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To compare rectal and oral acetaminophen for postoperative pain relief in children undergoing craniofacial surgery

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Abstract
Background and objectives: In newborns and infants who have just undergone major surgery, the plasma concentrations of the painkiller acetaminophen (INN, paracetamol) have not yet been determined in the research literature. As a result, we conducted a study in the intensive care unit of our hospital.
Study Methods: During elective craniofacial correction, 40 toddlers with a mean (standard deviation) age of 10.3 (2.3) months received 20 mg/kg of acetaminophen orally (n = 20) or rectally (n = 20) every 6 hours following a rectal loading dose of 40 mg/kg. Pain assessments were made every three hours, and blood samples were taken an hour before and two hours after the administration of acetaminophen maintenance dosages.
Results and discussion: The mean area under the concentration-time curve (AUC) for patients receiving rectal acetaminophen was 171.2 mg/h/L, while the mean AUC for patients receiving oral acetaminophen was 111.9 mg/h/L. Patients receiving oral acetaminophen reported greater pain scores. However, acetaminophen plasma concentrations and pain scores did not differ across the groups once the patients who vomited were removed from the oral acetaminophen group. Acetaminophen plasma concentrations and pain ratings did not correlate. Despite the fact that 9 out of 40 patients (or 22.5%) did not achieve the desired analgesic acetaminophen plasma concentrations of 10 to 20 mg/L, 7.5% of the pain scores on the visual analogue scale were higher than the 4 cm cutoff criterion.
Conclusion: These are the first results demonstrating that following major surgery in this age range, the analgesic acetaminophen plasma concentration does not always reach the 10 to 20 mg/L level. These results also demonstrate that the rectal route is the most effective approach to provide acetaminophen following craniofacial surgery once a rectal loading dosage of 40 mg/kg has been administered during surgery.

Keywords: Analgesic, children, efficacy, craniofacial surgery, rectal and oral

Introduction
Patients who are in moderate pain after surgery frequently benefit from the use of acetaminophen as a postoperative analgesic. The effects of acetaminophen on children's body temperatures, as well as the connections between dose and effect and dose and concentration, have been described in the scientific literature. Recent research findings published by our group describe the effects of giving acetaminophen to neonates who had undergone vacuum extraction. However, there is a lack of information regarding the plasma concentrations of the painkiller acetaminophen in newborns and babies following major surgical procedures [1].

