Comparison of Role of Different Doses of Rectal Paracetamol with Rectal Diclofenac as Pre-emptive Analgesics for Postoperative Pain Relief in Paediatric Surgeries.

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ABSTRACT

Background: Post operative pain is a major concern in children particularly in developing countries were opioids are not freely available. Use of opioids is associated with side effects increasing patient discomfort and delaying patient discharge from hospital. We conducted a study comparing the use of different doses of rectal paracetamol with rectal diclofenac when used as pre-emptive analgesics on postoperative pain and recovery in paediatric patients considering the relative risk of diclofenac to increase bleeding in surgeries like tonsillectomy, cleft lip and cleft palate. Methods: Study groups included 20 patients in each. Group P40 receiving 40 mg/kg rectal paracetamol, Group P20 receiving 20 mg/kg rectal paracetamol, Group D receiving rectal diclofenac 1 mg/kg. Pain scoring was done by TPPPS (Toddler Pre-schooler postoperative pain scale) time to first need of analgesia and total dose of analgesia was noted. The rates of recovery were evaluated by using “Modified Steward Coma Scale”at 5 and 10 minutes after extubation. Results: Time of first demand of analgesic was delayed in Group-P40 as compared to Group-D and Group-P20 and difference was statically significant. TPPPS of the three studied groups varied significantly at different time intervals in favour of Group-P40. Total duration of analgesia in Group-P40 was (646±9.94) min Group-D (501±10.63) min and in Group-P20 (294±23.17) min Total analgesic requirement was also low in Group P40 and the difference between groups was significant. Conclusion: Pre-emptive high dose rectal paracetamol appears to be more effective than rectal diclofenac sodium suppository for postoperative analgesia in children without additional risk of bleeding in surgeries like tonsillectomy and cleft lip and cleft palate repair. Hence, high dose rectal paracetamol can be used as an alternative to diclofenac sodium due to higher risks of bleeding with diclofenac sodium in surgeries with increased risk of bleeding.

Keywords: Pre-emptive Analgesics, rectal paracetamol, rectal diclofenac sodium, suppository, Toddler Pre-schooler postoperative pain scale.

INTRODUCTION

Surgery produces local tissue injury with consequent release of allogenic substances (prostaglandins, histamine, serotonin, bradykinin, substance P) and neurotrophins (e.g. nerve growth).\textsuperscript{[1]} Segmental reflex responses associated with surgery may be associated with increased skeletal muscle tone and spasm, with increases in oxygen consumption and lactic acid production.\textsuperscript{[1]} Stimulation of sympathetic neurons causes tachycardia, increased cardiac work and myocardial oxygen consumption.

Hence, the concept of pre-emptive analgesia has come in forefront whereby analgesic treatment is started prior to surgical intervention to prevent activation of these factors. Pre-emptive analgesia gives rise to a subsiding pain pattern, decreases analgesic requirements, thus their side effects. It also decreases surgical morbidity, promotes wellness and shortens hospital stay.\textsuperscript{[2-5]} Pre-emptive analgesia is directed either at central neurons by using NSAIDS, paracetamol and ketamine, or using local anaesthetics xylocaine/bupivacaine and opioids either alone or in combination.

Rectal diclofenac is widely used to treat acute postoperative pain in children.\textsuperscript{[6]} Paracetamol is an analgesic recommended for routine postoperative pain management.\textsuperscript{[7]} The analgesic effect of paracetamol is probably dependent on the rate and amount of active drug reaching the central nervous system (CNS).\textsuperscript{[8]} NSAIDs inhibit prostaglandin synthesis, thereby decreasing production of prostaglandins, which in turn reduces pain.

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synthesis in peripheral tissues, thus activation of pain. Paracetamol being free of side effects is usually well tolerated by children. Diclofenac sodium is an excellent analgesic but is associated with side effects like GI bleed, depression of platelet function, increased tendency of bleeding and decreases in renal and splanchnic blood flow.

