Vol. 1 No. 3 (2024)
ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081
Journal of Medical & Health Sciences Review

EFFECTIVENESS OF INTRAVENOUS VS RECTAL ACETAMINOPHEN FOR PAIN MANAGEMENT IN POST OPERATIVE NEONATES

Hasnain Aslam[1], Bilal Jawaid[1], Waqas Ahmad[1], Fareeba Sabir[2], Ali Raza Chaudhry[3], Mudassar Fiaz Gondal[4]

[1] Post Graduate Resident, Department of Paediatric Surgery, Holy Family Hospital, Rawalpindi, Pakistan, Email: hasanain.aslam@gmail.com
[2]Post Graduate Resident, DHQ Hospital Rawalpindi, Pakistan
[3]Senior Registrar, Department of Paediatric Surgery, Holy Family Hospital, Rawalpindi, Pakistan
[4]Associate Professor, Head of Department, Department of Paediatric Surgery, Holy Family Hospital, Rawalpindi, Pakistan

ARTICLE INFO:

Keywords:
Acetaminophen, Neonatal Analgesia, Postoperative Pain, Intravenous Administration, Rectal Administration, Randomized Controlled Trial

Corresponding Author:
Hasnain Aslam,
Post Graduate Resident, Department of Paediatric Surgery, Holy Family Hospital, Rawalpindi, Pakistan,
Email:
hasanain.aslam@gmail.com

Article History:
Published on September 1, 2024

ABSTRACT

Background: Adequate postoperative analgesia in neonates remains challenging due to pharmacokinetic variations and limited analgesic options. This study compared the efficacy of intravenous and rectal routes of acetaminophen administration for postoperative pain management in term neonates.

Methods: A single-blind randomized controlled trial enrolled 64 term postoperative neonates (≥37 weeks gestation, birth weight ≥2.5 kg) requiring analgesia for ≥12 hours. Participants were randomly allocated to receive acetaminophen 15 mg/kg intravenously (Group A, n=32) or rectally (Group B, n=32) every 6 hours for a maximum of 48 hours. Demographic characteristics included age, gender, and weight. Primary outcomes assessed were rescue analgesia requirement and time to rescue analgesia. Secondary outcomes included pain score reduction using the Neonatal Pain, Agitation and Sedation Scale (NPASS).

Results: Baseline demographic characteristics were comparable between groups. Rescue analgesia was required in 54.7% of the total study population. Notably, only 37.5% of neonates in Group A required rescue analgesia compared to 71.9% in Group B ($p = 0.012$). The mean time to rescue analgesia was significantly longer in Group A (4.82 ± 0.57 hours) versus Group B (3.18 ± 0.66 hours; $p < 0.001$). Intravenous acetaminophen produced a greater mean pain reduction of 6.09 ± 1.48 points compared to 4.50 ± 1.48 points with rectal administration ($p < 0.001$).

Conclusion: Intravenous acetaminophen demonstrated superior

analgesic efficacy compared to rectal administration in postoperative term neonates, with reduced rescue analgesia requirements and greater pain score reduction. These findings suggest that the intravenous route may be preferred for postoperative analgesia in term neonates when vascular access is available.

Introduction:

The early recognition of pain and its effective management among neonates is of paramount importance in order to achieve better physical as well as neuronal development[1]. Acetaminophen is the most commonly prescribed drug among neonates that not only acts as antipyretic but have analgesic characteristics as well[2]. The effectiveness of this drug is markedly varied when it comes to the route of administration among neonates and most commonly used routes of administration are oral, intravenous and rectal[3]. Various studies have tried to assess and validate the usefulness of various routes of acetaminophen administration; however, the usefulness of the rectal administration is the least understood in literature. Furthermore, the utilization of which route of acetaminophen is better is further depends on the Pharmacokinetic and pharmacodynamic properties of the drug being given[4].

The metabolism of the acetaminophen is of highly importance because the Cytochrome-P450 system among neonates is considered less efficient as compared to adult. Acetaminophen is metabolized in liver with renal clearance as a well-documented process; however, the hepatotoxicity is a factor that should be soughted when using this drug among neonates[5]. In this scenario the dose adjustment and route of administration come into light and studies have very well depicted the effectiveness of intravenous acetaminophen use with possible associated adverse effects, but the rectally used acetaminophen effectiveness and side effects is still a matter of debate[6]. Various formulations of per-rectal acetaminophen are devised so far and suppositories are most commonly used formulation among neonates[7]. However, there are still documented barriers related to per-rectal administration like loss of drug with each stool episode, and immature portal-rectal system for drug absorption and contraindications as in Necrotizing Enterocolitis and Thrombocytopenia [4].