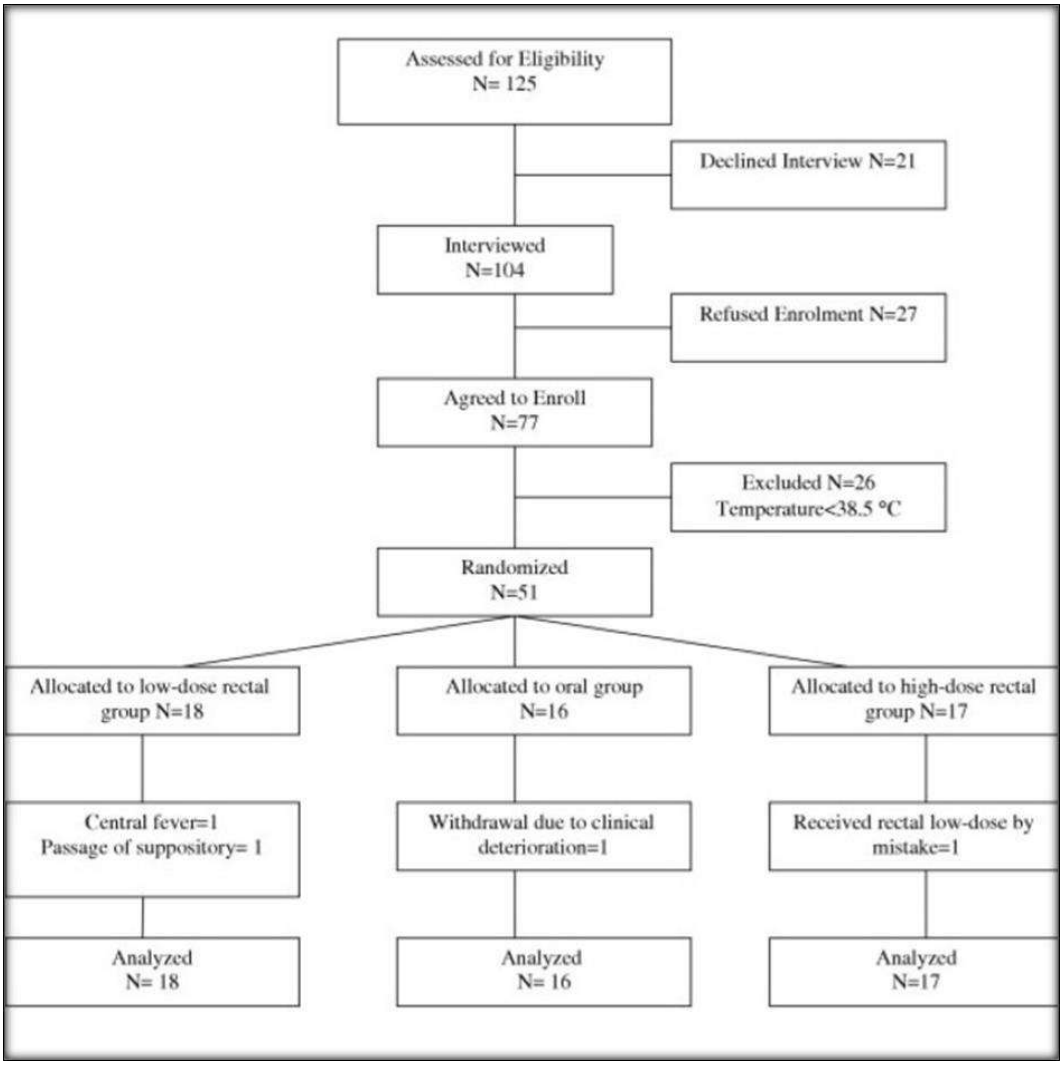

Fig 1: Oral and rectal effectiveness of acetaminophen (Mona et al., 2005) [1]

It is generally agreed that a plasma concentration of 10 mg/L of acetaminophen is required to provide adequate pain relief in paediatric patients having tonsillectomy who are between the ages of 2 and 15 years [2-4]. The ideal plasma concentration to elicit analgesia is commonly regarded to be 10 to 20 mg/L, a figure that is extrapolated from studies in adults. Because the absorption rate and bioavailability of acetaminophen taken orally differ from those of acetaminophen given rectally, and because taking oral drug might produce nausea and vomiting, it is essential to gather information regarding both routes of administration. The delayed and inconsistent absorption that occurs after rectal administration causes acetaminophen plasma concentrations to be unpredictable and does not reliably generate rapid onset analgesia [5]. An acetaminophen rectal loading dose of at least 30 to 40 mg/kg is therefore indicated to obtain acceptable pain relief. After an initial loading dose of 40 mg/kg, the maximum daily amount of acetaminophen that is recommended is between 90 and 100 mg/kg, which then allows for three doses of 20 mg/kg to be administered [6-10]. In a randomised controlled trial, we compared the efficacy of both oral and rectal acetaminophen administration in young children undergoing major craniofacial surgery. Specifically, we compared acetaminophen plasma concentrations with changes in scores for two validated pain measurement instruments for this age group. The results of this study showed that oral administration of acetaminophen was more effective than rectal administration [11-14]. The primary objective of this study was to compare the plasma concentrations of acetaminophen and the effects of the drug in children who were given either numerous doses of acetaminophen administered rectally or equal doses of oral acetaminophen following an initial loading dose administered rectally. Orally and rectally administered acetaminophen were both used in the study to accomplish a secondary objective that was aimed at determining a dose-plasma concentration and a plasma concentration-effect relation in children between the ages of three months and three years who had undergone elective major craniofacial surgery [15-17].

Patients and Methods

All paediatric surgical subspecialties receive referrals from The Children's Hospital, which is a level III referral facility. As a result, it is The India's sole designated paediatric craniofacial facility. Every year, about 200 significant craniofacial repairs are made. 45 children were enrolled consecutively between March 2020 and March 2021 after the Medical Ethical Committee of the University Hospital approved the trial and signed informed agreement from the parents was acquired.

Age between three months and three years was required for inclusion, as well as elective craniofacial repair for various types of craniosynostosis.

