Effect of Intravenous Paracetamol on Postoperative Recovery in Children Undergoing Hypospadias Repair under General Anaesthesia with Caudal Block: A Randomised Controlled Trial

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ABSTRACT

Objective: To explore the impact of perioperative intravenous (IV) paracetamol, administered with caudal ropivacaine on the quality of postoperative recovery in children undergoing hypospadias repair.

Study Design: Double-blinded randomised controlled trial.

Place and Duration of the Study: The operating room, post-anaesthesia care unit (PACU), and paediatric surgical ward at the Aga Khan University Hospital, from 31st January 2019 to 1st May 2022.

Methodology: Children aged 3-10 years undergoing hypospadias repair were randomly divided into two groups. Group P was administered IV paracetamol 15 mg/kg an hour before the completion of the repair procedure. Group C received a placebo instead of paracetamol. Modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) was measured at 15 and 30 minutes, and at 1, 2, 4, and 6 hours postoperatively. The sedation score was documented for four hours postoperatively.

Results: Out of total 59 children included in the analysis, 55% (n = 16) in the Group P and 45% (n = 13) in the Group C needed additional analgesia within the first six hours post-procedure. No significant variations were observed between the groups' CHEOPS scores and sedation levels.

Conclusion: The addition of perioperative intravenous paracetamol 15 mg/kg in combination with 0.25% ropivacaine through the caudal route, along with general anaesthesia, did not significantly affect the quality of postoperative recovery in children measured by pain score and sedation.

Key Words: *Intravenous paracetamol, Caudal* analgesia*, Ropivacaine, Paediatric patients*.

How to cite this article: Yousuf MS, Saleem A, Monem A, Nazir Z, Khan FA. Effect of Intravenous Paracetamol on Postoperative Recovery in Children Undergoing Hypospadias Repair under General Anaesthesia with Caudal Block: A Randomised Controlled Trial. *J Coll Physicians Surg Pak* 2025; **35(01)**:11-16.

INTRODUCTION

Postoperative pain control in the paediatric population is a challenge because of difficulty in communication, and if not controlled, can lead to agitation and physical and emotional effects.[1,2] Caudal analgesia has been frequently used in combination with general anaesthesia for perioperative pain control in infra-umbilical surgeries. It provides analgesia for four to eight of hours duration.[3,4] The role of Paracetamol as an adjuvant in caudal blocks is still uncertain. Previously, it was used with bupivacaine in caudal analgesia *via* the rectal route, yielding inconsistent outcomes.[5,6]

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Received: March 26, 2024; Revised: September 26, 2024; Accepted: December 10, 2024
DOI: https://doi.org/10.29271/jcpsp.2025.01.11

The pharmacokinetics of intravenous (IV) paracetamol in children and its efficacy in pain relief has been investigated by Anderson *et al*.[7] A mean serum concentration of 10 mg/L was achieved in children of 2-15 years of age who were administered a standard dose of 15 mg/kg over 15 minutes. The rationale of this study was that the addition of the mild-to-moderate analgesic effect of paracetamol can reduce the pain and discomfort in those areas not covered by the caudal block e.g., discomfort associated with intra-operative positioning. The quality of recovery was assessed through monitoring analgesia needs and sedation after surgery. The hypothesis was that the IV paracetamol group would require less rescue analgesia postoperatively because of the additive effect of intravenous paracetamol. The objective of the study was to investigate whether the addition of IV paracetamol with ropivacaine administered *via* the caudal route led to better postoperative pain and sedation management compared to the control group without IV paracetamol, in patients undergoing hypospadias repair.

METHODOLOGY

This prospective double-blind randomised controlled trial was conducted in the operating room, post-anaesthesia care unit (PACU), and paediatric surgical ward at the Aga Khan University Hospital. The study went through the Hospital Ethical Review Committee (ERC) (5445-Ane-ERC-18) and was registered with ClincalTrials.gov (NCT03781505). Patients were enrolled from the surgical out-patient clinic and written informed consent was given by the parents. Assent was obtained from older children (aged more than 7 years). The duration of the study was from January 2019 to 1st May 2022). Sixty-four children, aged 3-10 years, with ASA (American Society of Anaesthesiologists) physical Class I and II and scheduled for hypospadias correction surgery were recruited by a faculty unaware with the assessment of outcome. The criteria that were used to exclude patients were: A history of coagulopathy; consumption of any medication for pain during the week preceding surgery; pre-existing neurological, spinal, hepatic, or renal illness; malnourishment; severe hypovolaemia; uncontrollable seizures; parental-refusal, local infection of the skin at the area of the puncture., a previous failed caudal block; and history of allergy to local anaesthetics. Five patients were excluded from the study: Two due to parental-refusal (n = 1) and redo surgery (n = 1), and three due to being overweight (n = 2) and case cancellation (n = 1). The patients were assigned to either the placebo (Group-C), or intravenous paracetamol group (Group-P), by permuted block randomisation, performed by the Clinical Trial Unit (CTU) of the Aga Khan University. The randomisation process followed the CONSORT guidelines.