In resource-limited settings where Peripherally Inserted Central Catheters (PICC lines) or central venous catheters are unavailable for postoperative neonates, we rely primarily on intravenous (IV) cannulae for the administration of analgesics and therapeutic drugs. However, there are instances when even IV access becomes unattainable. In such situations, the least we can do is provide analgesia through alternative routes. This study aims to validate the effectiveness and compare the efficacy of two alternative routes in reducing postoperative pain among neonates, ensuring equal bioavailability of the administered dose between the two methods. Owing the variability in data and literature about acetaminophen administration route, this study aim to analyze the comparison of Intravenous versus rectal administration of acetaminophen and assessment of post-operative pain severity among neonates.

Materials and Methods:

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the Institutional Ethics Committee of the hospital ERB number is (RMU-RRF-SUR-008-23). Informed written consent was obtained from the parents or legal guardians of all enrolled neonates prior to participation in the study.

Study Design, Setting and Duration

This single-blind randomized controlled trial was conducted at the High Dependency Unit, Department of Pediatric Surgery, at a tertiary care hospital in Pakistan from December 2022 to December 2023. The study protocol was prospectively registered at ClinicalTrials.gov (NCT06638086) and reported according to CONSORT guidelines.

Sample Selection

Term postoperative neonates (≥37 weeks gestation) with birth weight ≥2.5 kg requiring analgesia for ≥12 hours were eligible. Exclusion criteria were: preterm birth, preoperative status, requirement for mechanical ventilation, need for central venous catheter, local/topical analgesia use, or presence of major congenital malformations.

Sample Size

The sample size was calculated based on a population size of 70, expected population proportion of 50%, 5% margin of error, and 95% confidence level ($\alpha = 0.05$, $\beta = 0.20$). The minimum required sample size was determined to be 60 neonates. The enrollment of 64 neonates provided adequate power for the study. Baseline demographic data were collected for all enrolled neonates including age (postnatal age in hours at time of enrollment), gender (male or female), and weight (birth weight in kilograms).

Eligible neonates were randomly allocated in a 1:1 ratio to receive acetaminophen via intravenous route (Group A, n=32) or rectal route (Group B, n=32). Randomization was performed using simple random sampling by lottery method. Treatment allocation was concealed from outcome assessors who remained blinded to group assignment throughout the study period.

Group A (Intravenous Administration): Neonates in Group A received acetaminophen 15 mg/kg intravenously diluted in 0.9% normal saline to a final volume of 5 mL over 15 minutes. The initial dose was administered within one hour of meeting pain assessment criteria (Neonatal Pain, Agitation and Sedation Scale [NPASS] score ≥4). Subsequent doses of 15 mg/kg were administered intravenously every 6 hours for a maximum of 48 hours or until discharge from the High Dependency Unit, whichever occurred first.

Group B (Rectal Administration): Neonates in Group B received acetaminophen 15 mg/kg as a rectal suppository or liquid formulation. The initial dose was administered within one hour of meeting pain assessment criteria (NPASS score ≥4). Subsequent doses of 15 mg/kg were administered rectally every 6 hours for a maximum of 48 hours or until discharge from the High Dependency Unit, whichever occurred first.

The primary outcome was the proportion of neonates requiring rescue analgesia within 48 hours of study drug administration, with secondary comparison of time to administration of rescue analgesia between groups. Secondary outcomes included differences in pain scores between study groups, pain reduction before and after analgesia.

Statistical Analysis:

Statistical analysis was carried out by using SPSS. V.26. The Qualitative variables were expressed in the form of frequencies and percentages, and Quantitative variables were expressed by using Mean and standard deviation. Difference between qualitative variables was judged by contingency table and difference between quantitative variables was judged by independent sample T-test. The P-value of less than 0.05 was taken as significant.

Results:

A total of 64 neonates were enrolled, evenly distributed between the two treatment arms (32 in each group). The overall male-to-female ratio was 1.2:1, with males comprising 54.7% of the study population. Gender distribution was similar between the groups, with 59.4% males in Group A (IV acetaminophen) and 50.0% in Group B (rectal acetaminophen), showing no statistically significant difference ($p = 0.451$). The mean age of neonates across the cohort was 4.91 ± 1.91 days, with Group A

and Group B showing nearly identical mean ages of 4.94 ± 1.98 and 4.88 ± 1.88 days, respectively (p = 0.897). Similarly, the mean body weight was comparable between both groups (2.81 ± 0.22 kg in Group A vs. 2.84 ± 0.23 kg in Group B; p = 0.548). These findings indicate that the two groups were well balanced in baseline demographic and clinical characteristics, ensuring comparability before assessing the analgesic outcomes.