The following conditions were excluded: craniotomies performed due to tumours, hydrocephalus, or trauma; preexisting liver or kidney disorders as indicated by abnormal liver enzyme, bilirubin, urea, and creatinine values; severe mental retardation; Glasgow Coma Score 8; and known acetaminophen allergy.

Table 1: Patients Data

	Rectal Group	Oral Group
Age (month) Mean (SD)	**10.6 (1.9)**	**10.0 (2.7)**
Range	8-15	6-20
Weight (kg))		
Mean (SD)	9.4 (1.6)	9.2 (1.1)
Range	5. 4-12.2	6.7-11.0
Sex		
Male	15	14
Female	5	6
Condition requiring operative correction		
Scaphocephaly	10	10
Trigonocephaly	6	1
Plagiocephaly	2	7
Brachycephaly	2	2
Duration of operation (min)		
Mean (SD)	221 (40)	214 (26)
Range	175-315	170-270
Amount of blood loss (mL)		
Mean (SD)	983 (560)	741 (448)
Range	400-2800	300-2000
Baseline heart rate (beats/min)		
Mean (SD)	141 (26)	148 (23)
Range	75-195	105-195
Baseline mean arterial pressure (mm Hg)		
Mean (SD)	78 (15)	73 (12)
Range	53-106	48-93

There were 50 patients who qualified. 45 children were included in this study since the parents of 05 children did not provide informed consent. Five of the 45 patients who were initially included in the analysis were later excluded for a variety of reasons, including the following: logistical issues with the delivery of the study medication (2 patients), leaving the operating room with mechanical ventilation (1 patient), and withdrawal of parental informed consent during the study (2 patients). Regarding the surgical process, blood loss, and pain levels, it was discovered that these 5 individuals did not differ from the other 40 patients who were included. So, for this study, the data of 40 patients—20 of whom received acetaminophen orally and 20 of whom received it were evaluated.

Procedure

There were 50 eligible patients. The parents of 05 children did not give their informed consent, thus 45 kids were included in the study. Five of the 45 patients who were initially included in the analysis were later removed for a number of reasons, including: logistical problems with the delivery of the study medication (2 patients); leaving the operating room with mechanical ventilation (1 patient); and withdrawal of parental informed consent throughout the study (2 patients). It was shown that these 5 patients did not differ from the other 40 patients in terms of the surgical procedure, blood loss, or discomfort levels. Therefore, for this study, the data of 40 patients were reviewed, of whom 20 received acetaminophen orally and 20 received it rectally.

Statistical Methods

The Mann-Whitney U test was used to compare the area under the concentration-time curve (AUC) of the acetaminophen plasma concentrations and the pain scores of patients taking either oral or rectal acetaminophen. Multiple regression analysis was done to determine the relationship between mean acetaminophen plasma concentrations and mean pain scores after logarithmic transformation of the mean acetaminophen plasma concentrations and mean pain scores. Corrections were made for patients who received oral or rectal acetaminophen, for those who received an additional dose, and for those who vomited while taking oral acetaminophen.

Masking Method

Patients who were given acetaminophen by rectal administration were given acetaminophen suppositories and a placebo elixir for the course of the research trial, whereas patients who were given acetaminophen via oral administration were given acetaminophen elixir and placebo suppositories. Patients, nurses, and researchers were all kept in the dark regarding the route of the actual acetaminophen administration. This was made possible by the fact that all children were given both an elixir and a suppository. In addition, the acetaminophen suppositories, elixir, and placebos were all manufactured in the same department of the hospital pharmacy.

Results

Analysis and Confounders

The patients receiving oral acetaminophen had an average age of 10.0 months and a mean weight of 9.2 kg. The average age and weight of the patients receiving rectal acetaminophen were 10.6 months and 9.4 kg, respectively. Regarding age, weight, gender, baseline heart rate, baseline mean arterial pressure, operation time, blood loss, and surgical techniques, there were no significant differences between patients getting oral acetaminophen and patients receiving rectal acetaminophen.

Three patients from each group needed an additional dose of acetaminophen. Twelve individuals who received oral acetaminophen and eleven patients who received rectal acetaminophen both experienced occasional vomiting. While 3 of the former required metoclopramide and 2 of the latter required ondansetron, 5 of the latter required domperidone. Three patients receiving oral acetaminophen and two patients receiving rectal acetaminophen both received midazolam due to restlessness or assumed fear.