All patients were administered general anaesthesia in a standardised manner. Induction was through an inhalational route with 8% sevoflurane added to a 50% oxygen-nitrous oxide mixture. Further anaesthetic management included insertion of appropriate age laryngeal mask airway (LMA) and maintenance with sevoflurane (MAC 1-2%). The 40% oxygen-nitrous mixture was used to maintain anaesthesia while allowing for spontaneous breathing. The standard American Society of Anesthesiology monitoring was used.

Caudal block was performed in the lateral position with 1 ml/kg of 0.25% ropivacaine and time was noted. The time of block completion and surgical incision was recorded. The effectiveness of caudal analgesia was evaluated by monitoring the heart rate (HR) and blood pressure (BP) in response to incision. Sevoflurane concentration was modified in cases of tachycardia (more than 20% from baseline) and hypertension (greater than 20% from baseline). Rescue analgesia was provided with morphine 0.1mg/kg if tachycardia persisted.

Clinical Trials Unit of the hospital supplied the medicines and transported the study medications. An intravenous dosage of 15 mg/kg of paracetamol was given to Group P over a period of 15 to 20 minutes, approximately 60 minutes prior to the conclusion of the procedure. Group C was given a comparable volume of placebo (0.9% normal saline). The anaesthesiologists administering these medicines and monitoring variables were blinded. Time of administering intravenous paracetamol or placebo was noted.

Arrival time in the PACU was recorded. Mean arterial pressure (MAP), HR, oxygen saturation (SPO_2), respiratory rate (RR), and the quality and period of analgesia were measured by a trained research assistant who was blind to group allocation at 15 and 30 minutes, and at 1, 2, 4, and 6 hours after transfer to the PACU. Sedation was graded using a five-point scale (0: Awake; 1: Minor sedation; 2: Asleep but able to wake up; 3: Regularly tired, arousable, falls off to sleep during conversation; 4: Profound sleep, impossible to get up) for four hours postoperatively. The motor block was evaluated for four hours using the Modified Bromage scale (0 = no block, 1 = able to move legs, 2 = unable to move legs).[6] Modified Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) was used for measuring the requirement and quality of postoperative analgesia. All measurements were taken by the same research assistant.

The time between caudal block and the first rescue analgesic dosage was noted. Rescue analgesia for a CHEOPS score of more than 4 was provided with 0.025 mg/kg morphine and administration time of additional doses was noted. Complications such as persistence of motor block and hypotension were monitored and recorded in the postoperative period. The data noted were: Need to increase sevoflurane concentration after incision, interval between caudal block, time between caudal block and end of surgery, requirement for rescue analgesics in the PACU and operating room, discharge time from recovery, and the time of taking oral fluids postoperatively.

The sample size estimation was based on "the time of first analgesic requirement" of patients as found in a previous study on similar outcomes.[6] Considering that a clinically important difference in first analgesic requirement time would be a 10% absolute increment in the combined intravenous paracetamol and caudal ropivacaine group compared with caudal analgesia alone group, 29 patients in each group were needed for an experimental design incorporating two equal-sized groups, using an $\alpha = 0.05$ and $\beta = 0.2$. To minimise any effect of data loss, initially recruited 32 patients were in each group assuming a 10% dropout rate.

