**Title of study: Effect of Intravenous Paracetamol in combination with caudal ropivacaine on quality of postoperative recovery in paediatric patients undergoing hypospadias repair.**

**Institute: Department of Anaesthesiology, Aga Khan University Hospital.**

**Clinical Trial Registration: NCT03781505**

**Date: 28th June 2018**

## INTRODUCTION

Postoperative pain control in paediatric population is a challenge because of difficulty in communication and, if not controlled can lead to agitation and lead to physical and emotional effects.[1] Caudal analgesia has been frequently used in combination with general anaesthesia for both intraoperative and postoperative pain control in infraumbilical surgeries. It provides analgesia of 4 to 8 hours duration.[2] Several adjuvants have been used with local anesthetics to improve quality and prolong effects. These include; opioids,[3] clonidine,[4] ketamine,[5] epinephrine [2] and neostigmine.[6]

Paracetamol is widely accepted and most commonly used as an adjuvant for postoperative analgesia. It also improves the quality of recovery by attenuating the pain associated with the surgical position and is not associated with complications seen by other adjuvants like narcotics. Adverse effects associated with the paracetamol are rare <1/10000, which includes malaise, increased level of hepatic transminases and hypersensitivity reaction. It has been studied in combination with caudal analgesia with bupivacaine through the rectal route [7,8] with variable results.

Caudal anaesthesia is effective in alleviating pain below the umbilicus but may not counteract pain due to positioning. Also if the caudal block is administered at the beginning of surgery, the effect will start wearing off 2 to 3 hours post surgery. Administration of paracetamol towards end of surgery may help with both these issues. In this study we aim to investigate the effect of adding intravenous paracetamol in combination with caudal analgesia with ropivacaine, hoping that it may improve quality of postoperative analgesia and recovery.

**OBJECTIVE**

To investigate whether the addition of intravenous paracetamol with caudal ropivacaine leads to better quality of postoperative recovery in patients undergoing hypospadius repair than caudal ropivacaine alone. The quality of recovery will be judged by postoperative analgesia requirement and lesser agitation in the postoperative period.

**Operational Definitions:**

**Postoperative analgesia requirement:**

The time from the performance of caudal block to the first analgesic dose administered postoperatively. Quality of analgesia will be monitored by CHEOPS scale.

**Postoperative Agitation:**

A state of consciousness in which the child is inconsolable, irritable, uncooperative, typically thrashing or crying.

**Hypothesis:**

$H_o$: There is no difference in treatment of intravenous paracetamol to caudal ropivacaine and caudal ropivacaine alone in term of mean time of first analgesic requirement.

$H_A$: There is difference in treatment of intravenous paracetamol to caudal ropivacaine and caudal ropivacaine alone in term of mean time of first analgesic requirement.

**MATERIAL AND METHODS**

**STUDY DESIGN:**

A prospective, double-blind, randomized controlled study.

**SETTING:**

This study will be conducted in Postanaesthesia care unit (PACU) and paediatric surgical ward of Aga Khan University Hospital, Karachi.

**DURATION OF STUDY:**

The duration of study is 6 to 12 months after approval of ERC.

**SAMPLE SIZE:**

The sample size estimation is based on"the time of first analgesic requirement" of patients. A previous study on similar outcome by OZYUVACI reported a first analgesic requirement time in caudal alone was 3020±39.28 minutes.[8] For the purpose of sample size calculation, we considered that a clinically important difference in first analgesic requirement time would be a 10% absolute increment in the intravenous paracetamol in combination with caudal ropivacaine compared with the caudal alone. We calculated that 29 patients per group would be required for an experimental design incorporating two equal-sized groups, using an alpha =0.05 and beta =0.2. To minimize any effect of data loss, we will recruiting 32 patients in each group into our study assuming a 10% dropout rate.

**SAMPLING TECHNIQUE:**

Non-Probability Consecutive sampling.