Table 1. Baseline Demographic Characteristics of Neonates

Variable		Overall	Group A	Group B	p-Value
Gender	Male	35 (54.7%)	19 (59.4%)	16 (50.0%)	0.451
	Female	29(45.3%)	13(40.6%)	16(50.0%)	
Age		4.91±1.91	4.94 ± 1.98	4.88 ± 1.88	0.897
Weight		2.82±0.23	2.81 ± 0.22	2.84 ± 0.23	0.548

Rescue analgesia was required in 35 (54.7%) of the total 64 neonates enrolled in the study. A marked intergroup difference was observed, with only 12 (37.5%) neonates in Group A (intravenous acetaminophen) requiring rescue analgesia, compared to 23 (71.9%) in Group B (rectal acetaminophen). Conversely, 62.5% of neonates in Group A did not require additional analgesia, whereas only 28.1% in Group B remained comfortable without it. The difference between the two treatment groups was found to be statistically significant (p = 0.012, Chi-square test), indicating that intravenous acetaminophen provided more effective postoperative analgesia and reduced the need for rescue analgesics compared to rectal administration.

Table 2. Comparison of Rescue Analgesia Requirement Between Groups

		Group		Total	p-Value
		Group A (IV)	**Group B (Rectal)**		
Rescue Analgesia	Yes	12	23	35	0.012
		37.5%	71.9%	54.7%	
	No	20	9	29	
		62.5%	28.1%	45.3%	
Total		32	32	64	
		100.0%	100.0%	100.0%	

The time to rescue analgesia differed notably between the two administration routes. Neonates receiving intravenous paracetamol had a mean time to rescue analgesia of 4.82 ± 0.57 hours, whereas those administered paracetamol per rectum required rescue analgesia sooner, with a mean time of 3.18 ± 0.66 hours. This difference was statistically significant (p < 0.001), indicating a faster onset of analgesic effect with rectal administration in this cohort. Additionally, the magnitude of pain reduction varied between the groups. Intravenous paracetamol produced a mean decrease in pain score of 6.09 ± 1.48 points, while the rectal route yielded a smaller reduction of 4.50 ± 1.48 points. This difference was also statistically significant (p < 0.001), highlighting that intravenous administration provided more effective postoperative pain relief in neonates compared to the rectal route.

Table 3. Comparison of Time to rescue analgesia and Pain between Groups

Parameter	Group A	Group B	p-value
Time to rescue analgesia	4.82 ±0.57	3.18±0.66	<0.001
Pain before analgesia	8.41 ± 0.82	8.28 ± 0.90	0.536
Pain after analgesia	2.33 ± 1.55	3.78 ± 1.74	<0.001
Pain reduction	6.08 ± 1.51	4.49 ± 1.50	<0.001

Discussion

Effective postoperative pain management in neonates remains a priority in pediatric surgical practice. This study demonstrated that intravenous acetaminophen provides superior analgesia compared to rectal administration for postoperative pain relief in term neonates, with significantly reduced requirements for rescue analgesics. These findings have important implications for clinical decision-making in neonatal pain management protocols. The primary finding of this study was that only 37.5% of neonates receiving intravenous acetaminophen required rescue analgesia compared to 71.9% receiving rectal administration ($p = 0.012$). This substantial difference underscores the clinical superiority of the intravenous route in the immediate postoperative period. Extended time to rescue analgesia in the intravenous group (4.82 ± 0.57 hours) versus the rectal group (3.18 ± 0.66 hours, $p < 0.001$) reflects the pharmacokinetic advantages of parenteral administration.

A recent systematic review and network meta-analysis by Osorio et al. (2024) evaluating 14 randomized controlled trials with 829 pediatric participants found that while both intravenous and rectal acetaminophen were more effective than placebo in pain relief, the certainty of evidence comparing routes remained low to very low due to heterogeneity in dosing regimens and measurement instruments. However, the same review acknowledged that intravenous administration achieves rapid analgesic plasma concentrations and may be preferred when rescue medication is needed for breakthrough pain[9].

The pain score reduction of 6.09 ± 1.48 NPASS points with intravenous administration versus 4.50 ± 1.48 with rectal administration ($p < 0.001$) represents clinically meaningful pain relief. This distinction is important given evidence that inadequate neonatal analgesia may result in altered pain perception and heightened pain responses in subsequent procedures [10].

