n=47)	Group N (n=30)
1	1	2	3
2	0	2	9
3	19	15	16
4	28	28	2

Table 5: Mean observational pain scores (OPS) (Hourly)

	Group H (n = 48)	Group L (n=47)	Group N (n=30)	P value	
				H vs N	L vs N
OPS 1-2 (hrs)	5.77	6.17	8.20	<0.001	0.002
OPS 2-3 (hrs)	5.27	5.23	5.80	0.184	0.042
OPS 3-4 (hrs)	5.38	5.15	5.60	0.792	0.122
OPS 4-5 (hrs)	5.02	5.23	5.80	0.001	0.003
OPS 5-6 (hrs)	5.04	5.00	7.00	0.015	0.009
OPS 6-7 (hrs)	5.20	5.40	5.18	0.976	0.340
OPS 7-8 (hrs)	5.00	5.04	5.80	0.001	0.001

*Difference between group H and L is not significant at any time interval

(10%) required rescue analgesia compared to group L (23%), the difference was not statistically significant. We did not use rectal acetaminophen as the sole analgesic agent intraoperatively in the absence of randomized studies of efficacy of rectal acetaminophen in ophthalmic surgeries and administered fentanyl 2 mcg/kg IV to all our patients. Maximum plasma concentrations of rectal acetaminophen 40 mg/kg are achieved about 2-3 hours after administration.^[10] In our study, 5 children in group N required intraoperative fentanyl top-ups while none required it in group H and L. Recovery scores were also better in group H and L as compared to group N indicating toward an earlier onset of rectal acetaminophen. Bioavailability of rectal acetaminophen is variable. It is approximately 80% of that of oral dose and the rate of absorption is slower. The rectal bioavailability is formulation dependent and decreases with age.^[3] Smaller dose suppositories dissolve more rapidly, but once the process of dissolution is completed, the bioavailability of the free drug is independent of the suppository size. Factors which can contribute to unpredictable absorption pattern from acetaminophen suppositories are premature defecation, rectal pH, rectal contents, and administration of multiple suppositories. These factors should be taken in account in dosing and timing of acetaminophen in surgical patients.

Acetaminophen plasma concentrations were found to be higher in children receiving rectal acetaminophen as compared to those receiving oral acetaminophen postoperatively after a rectal loading dose of 40 mg/kg given intraoperatively during craniofacial surgery.^[11] However, no relationship between acetaminophen concentrations and pain scores was reported. Single doses of rectal acetaminophen 40 mg/kg and 60 mg/kg were found to significantly improve postoperative analgesia in pediatric day-care surgery compared to placebo and 20 mg/kg.^[4] Rectal suppositories achieved equivalent pain control as oral medication with few side-effects and good tolerance.^[12] Rectal acetaminophen 40 mg/kg is effective in reducing pain and postoperative analgesic requirement after tonsillectomy.^[13]

Single doses of rectal acetaminophen were not found to be clinically efficacious for the postoperative pain in a study on infants and small children undergoing cleft palate repair.^[5] However, in this study no intraoperative opioids were given and postoperative pain scores were studied only up to 60–70 minutes.^[5] In a study, combining rectal acetaminophen with ibuprofen did not improve pain control in the immediate postoperative period compared with either drug alone after pediatric day care adenoidectomy.^[8] Type of surgery has a significant effect on the analgesic efficacy of rectal acetaminophen and on the additional postoperative opioid requirements.^[5] In our study, single dose of rectal acetaminophen was quite efficacious over 24 hour period in pediatric ophthalmic surgery, at both low and high doses when compared to the control group and could significantly improve postoperative analgesia. A rectal loading dose of 40 mg/kg followed by 20 mg/kg every 6 hours to maintain serum concentrations at a target range of 10–20 mcg/ml is recommended.^[6] Repeat rectal acetaminophen administration is unnecessary after mild to moderate intensity surgery and it can potentially increase psychological and physical discomfort for the child.

Neonates and infants can form a reactive intermediate metabolite that causes hepatocellular damage, particularly after repeated doses. There are concerns about safety of repeated dosing of acetaminophen in children and reports of toxicity after repeated therapeutic doses and supra-therapeutic doses.^[2] Single dose acetaminophen rectal suppository (40 mg/kg) in children with chronic liver disease was found to be a satisfactory analgesic alternative.^[14] 40 mg/kg rectal acetaminophen was compared to 15 mg/kg acetaminophen given IV and found to provide longer analgesia for moderately painful procedures in children.^[15] Preoperative rectal diclofenac offers no advantage over acetaminophen with respect to postoperative analgesia in tonsillectomy patients and increases intraoperative blood loss.^[16]

There is a great variability in the incidence of PONV in ophthalmic procedures. The difference in distribution of

surgical procedures among three groups is not statistically significant in our study ($P=0.064$). We did not use any prophylactic antiemetics but the overall incidence of PONV was low in our study. PONV is a good predictor of pain relief in children.^[17] The lowest requirement of antiemetic in group H is an indirect pointer toward analgesic efficacy of high dose acetaminophen. As pain may contribute toward PONV, it is reasonable to assume that more effective pain management in group H resulted in a lower PONV incidence.