Statistical analyses were carried out using RStudio 4.1.2. mean (SD), and median (interquartile range) values were calculated for continuous variables such as age, BMI, heart rate, surgical time, anaesthesia time, and systolic and diastolic blood pressure. The Shapiro-Wilk's test was used to validate the continuous variables' normality assumption. Only the heart rate variable was discovered to be a normal variable, whereas the others were not. Independent student's t-test was used for the normal variable and the Mann-Whiney U test for the non-normal variable to explore if there was any statistically significant difference between the means of the C and P groups. CHEOPS pain, modified Bromage, and sedation scores were categorical variables that were analysed using the Chi-square or Fisher's exact and Z-score proportional tests, with frequency and percentages reported. Kaplan-Meier survival analysis with log-rank (Mantel-Cox) was also performed to compare the time to first analgesic administration between groups. A $p < 0.05$ was used to determine statistical significance.

RESULTS

A total of 64 children were initially recruited, out of which 59 children were eligible for inclusion (29 in the C Group and 30 in P Group). Five patients were excluded due to the cancellation of surgery or parental refusal. There were no dropouts after drug allocation. The patient's demographic characteristics and baseline parameters are summarised in Table I. There were no differences observed between groups in terms of BP and HR. The median time interval and interquartile range from skin incision to caudal block, caudal block to administration of IV paracetamol, and between the caudal block and end of surgery were also given in Table I.

Intraoperatively five children in Group P and four in Group C needed rescue analgesia. This was not significantly different. The children did not receive any other sedative agent intraoperatively.

Postoperatively, 11 and 9 patients in the P Group and C Group, respectively required rescue analgesia during the first six hours. Median duration of analgesia was 148 minutes (Q1, Q3, 115-157) in the C Group and 150 minutes in the P Group (Q1, Q3, 126-166, p = 0.46). This information is also presented in the Kaplan-Meier Curve in Figure 1.

The CHEOPS pain scores of less than four observed in PACU and up to six hours postoperatively are shown in Table II.

No significant difference was observed between groups. The modified Bromage score and sedation scores were found to be comparable up to four hours postoperatively. Sedation scores are given in Table III. No difference was observed in Sedation score within groups C and P.

No other side effects were observed. No difference was observed among groups as regards the time of taking oral fluids (p = 0.18).

Table I: Patient demographic characteristics, baseline parameters, and time intervals between Group C and Group P.

Variables	Group C (n = 29)	Group P (n = 30)	p-value
[a]Age (years), median [IQR]	4.1 [3.11 - 6]	5.0 [3.13 - 6]	0.95
[a]BMI, median [IQR]	14.8 [14.0 - 16.5]	14.1 [12.1 - 16.3]	0.26
[b]Heart rate (beats/min), mean (SD)	103 (16.1)	104 (13.3)	0.91
[a]Surgical time (minutes), median [IQR]	65 [44.3 - 93]	65 [42 - 79]	0.63
[a]Anaesthesia time (minutes), median [IQR]	120 [98 - 150]	109 [76.3 - 128]	0.15
[a]Blood Pressure (systolic), median [IQR]	92 [85 - 100]	99 [88.5 - 107]	0.37
[a]Blood Pressure (diastolic), median [IQR]	51 [43 - 60]	60 [45.3 - 63.3]	0.31
Skin incision and caudal block (minutes)	18 [12 - 20]	15 [11 - 18]	0.16
Caudal block and IV paracetamol/placebo (minutes)	40 [20 - 63]	42 [25 - 63.8]	0.88
Caudal block and end of surgery (minutes)	85.5 [66 - 111]	79 [50 - 93]	0.27
End of surgery to oral fluid intake (minutes)	265 [201 - 405]	222 [201 - 320]	0.18

[a]Mann-Whiney U test; [b]Independent t-test. Values are presented as median [IQR] or mean (SD). SD, Standard deviation; IQR, Interquartile range; BMI, Body mass index.

Table II: Comparison of CHEOPS pain score less than four within C and P groups n/total N(%).

Time	Group C (N = 29)	Group P (N = 30)	RR (95% CI)	p-value
[c]15 minutes	25 (86)	23 (77)	1.12 (0.89 to 1.42)	0.35
[c]30 minutes	21 (72)	24 (80)	0.90 (0.69 to 1.19)	0.49
[c]1 hour	25 (86)	26 (87)	0.96 (0.81 to 1.15)	0.95
[c]2 hours	28 (97)	30 (100)	0.97 (0.95 to 0.98)	0.31
[c]4 hours	29 (100)	29 (97)	-	0.32
[c]6 hours	29 (100)	29 (97)	-	0.32

[c]Z – score proportion test. Data presented as N (%).

Table III: Comparison of sedation score within C and P groups n/total N (%).