Plasma levels of Acetaminophen

The plasma concentrations of acetaminophen were significantly variable following the rectal loading dose of 40 mg/kg. Following the rectal loading dosage, there was no change in the mean acetaminophen plasma concentrations between the oral and rectal groups. Individuals receiving rectal acetaminophen had considerably greater AUCs of acetaminophen plasma concentrations than patients receiving oral acetaminophen. There was no longer a significant difference in the AUCs between the two groups after patients who vomited in the oral group were excluded. At the time of the further acetaminophen dose, the plasma concentrations of acetaminophen in the patients receiving rectal acetaminophen were 5.5, 13.5, and 0.9 mg/L and 15.8,

7.5, and 4.9 mg/L in the patients receiving oral acetaminophen.

Discussion

Individuals taking rectal acetaminophen had plasma concentrations of acetaminophen that were noticeably higher than patients receiving oral acetaminophen. This is unexpected because prior research comparing rectal delivery to oral treatment at the same doses revealed lower amounts. It's possible that individuals in the oral group who vomited received little to no acetaminophen at a certain time point, which could account for the lower quantities following oral administration. In fact, there was no discernible difference in acetaminophen plasma concentrations once these patients were excluded, despite the fact that rectal concentrations were still higher than oral concentrations. Another possibility is that because samples were taken two hours after the maintenance dose was given, the peak acetaminophen plasma concentration following oral delivery was missed. Following oral acetaminophen treatment, the peak plasma concentration is typically anticipated within 30 to 60 minutes. It is less likely that the peak plasma concentration will be missed since patients with general anaesthesia have slower gastric emptying, which results in a peak plasma concentration after 90 to 120 minutes. Additionally, until the age of 6 to 8 months, the typical adult rate of stomach emptying may not be attained. 9 Stomach emptying is sluggish and unpredictable until normal adult rates are established, and narcotic analgesics prevent gastric emptying and medication absorption [18, 19].

Patients who were receiving oral acetaminophen had considerably higher pain scores, which was inversely related to their lower plasma acetaminophen concentrations. Acetaminophen plasma concentrations and pain scores, however, did not significantly correlate. It has also been reported that there is no such relationship among infants delivered by vacuum extraction at term in other research. It is highly improbable that a single dose of these antiemetics had any effect on the pain scores because ondansetron does not have any psychoactive qualities and domperidone and metoclopramide only had somewhat more psychoactive properties. On the other hand, given this rating scale serves as a tool for measuring distress, midazolam, which has negligible analgesic qualities, might have had an impact on the pain scores, particularly on the COMFORT score. However, midazolam shouldn't have an impact on the VAS score. 22.5% of all patients failed to reach the necessary analgesic acetaminophen plasma concentrations of 10 to 20 mg/L over the course of the 24-hour observation period. Still, more than 92.5% of these individuals' VAS values fell below the 4 cm threshold. Studies on adults revealed that sufficient analgesia is produced by acetaminophen plasma concentrations of 6 to 24 mg/L following intravenous treatment. Since all of the children in our study had acetaminophen plasma concentrations below 5 mg/L and more than 92.5% of their VAS ratings fell below 4 cm, the analgesic range for this age group may well be between 10 and 20 mg/L [20-22].

Conclusion

The children's faces swelling up after the procedure and their inability to open their eyes for several hours afterward is evidence of their agony. Differences in the activity of the enzymes involved in the metabolism of acetaminophen are another element that helps to explain the widely varied acetaminophen plasma concentrations. These variations are primarily caused by variations in the patients' ancestry. Age-related maturation of enzyme activity cannot be held accountable for the variations in activity as all of our patients were roughly the same age. The goal of future studies should be to identify variations in enzyme activity and link genetic background to the vast variation in acetaminophen plasma concentrations. According to our analysis, these are the first data demonstrating that following major surgery in this age range, the analgesic acetaminophen plasma concentration does not always reach the 10 to 20-mg/L limit. Acetaminophen plasma concentrations and pain scores did not correlate, nevertheless. These results also demonstrate that the rectal route is the most effective approach to provide acetaminophen following craniofacial surgery once a rectal loading dosage of 40 mg/kg has been administered during surgery. Following craniofacial surgery, rectal administration of acetaminophen has become normal practice in our PSICU as a result of this study.