The superior performance of intravenous acetaminophen reflects fundamental differences in drug bioavailability. The intravenous route achieves absolute bioavailability of approximately 100% with rapid onset of action within 5-10 minutes and peak plasma concentrations within 30 minutes. In contrast, rectal acetaminophen exhibits highly variable bioavailability ranging from 40-80% with delayed and unpredictable absorption, particularly in the immediate postoperative period when rectal blood flow may be compromised[11,12]. Khalili et al. (2016) conducted a placebo-controlled trial comparing preemptive intravenous versus rectal acetaminophen in 120 children undergoing inguinal herniorrhaphy. While both acetaminophen formulations demonstrated significantly lower pain scores than placebo during the first two postoperative hours, intravenous paracetamol produced the largest analgesic effect during the first postoperative hour with highest sedation levels in the recovery room [13]. These findings align with our observation of superior efficacy of the intravenous route.

The rectal route, despite being non-invasive and traditional, has documented limitations in neonatal populations. A cross-sectional study by Rubab et al. (2019) conducted at Services Hospital Lahore examined awareness and acceptance of rectal suppositories for postoperative analgesia among 167 preoperative patients. The study found that only 6% of subjects knew about the pain relief properties of suppositories, and 50.3% accepted rectal administration only after counseling about its benefits [14]. This reflects both limited knowledge and cultural hesitance regarding rectal drug administration in South Asian populations.

From a pharmacological perspective, rectal absorption of acetaminophen is slow and incomplete in neonates. The composition of suppository formulations (lipophilic versus hydrophilic), rectal pH variations, and postoperative changes in mesenteric blood flow all contribute to unpredictable drug

delivery[15]. Additionally, formulation variability between different suppository brands and sizes further compromises reliability of this route in acute postoperative pain management.

The superior efficacy of intravenous acetaminophen supports its integration into multimodal postoperative analgesia protocols. Ceelie et al. (2013) demonstrated in a landmark randomized controlled trial of 71 neonates undergoing major surgery that intravenous paracetamol resulted in a 66% reduction in cumulative morphine requirements over 48 hours compared to continuous morphine infusion alone, with median morphine doses of 121 μg/kg per 48 hours in the paracetamol group versus 357 μg/kg in the morphine group ($p < 0.001$) [16]. This opioid-sparing effect is particularly valuable in neonates where opioid-related adverse effects, including respiratory depression, prolonged ventilation requirements, and withdrawal phenomena, represent significant clinical concerns.

This study was conducted at a tertiary care pediatric surgery center in Pakistan, contributing valuable evidence to the limited literature on neonatal pain management in South Asian healthcare settings. The pediatric surgery infrastructure in Pakistan has made significant advances, with major teaching centers at Aga Khan University Hospital (Karachi) and National Institute of Child Health establishing evidence-based pain management protocols[17].

The acetaminophen dosing regimen of 15 mg/kg intravenously every 6 hours employed in this study aligns with pediatric guidelines. Anderson and Holford (2008) demonstrated through population pharmacokinetic analyses that neonates have prolonged acetaminophen elimination half-lives (2.5-3 hours) compared to older children, supporting the appropriateness of 6-hour dosing intervals in this population. The maximum total daily dose of 60 mg/kg remains well within established safety limits of 90 mg/kg per day[18].

This study utilized the Neonatal Pain, Agitation and Sedation Scale (NPASS), a validated instrument specifically developed for neonatal populations with demonstrated inter-rater reliability and construct validity. The NPASS provides standardized assessment of pain in both mechanically ventilated and non-ventilated neonates, enabling comparison with international literature[19].

Based on the findings of this study and supporting evidence, intravenous acetaminophen should be incorporated into postoperative analgesia protocols for term neonates when vascular access is present. The marked reduction in rescue analgesia requirements (37.5% versus 71.9%) and superior pain relief demonstrate clear clinical advantage over rectal administration. The rectal route, if considered, should be reserved for situations where intravenous administration is contraindicated or not feasible. The extended analgesic duration achieved with intravenous administration (4.82 hours) reduces frequency of medication administration and nursing workload, providing additional practical benefits beyond superior pain control. These advantages support prioritization of intravenous acetaminophen as a cornerstone of neonatal postoperative multimodal analgesia in tertiary care surgical settings.