**SAMPLE SELECTION**

**Inclusion criteria**

1. Age 3–10 years
2. ASA I and II
3. Undergoing hypospadias repair surgery

**Exclusion criteria**

1. Coagulopathy
2. Aspirin or any other analgesic ingestion in the preceding week
3. Preexisting neurological or spinal disease
4. Hepatic, renal disease and malnutrition

5. Severe hypovolemia
6. Uncontrolled convulsions
7. Refusal of the parents
8. Local Skin infection at the puncture site
9. Allergy to local anesthetics
10. Patient previously involved in other studies

**METHOD**

After obtaining approval from Ethical Review Committee (ERC) of Aga Khan University Hospital Karachi (AKUH) and inform about the study to primary surgeon (who ever doing the surgical procedure on this time), informed written consent will be obtained from the parents of patients fulfilling the inclusion criteria schedule for surgical procedures on the day before surgery. Assent will be obtained from older children.

The patients will be assigned to one of the two groups by randomization through sealed opaque envelope technique. The envelopes will be prepared using a computer generated randomization table. Randomization envelopes will be used in consecutive order. The randomisation process will follow the CONSORT guidelines [A].

Patients will be allocated to either placebo group, who will not receive intravenous paracetamol, or group who will receive intravenous paracetamol.

All patient will be given general anesthesia as per standard of care. Anaesthesia will be standardized as follow. Anaesthesia will be induced by the inhalational route with application of facemask with 8% sevoflurane in 50% oxygen-nitrous oxide mixture. Airway will be managed by LMA of appropriate size as recommended by manufacturer and anesthesia will be subsequently maintained with (MAC 1–2%) sevoflurane in 40% oxygen-nitrous mixture with spontaneous ventilation via LMA. Heart rate, noninvasive blood pressure, core body temperature (oral/nasal probe), end-tidal carbondioxide (ETCO2) and SpO2 will be monitored throughout.

After induction of anaesthesia, patients will be turned to lateral position and maximum safe dose of ropivacaine will be calculated (3mg/kg) and documented. After all aseptic measures, butterfly needle (size 23 guage) will be inserted into the sacral hiatus. A total volume of 1 ml/kg of 0.25%

ropivacaine solution will be injected in caudal space. The time of performing block will be noted. The success of caudal analgesia will be assessed by monitoring the parameters like heart rate and blood pressure in response to incision. In case of tachycardia (>20% from baseline) and hypertension (>20% from baseline), the concentration of sevoflurane will be adjusted. If tachycardia persists for more than 5 minutes despite increasing the sevoflorane concentration, rescue analgesia in the form of fentanyl 1mcg/kg will be administered.

Study drugs will be prepared and dispatch by CTU pharmacy. Eligible consecutive randomized patients belonging to study group will receive intravenous paracetamol approximately about an hour before the end of surgery with a dose of 15mg/kg over 15 to 20 minutes. While the patients belonging to other group will receive placebo. Time of intravenous paracetamol administration will be noted.

After emergence, the children will be taken to the postanesthesia care unit (PACU) where parents will be called to stay with their child. Time of arrival in the recovery room will be noted.The MAP, HR, SPO2, respiratory rate (RR), sedation, agitation, quality and duration of analgesia will be recorded at 15 and 30 min and will be followed by 1, 2, 4, and 6 h following recovery from anaesthesia.

The analgesic status of the patient will be evaluated by trained Research Assistant in the PACU and in the ward by using Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). This includes crying, facial expression, verbal response, touching the wound and torso and leg movement. It is given in the Appendix.

Sedation will be assessed using a five point scale (0: awake; 1: mild sedation; 2: sleeping, but able to wake; 3: in deep sleep, unable to wake). These observations will be recorded by the same investigator blinded to the medication administered. Same observer will perform the measurements for all patients. A pain score lower than 4 will be considered adequate analgesia. Rescue analgesia will be provided by 0.1 mg/kg i.v. morphine in divided doses (0.025 mg aliquots) and time of doses will be noted on the form.

Analgesia requirement in the postoperative period will be define as a CHEOPS score of 7 (Should be 4) or more. Time to the first analgesic requirement will be calculated as the time from the performance of caudal block to the first analgesic dose administered.