Score	Group C (n = 29)	Group P (n = 30)	RR (95% CI)	p-value
[d]Baseline				0.99
0-2	23/29 (79%)	23/30 (77%)	1.03 (0.80 to 1.34)	
3-4	6/29 (21%)	7/30 (23%)		
[d]30 minutes				0.99
0-2	25/29 (86%)	26/30 (87%)	0.99 (0.82 to 1.20)	
3-4	4/29 (14%)	4/30 (13%)		
[d]1 hour				0.89
0-2	29/29 (100%)	30/30 (100%)		
3-4	0/29 (0%)	0/30 (0%)	-	
[d]2 hours				0.896
0-2	29/29 (100%)	30/30 (100%)	-	
3-4	0/29 (0%)	0/30 (0%)		
[d]4 hours				0.896
0-2	29/29 (100%)	30/30 (100%)	-	
3-4	0/29 (0%)	0/30 (0%)		

[d]Chi-square or Fisher's exact test. RR, Relative risk; CI, Confidence interval.

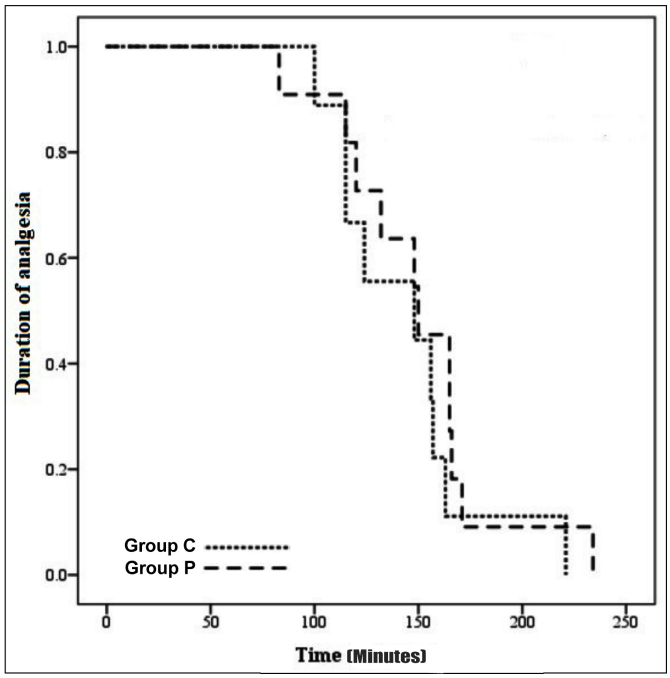

Figure 1: Kaplan-Meier curve comparing the duration of analgesia in C and P groups (Log-rank test, p-value = 0.38).

DISCUSSION

There is a paucity of published data on the use of the combination of paracetamol and caudal block and its effect on postoperative analgesia and other physiological parameters. This study has demonstrated that the quality of immediate postoperative recovery as measured by the pain scores, analgesic requirement, and sedation was unaffected by using a combination of IV paracetamol with 0.25% caudal ropivacaine. This was in comparison with the control group, receiving caudal ropivacaine alone, in patients undergoing hypospadias repair under general anaesthesia. The CHEOPS pain scores of less than four were observed in the majority of the patients in both groups during recovery from anaesthesia and up to six hours postoperatively.

In children, hypospadias surgery is a common procedure. Application of different anaesthetic techniques have been reported in the literature but one of the most well-known procedures in paediatric anaesthesia is caudal epidural blocking using a local anaesthetic solution, especially in low-resource environments.[8,9] Ropivacaine was chosen for the caudal analgesia because it offers superior sensory and motor effects along with analgesic efficacy comparable to bupivacaine.[10,11]Paracetamol has also received widespread acceptability as a simple analgesic for perioperative usage in children. It has a favourable therapeutic profile, a good safety record in recommended doses, and no significant medicine interactions. It is considered suitable for use in children at any age.[12-14] Intravenous paracetamol was administered over 15-20 minutes, approximately 60 minutes before the end of surgery in the intervention group to ensure that its analgesic effect overlapped with the effect of caudal block during the immediate recovery period.