Conclusion

This study provides evidence that intravenous acetaminophen offers superior postoperative analgesia compared to rectal administration in term neonates, with significantly reduced rescue analgesic requirements, prolonged analgesic duration, and greater pain relief. These findings support the incorporation of intravenous acetaminophen into multimodal postoperative pain management protocols at tertiary care pediatric surgery centers. Implementation of evidence-based pain management utilizing intravenous acetaminophen represents an important advance in optimal perioperative care of surgical neonates in Pakistan and South Asia.

References:

1. McLean MA, Scoten OC, Chau CM, Synnes A, Miller SP, Grunau RE. Association of neonatal pain-related stress and parent interaction with internalizing behaviors across 1.5, 3.0, 4.5, and 8.0 years in children born very preterm. JAMA Network Open. 2022 Oct 3;5(10):e2238088.
2. Locci C, Cuzzolin L, Capobianco G, Antonucci R. Paracetamol overdose in the newborn and infant: a life-threatening event. European journal of clinical pharmacology. 2021 ;77(6):809-15
3. Charlton K, Limmer M, Moore H. Intravenous versus oral paracetamol in a UK ambulance service: a case control study. British Paramedic Journal. 2020 Jun 1;5(1):1-6.
4. Shahramian I, Jahanpanah A, Rashki N, Shiehzadeh F, Hamedi-Shahraki S, Ostadrahimi P, Tahani M, Moradi M. Rectal versus intravenous administration of acetaminophen; Clinical investigation of plasma level, analgesic, and antipyretic effects on 6-month to 6-year-old children in Zabol city, Iran. InAnnales Pharmaceutiques Françaises 2024 82(5): 898-904.
5. Locci C, Cuzzolin L, Capobianco G, Antonucci R. Paracetamol overdose in the newborn and infant: a life-threatening event. European journal of clinical pharmacology. 2021;77(6):809-15.
6. Gyamfi D, Amoafo EB, Kwapong AA, Fredua-Agyeman M, Amponsah SK. Drug Disposition in Neonates and Infants. Basics and Clinical Applications of Drug Disposition in Special Populations. 2025 Mar 7:179-201.
7. Allegaert K. A critical review on the relevance of paracetamol for procedural pain management in neonates. Frontiers in Pediatrics. 2020; 8:89.
8. Capici F, Ingelmo PM, Davidson A, Sacchi CA, Milan B, Sperti LR, Lorini L, Fumagalli R. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. British journal of anaesthesia. 2008 Feb 1;100(2):251-5.
9. Osorio D, Maldonado D, Rijs K, van der Marel C, Klimek M, Calvache JA. Efficacy of different routes of acetaminophen administration for postoperative pain in children: a systematic review and network meta-analysis. Can J Anesth. 2024; 71:1103-1116.
10.Ranger M, Chau CM, Garg A, et al. Neonatal pain and developmental outcomes in children born very preterm. Pediatrics. 2013;131(3): e773-e782.
11. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008; 48:303-332.
12.De Boer AG, Moolenaar F, de Leede LG, Breimer DD. Rectal drug administration: clinical pharmacokinetic considerations. Clin Pharmacokinet. 1982;7(4):285-311.
13. Khalili GR, Shafa A, Yousefi R. Comparison of the effects of preemptive intravenous and rectal acetaminophen on pain management after inguinal herniorrhaphy in children: a placebo-controlled study. Middle East J Anaesthesiol. 2016; 23:543-548.
14.Rubab K, Ahmad N, Khalid R, Butt UI. Acceptance of rectal suppositories for pain relief among preoperative patients at Services Hospital Lahore. Pak J Med Health Sci. 2019;13(2):200-203.
15.Capici F, Ingelmo PM, Davidson A, et al. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophen after adenotonsillectomy in children. Br J Anaesth. 2008;100(2):251-255.
16.Ceelie I, de Wildt SN, de Jong NG, et al. Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery. JAMA. 2013;309(2):149-154.
17.Khan MN, Hashmi AS, Malik AS, et al. Current practices in pediatric anesthesia: a survey from teaching hospitals in Punjab Province, Pakistan. Anaesth Singapore. 2019;13(3):156-163.
18.Anderson BJ, Holford NH, Woollard GA, Henneberg SW. Perioperative

pharmacodynamics of acetaminophen analgesia in children. Anesthesiology. 1997;86(3):555-565.
19.Ceelie I, Smeets KG, de Wildt SN, et al. Intravenous paracetamol in infants: pharmacokinetics, analgesic efficacy, and safety data from clinical studies. Drug Saf. 2016;39(9):855-874.
20.Hummel P, Puchalski M, Creech SD, Weiss MG. Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged sedation. J Perinatol. 2008;28(1):55-60.