Our study has a few limitations. We had to use multiple suppositories in children which may have interfered with the blood levels of acetaminophen achieved. We did not do pharmacokinetic study for the plasma levels of acetaminophen. On *post hoc* analysis of our data we found that our study had 90% power to detect the difference between the control group (N) and the treatment groups (H and L) but was weakly powered to detect the difference between the two treatment groups (H and L). We studied a variety of ophthalmic surgical procedures which vary in intensity of postoperative pain. This could have led to bias in the results. However, in our study recovery score and pain scores did not vary significantly with the type of surgery.

Conclusions

Rectal acetaminophen is a simple, safe, and effective technique for pain relief in pediatric ophthalmic surgeries for postoperative analgesia. Based on the results of this study we can conclude that single dose rectal acetaminophen can provide effective postoperative analgesia for pediatric ophthalmic surgery at both doses high (40 mg/kg) and low (20 mg/kg) both in the early postoperative and over a 24 hour period. Further studies involving larger number of patients should be conducted to compare the efficacy of high dose and low dose rectal acetaminophen in pediatric ophthalmic surgeries.

Acknowledgment

Mrs Parul Takkar Chugh, Statistician, Department of Research, Sir Ganga Ram Hospital.

References

- Anderson BJ. Paracetamol (Acetaminophen): Mechanisms of action. *Pediatric Anesth* 2008;18:915-21.
- Anderson BJ, Holford NH, Woollard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. *Anesthesiology* 1999;90:411-21.
- Anderson BJ, Van Lingen RA, Hansen TG, Lin YC, Holford NH. Acetaminophen developmental pharmacokinetics in premature neonates and infants: A pooled population analysis. *Anesthesiology* 2002;96:1336-45.
- Korpela R, Korvenoja P, Meretoja OA. Morphine-sparing effect of acetaminophen in paediatric day-case surgery. *Anesthesiology* 1999;91:442-7.
- Bremerich DH, Neidhart G, Heimann K, Kessler P, Behne M. Prophylactically administered rectal acetaminophen does not reduce postoperative opioid requirements in infants and small children undergoing elective cleft palate repair. *Anesth Analg* 2001;92:907-12.
- 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.
- Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchidexy pain pediatric ambulatory surgery. *Anesthesiology* 1987;66:832-4.
- Viitanen H, Tuominen N, Vaaraniemi H, Nikanne E, Annala P. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. *Br J Anaesth* 2003;91:363-7.
- Watcha MF, Ramirez-Ruiz M, White PF, Jones MB, Laguere RG, Terkonda RP. Perioperative effects of oral ketorolac and acetaminophen in children undergoing bilateral myringotomy. *Can J Anaesth* 1992;39:649-54.
- Romsing J, Moiniche S, Dahl JB. Rectal and parenteral paracetamol, and paracetamol in combination with NSAIDs, for postoperative analgesia. *Br J Anaesth* 2002;88:215-26.
- Van der Marel CD, Van Lingen RA, Plum MA, Scoones G, Van Dijk M, Vaandrager JM, *et al.* Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. *Clin Pharmacol Ther* 2001;70:82-90.
- Owczarzak V, Haddad J Jr. Comparison of oral versus rectal administration of acetaminophen with codeine in postoperative pediatric adenotonsillectomy patients. *Laryngoscope* 2006;116:1485-8.
- Dashti GA, Amini S, Zanguee E. The prophylactic effect of rectal acetaminophen on postoperative pain and opioid requirements after adenotonsillectomy in children. *Middle East J Anaesthesiol* 2009;20:245-9.
- Cormack CR, Sudan S, Addison R, Keating J, Sherwood RA, Ashley EM, *et al.* The pharmacokinetics of a single rectal dose of paracetamol (40 mg \times kg⁻¹) in children with liver disease. *Paediatr Anaesth* 2006;16:417-23.
- 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;100:251-5.
- Schmidt A, Bjorkman S, Akeson J. Preoperative rectal diclofenac versus paracetamol for tonsillectomy: effects on pain and blood loss. *Acta Anaesthesiol Scand* 2001;45:48-52.
- Ku CM, Ong BC. Postoperative nausea and vomiting: a review of current literature. *Singapore Med J* 2003;44:366-74.

How to cite this article: Gandhi R, Sunder R. Postoperative analgesic efficacy of single high dose and low dose rectal acetaminophen in pediatric ophthalmic surgery. *J Anaesthesiol Clin Pharmacol* 2012;28:460-4.
Source of Support: Nil, **Conflict of Interest:** None declared.