The literature shows only a few studies focusing on the combined use of paracetamol and caudal analgesia. Mercan *et al*. studied rectal paracetamol administered in a dose of 20-25 mg/kg in the third or the fourth postoperative hour in patients undergoing inguinal hernia repair.[5] All children had caudal anaesthesia intraoperatively with 0.25% bupivacaine 1 ml/kg. They found that paracetamol given in the fourth hour enhanced the quality of postoperative analgesia. They measured the quality of pain relief by measuring the need for postoperative analgesia after caudal block. Ozyuvaci *et al*. found no difference in duration and on intensity of postoperative analgesia with the addition of preoperative or postoperative rectal paracetamol administered in a dose of 20-25 mg/kg in combination with caudal epidural bupivacaine 0.25% 0.5 ml/kg in 60 children undergoing hypospadias repairs.[6] While the cohort and results in this study were similar to the later studies, a key difference was that the previous studies investigated the role of paracetamol in extending the effects of caudal analgesia. In contrast, this study aimed to evaluate any additive effect of paracetamol on the analgesic impact of the caudal block, particularly in managing discomfort from areas not covered by the block during the immediate postoperative period. One example is the discomfort seen due to positioning.

Another major difference between these two studies and the present study was the route whereby paracetamol was administered. Although rectal route for paracetamol administration has been used for children, it does not consistently reduce a rapid onset of pain relief compared to its intravenous route due to delayed absorption and unpredictable paracetamol plasma concentrations.[15,16] The recommended dose of paracetamol through the rectal route by Hahn *et al*. is 35 mg/kg loading dose followed by 25 mg/kg rectal paracetamol every six hours.[17]

In both the studies conducted by Mercan and Ozyuvaci, the plasma levels of paracetamol may not have reached the therapeutic levels, which were not measured, potentially contributing to inconsistent results.[5,6] In contrast, the present study utilised the IV route, ensuring more consistent therapeutic levels. Additionally, a difference was observed in the dose of caudal anaesthesia, as Ozyuvaci *et al.* used a smaller dose of 0.5 ml/kg,[6] whereas this study employed ropivacaine as the local anaesthetic for caudal analgesia instead of bupivacaine.

The major strength of this study was that only a single type of surgery was included, i.e., hypospadias repair, and the more commonly used and reliable IV route for paracetamol. A single type of surgical procedure was selected as it has been shown that analgesic requirements in infra-umbilical surgery may vary with different procedures. Higher levels of pain and

greater analgesic requirements following orchidopexy in comparison with a herniorrhaphy group were reported by Warth *et al*.[18] This may be an area for further research.

One of the limitations of this study was the inclusion of cases requiring intraoperative rescue analgesia. The number of such cases was small and similar in the two groups and the group difference was not significant. Additionally, emergence agitation during the recovery period was not separately measured. Postoperative pain, which appears to be an aggravating factor, may have behavioural manifestations that confound the diagnosis of emergence agitation.[19,20]

Further studies are needed to improve the knowledge and benefits of the addition of intravenous paracetamol used in conjunction with caudal ropivacaine in specific paediatric procedures.

CONCLUSION

The use of perioperative IV paracetamol administered approximately 60 minutes before the end of the surgery, in children undergoing hypospadias repair under GA and 0.25% caudal ropivacaine did not provide any significant additional benefit to the quality of postoperative recovery as measured by the need for analgesia and sedation in the immediate postoperative period in comparison to caudal ropivacaine alone. This can be further investigated by varying the timing of administration of IV paracetamol.

ACKNOWLEDGEMENTS:
This study was presented at the National Anaesthesia Research Symposium: Enhancing the Quality of Anaesthesia Research in the Developing World, held at the Aga Khan University, Karachi, from September 8-10 2023. The abstract from this conference was subsequently published in. *Anesth Analg* 2024; 138(5S1) 1-51, doi: 10.1213/01.ane.0000998312.89349.68.

FUNDING:
This study was funded by a grant from the Department of Anaesthesiology, The Aga Khan University (77,960 PKR = 553 USD).

ETHICAL APPROVAL:
The study was conducted after receiving approval from the Ethical Committee of The Aga Khan University and Hospital, Karachi (Ethical Approval No: 5445-Ane-ERC-18).

PATIENTS' CONSENT:
Informed consent was taken from the parents of the patients and assent was obtained from children older than 7 years.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MSY: Design, literature review, supervision, and writing.
AS: Drafting, and data collection.
AM: Protocol review, data collection, data interpretation, and manuscript review.
ZN: Protocol review, data collection, and manuscript review.
FAK: Design, concept, supervision, data analysis, writing, and critical review.
All authors approved the final version of the manuscript to be published.

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