Complications like motor block, hypotension and urinary retention will be monitored and recorded in the postoperative period. Modified Bromage Scale will be used to assess motor block i.e 0= No block, 1= Able to move legs, 2= Unable to move legs.

**Adverse effects**

Adverse Events are defined as 'Any untoward medical occurrence in a trial patient to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure (18).'

Adverse effects associated with the paracetamol are rare <1/10000, which includes malaise, increased level of hepatic transminases and hypersensitivity reaction.

**Serious Adverse Events**

Serious Adverse Events are defined as an untoward event that: Results in death; Is life-threatening*; Requires hospitalization** or prolongation of existing hospitalization; Results in persistent or significant disability or incapacity; Or, is otherwise considered medically significant by the Investigator (18).

*The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Patients must be formally admitted – waiting in out-patients or A&E does not constitute an SAE (even though this can sometimes be overnight). Similarly, planned hospitalizations that clearly are not related to the condition under investigation or hospitalizations/prolongation of hospitalization due to social reasons should not be considered as SAEs (18).

The following data will be collected by an observer in postoperative period: age, weight, height, surgical time, anesthesia time, recovery time, discharge time, need to increase sevoflurane concentration after incision, the need for rescue analgesia in OR and PACU, time of voiding urine and time of taking oral fluids, while subjective complaint of heaviness in legs will be asked from children above 3 years only.

**Data and Record handling:**

The data would be handled by the primary investigator and hard copies of the data will be saved by a lock and key method and soft copies will be saved on a computer and the data will be password protected. Due to regulatory requirement this data will be saved for 15 years. The study and data would be published after it has been approved as a dissertation by the CPSP and identity of the subjects will be kept confidential.

The study will be monitored by the supervisors and samples will be randomly picked for protocol compliance, ethical standards, regulatory compliance and data quality at the clinical site, including review of records, consent forms and Performa are up to the mark.

**Data Analysis Procedure:**

Statistical analyses will be performed using SPSS 19.0 (SPSS Inc., Chicago, IL). Point estimation will be computed as mean ± SD or number of patients (%). A normality test will be performed using Kolmogorov–Smirov and Shapiro–Wilk tests. Continuous variables with a normal distribution will be analyzed using independent sample t test, and non-normal data will be analyzed by Mann Whiney U test. Categorical data will be analyzed by chi-square test or fisher exact test. A P value 0.05 was considered significant.

**REFERENCES**


1. Miller RD. *Anesthesia*. 7th ed. [United States]: Elsevier Science Health Science div; 2010.

2. Samuel M, Hampson-Evans D, Cunnington P. Prospective to a randomized double-blind controlled trial to assess efficacy of double caudal analgesia in hypospadias repair. J Ped Surg 2002; 37: 168–174.

3. Gauntlett I. A comparison between local anaesthetic dorsal nerve block and caudal bupivacaine with ketamine for paediatric circumcision. Paediatr Anaesth 2003; 13: 38–42.

4. Sharpe P, Klein JR, Thompson JP et al. Analgesia for circumcision in a paediatric population: comparison caudal bupivacaine plus two doses of clonidine. Paediatr Anaesth 2001; 11: 695–700.

5. Lee HM, Sanders GM. Caudal ropivacaine and ketamine for postoperative analgesia in children. Anaesthesia 2000; 55: 806– 810.
6. Turan A, Memis D, Basaran UM et al. Caudal ropivacaine and neostigmine in pediatric surgery. Anesthesiology 2003; 98: 719– 722.
7. Mercan A et al. When to add supplemental rectal paracetamol for postoperative analgesia with caudal bupivacaine in children? A prospective, double-blind, randomized study. Pediatric Anesthesia 2007; 17: 547–551.

8. Ozyuvaci E et al. Evaluation of adding preoperative or postoperative rectal paracetamol to caudal bupivacaine for postoperative analgesia in children. Pediatric Anesthesia 2004 ;14: 661–665.