References

1. Nabulsi M *et al*., Equal antipyretic effectiveness of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN11886401]. BMC Pediatrics. 2005;5(1):35.
2. van der Marel CD, van Lingen RA, Pluim MA, Scoones G, van Dijk M, Vaandrager JM *et al*. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clinical Pharmacology & Therapeutics. 2001;70(1):82-90.
3. van Lingen RA, Deinum HT, Quak CM, Okken A, Tibboel D. Multiple-dose pharmacokinetics of rectally administered acetaminophen in term infants. Clinical Pharmacology & Therapeutics. 1999;66(5):509-515.
4. van der Marel CD, Anderson BJ, van Lingen RA, Holford NH, Pluim MA, Jansman FG *et al*. Paracetamol and metabolite pharmacokinetics in infants. European journal of clinical pharmacology. 2003;59(3):243-251.
5. Lin YC, Sussman H, Benitz W. Plasma concentrations after rectal administration of acetaminophen in preterm neonates. Pediatric Anesthesia. 1997;7(6):457-459.
6. Van Lingen RA, Deinum JT, Quak JME, Kuizenga AJ, Van Dam JG, Anand KJS *et al*. Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates: Presented in part at the annual meeting of the European Society for Pediatric Research, Rotterdam, The Netherlands, July 3–6 1994. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1999;80(1):F59-F63.
7. Holmér Pettersson P, Jakobsson J, Öwall A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. Acta anaesthesiologica scandinavica. 2006;50(6):673-677.
8. Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. European journal of clinical pharmacology. 2001;57(8):559-569.
9. Hansen TG, O'Brien K, Morton NS, Rasmussen SN. Plasma paracetamol concentrations and pharmacokinetics following rectal administration in neonates and young infants. Acta anaesthesiologica scandinavica. 1999;43(8):855-859.

10. Van der Marel CD, Peters JWB, Bouwmeester NJ, Jacqz-Aigrain E, Van den Anker JN, Tibboel D. Rectal acetaminophen does not reduce morphine consumption after major surgery in young infants. British journal of anaesthesia. 2007;98(3):372-379.
11. Hahn TW, Mogensen T, Lund C, Schouenborg L, Rasmussen M. High-dose rectal and oral acetaminophen in postoperative patients–serum and saliva concentrations. Acta anaesthesiologica scandinavica. 2000;44(3):302-306.
12. Anderson B, Kanagasundarum S, Woollard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. Anaesthesia and intensive care. 1996;24(6):669-673.
13. 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. British journal of anaesthesia. 2008;100(2):251-255.
14. 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. Anesthesia & Analgesia. 2001;92(4):907-912.
15. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP. Plasma concentrations after high-dose (45 mgz· kg− 1) rectal acetaminophen in children. Canadian journal of anaesthesia. 1995;42(11):982-986.
16. Haddadi S, Marzban S, Karami MS, Heidarzadeh A, Parvizi A, Nabi BN. Comparing the duration of the analgesic effects of intravenous and rectal acetaminophen following tonsillectomy in children. Anesthesiology and pain medicine. 2014;4(1):e13175.
17. Birmingham PK, Tobin MJ, Henthorn TK, Fisher DM, Berkelhamer MC, Smith FA *et al*. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. The Journal of the American Society of Anesthesiologists. 1997;87(2):244-252.
18. Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. The Laryngoscope. 2000;110(11):1824-1827.
19. Rømsing J, Østergaard D, Senderovitz T, Drozdziewicz D, Sonne J, Ravn G. Pharmacokinetics of oral diclofenac and acetaminophen in children after surgery. Pediatric Anesthesia. 2001;11(2):205-213.
20. Alhashemi JA, Daghistani MF. Effects of intraoperative iv acetaminophen vs im meperidine on post-tonsillectomy pain in children. BJA: British Journal of Anaesthesia. 2006;96(6):790-795.
21. Schuitmaker M, Anderson BJ, Holford NHG, Woollard GA. Pharmacokinetics of paracetamol in adults after cardiac surgery. Anaesthesia and intensive care. 1999;27(6):615-622.
22. 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. Pediatric Anesthesia. 1997;7(6):445-449.