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S. No: _____

# PROFORMA

Subject ID _____

Age (years) _____

Date of birth _____

Weight (kg) _____

Date of Surgery _____

Gender M F

## OPERATING ROOM

**Baseline ParametersChange in parameters (20%)**

- Heart Rate _____ _____
- Blood Pressure _____ _____
- Maximum safe dose of Ropivacaine (3mg/kg) _____
- Dose of Ropivacaine administered _____
- Time of performing Caudal Block _____
- **Anesthesia Time**: Induction _____ Ready for surgery _____
- **Surgical Time**: Skin Incision _____ Skin Dressing _____
- Increase in Sevoflorane concentration Y N

- Rescue Analgesia Y N

**If Yes;**

- Analgesia _____ Dose _____ Time of Administration _____

## RECOVERY ROOM

- Time of Arrival in RR:_____
- Rescue Analgesia (If CHEOPS >4) Y N

**If Yes;**

- Analgesic _____ Dose _____ Time of Administration _____
- Time of voiding urine: _____
- Complaint of leg heaviness (age > 3 years): Y N
- Time of taking oral fluids: _____
- Recovery Time: _____
- Discharge Time: _____

## MODIFIED BROMAGE SCALE

| Baseline | 30 min | 1 Hour | 2 Hour | 4Hour |
|---|---|---|---|---|
| 0= No motor Block | 0= No motor Block | 0= No motor Block | 0= No motor Block | 0= No motor Block |
| 1= Can flex knee, move foot, but cannot raise leg | 1= Can flex knee, move foot, but cannot raise leg | 1= Can flex knee, move foot, but cannot raise leg | 1= Can flex knee, move foot, but cannot raise leg | 1= Can flex knee, move foot, but cannot raise leg |
| 2 =Can move foot only | 2 =Can move foot only | 2 =Can move foot only | 2 =Can move foot only | 2 =Can move foot only |
| 3 =Cannot move foot | 3 =Cannot move foot | 3 =Cannot move foot | 3 =Cannot move foot | 3 =Cannot move foot |

| | | | | |
|---|---|---|---|---|
| or knee | or knee | or knee | or knee | or knee |

**Total Score:**

**Baseline: 30 min: 1st Hour: 2nd Hour: 4th Hour:**

## SEDATION SCORE

| Baseline | 30 min | 1 Hour | 2 Hour | 4Hour |
|---|---|---|---|---|
| 0= Awake | 0=Awake | 0= Awake | 0= Awake | 0= Awake |
| 1= Mild Sedation | 1= Mild Sedation | 1= Mild Sedation | 1= Mild Sedation | 1= Mild Sedation |
| 2 =Sleep but able to awake | 2 =Sleep but able to awake | 2 =Sleep but able to awake | 2 =Sleep but able to awake | 2 =Sleep but able to awake |
| 3 = Deep sleep, unable to awake | 3 = Deep sleep, unable to awake | 3 = Deep sleep, unable to awake | 3 = Deep sleep, unable to awake | 3 = Deep sleep, unable to awake |

**Total Score:**

**Baseline: 30 min: 1st Hour: 2nd Hour: 4th Hour:**

## CHEOPS PAIN SCALE

| Parameter | Finding | Point | 15 min | 30 min | 1 hr | 2 hrs | 4 hrs | 6 hrs |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **CRY** | no cry | 0 | | | | | | |
| | crying, moaning | 1 | | | | | | |
| | scream | 2 | | | | | | |
| **FAICAL** | smiling | 0 | | | | | | |
| | composed | 1 | | | | | | |
| | grimace | 2 | | | | | | |
| **CHILD VERBAL** | positive | 0 | | | | | | |
| | none or other complain | 1 | | | | | | |
| | Pain Complaint | 2 | | | | | | |
| **TORSO** | neutral | 0 | | | | | | |
| | Shifting, tense, upright | 1 | | | | | | |
| | restrained | 2 | | | | | | |
| **LEGS** | neutral | 0 | | | | | | |
| | kick, squirm, drawn-up | 1 | | | | | | |
| | restrained | 2 | | | | | | |
| | | | | | | | | |

**Total Score = _____** **Research Assistant Name and Signature:**

**Date:**