In the present study, we compared the pre-emptive rectal paracetamol in different doses with rectal diclofenac sodium for postoperative pain relief in pediatric surgeries.

**Aims and objectives**

1. To emphasize the importance of pre-emptive analgesics in postoperative pain management and smooth recovery after surgery
2. To compare the effect of different doses of rectal paracetamol and rectal diclofenac sodium as preemptive analgesics in various paediatric surgeries

**MATERIALS AND METHODS**

The present prospective study was conducted in the Postgraduate Department of Anaesthesiology, Government Medical College, Srinagar.

**Inclusion Criteria**

- Children aged between 2-10 years undergoing various pediatric surgeries
- ASA grade I & II

**Exclusion Criteria**

- Children with known allergy to study drugs,
- hypovolemia
- hepatic and renal diseases
- hemorrhagic diathesis and
- bronchial asthma

After getting informed consent from parent and clearance from institutional ethical committee, the recruiting children were randomly divided into three groups by random sampling, twenty in each group. The Group P20 received paracetamol 20mg/kg body weight per rectum, Group P40 received paracetamol 40mg/kg body weight per rectum and Group D received diclofenac sodium 1 mg/kg body weight per rectum – half an hour before induction of anaesthesia. The administered dose was maintained close to the calculated dose. Patient’s data was collected in prescribed forms containing patient’s particulars, preoperative baseline (Pulse, blood pressure, temperature) intraoperative and postoperative parameters. After pre-oxygenation for 3 mins with 100% oxygen, induction of anaesthesia was done with thiopentone sodium 4-5 mg/kg IV and tracheal intubation was done after giving Inj. Suxamethonium 1.5 mg/kg IV. Intra operative analgesia was maintained by Fentanyl 1 μg/kg at the time of induction and DNS fluid was used intraoperatively using standard calculated rate and volume. Maintenance of anaesthesia was done with N₂O 70%, O₂ 30%, Isoflurane – 0.5%-1% and muscle relaxant atracuriumbesylate 0.5 mg/kg body weight boluses.

At completion of surgery, Residual effect of neuromuscular blocking drug was reversed by Inj. neostigmine 40 mcg/kg with atropine 20 mcg/kg and patient was extubated.

Children were assessed both preoperatively and at 15mins, 1 hour, 4 hours, and 8 hours in the postoperative ward by nurse who was blinded to the drug received by each patient. Study parameters included TPPPS® (Toddler Pre-schooler post operative pain scale) for measuring pain intensity at 15 min, 1, 4 hour and 8 hours afterward surgery. If TPPPS >3 then injection IV Tramadol 1 mg/kg body weight, was administered, Time of first demand of analgesia, heart rate, blood pressure, temperature, complications like nausea, vomiting, sedation, bleeding, recovery were observed. After first demand of analgesia, pain was managed with standard doses of paracetamol. Total dose of paracetamol received by each patient up to 24 hr in postoperative period after first demand of analgesia was noted.

**Table: Toddler-Preschooler Postoperative Pain Scale (TPPSS)⁹**

| Pain Expression          | Behaviors                              | Score |
|--------------------------|----------------------------------------|-------|
| Verbal                   | verbal pain complaint and/or cry       | 1     |
|                           | Scream                                | 1     |
|                           | groan moan grunt                       | 1     |
| Facial                   | open mouth with lips pulled back at corners | 1     |
|                           | squint closed eyes                     | 1     |
|                           | furrowed forehead brow bulging        | 1     |
| Bodily                   | restless motor behavior and/or rubbing-touching painful area | 1     |

Where:

- Verbal pain complaint: any word phrase or statement that refers to pain hurt or discomfort; it must be a statement and not a question.
- Cry: tears in eyes and/or running down face and/or making sobbing sounds; this should not include crying initiated by separation from parents unless the child is undergoing a potentially painful procedure.
- scream: acute loud high-pitched cry
- groan moan grunt: deep low-pitched sounds; may be drawn out (moan) or abrupt (grunt)
- open mouth with lips pulled back at corners: open mouth with lips pulled back at corners with a downward pull on the jaw
- Squint closed eyes: eyelids taut stiff closed or nearly closed with wrinkling of the skin at the lateral aspect of the eyes.
• furrowed forehead: creasing or furrows above the eyebrows
• brow bulging: bulging between the eyebrows
• restless motor behavior: unrestrained motor activity with the body and/or head never still; may appear random or lack goal directions
• Rubbing-touching painful area: touching rubbing massaging body part where the medical or surgical procedure was performed

Scoring: Each behaviour group was given a score of 1
• If any behavior as explained above is present during a 5 minute observation period score of 1 is given
• If any behavior as explained above is absent during a 5 minute observation period score of 0 is given
• Pain score is SUM of number of above behaviors present in a patient

Interpretation: minimum score: 0 maximum score: 7

The recovery status of the patients in this study was assessed. The rates of recovery were evaluated by using “Modified Steward Coma Scale”\textsuperscript{[10]} at 5 and 10 minutes after extubation.

**Recovery Scoring System Modified from Steward\textsuperscript{[10]}**

**Consciousness:**
- Awake 3
- Responds to verbal stimuli 2
- Responds to tactile stimuli 1
- Not responding 0

**Airway:**
- Cough on command or cry 2
- Maintains good airway 1
- Require airway assistance 0

**Motor:**
- Moves limbs purposefully 2
- Non-purposeful movements 1
- Not moving 0

### Statistical Analysis
All results were expressed as mean ± SD calculated for each of the variable at all observation time of all children in each group. The data was compiled and analyzed with the help of chi-square and one-way ANOVA test. Values were expressed as significant if p<0.05.

**Table 1: Demography of the studied groups.**

| Time Interval | Group P20 (Mean±SD) | Group P40 (Mean±SD) | Group D (Mean±SD) | P-value (ANOVA) |
|---------------|---------------------|---------------------|-------------------|----------------|
| Age (years)   | 6.5±1.357           | 6.9±1.137           | 6.7±1.461         | 0.705 (SNSD)   |
| Gender (M/F)  | (12/8)              | (11/9)              | (10/10)           | 0.817 (SNSD)   |
| Weight (kg)   | 20.3                | 20.4                | 20.3              | 0.223 (SNSD)   |

SNSD: Statistically non-significant difference Values are expressed as mean ± SD

**Table 2: Comparison of mean heart rate (beats/min) at different time period of the studied groups.**

| Time Interval | Gr-P20 | Gr-P40 | Gr-D | P-value (ANOVA) |
|---------------|--------|--------|------|----------------|
| Base Line     | 93.00  | 92.80  | 92.90| 0.855 (SNSD)   |
| Induction     | 112.20 | 109.90 | 113.70| <0.001 (SSD)  |
| 5 min         | 109.30 | 105.60 | 110.20| <0.001 (SSD)  |
| 15 min        | 103.50 | 106.20 | 108.70| <0.001 (SSD)  |
| Extubation    | 111.80 | 108.30 | 115.60| <0.001 (SSD)  |
| 15 min        | 107.60 | 105.50 | 109.20| <0.001 (SSD)  |
| 1 hr          | 99.70  | 99.40  | 100.20| 0.331 (SNSD)   |
| 4 hr          | 104.20 | 94.60  | 95.40 | <0.001 (SSD)   |
| 8 hr          | 102.5  | 97.1   | 100.8 | <0.001 (SSD)   |

SNSD: Statistically non-significant difference SSD: Statistically significant difference

Values are expressed as mean. Between group analyses was done by one way ANOVA, values are expressed as significant if p < 0.05.

**Table 3: Comparison of mean blood pressure (mm of Hg) at different time period in the studied groups.**

| Time Interval | Gr-P20 | Gr-P40 | Gr-D | P-value (ANOVA) |
|---------------|--------|--------|------|----------------|
| Base Line     | 76.3   | 75.7   | 76.2 | 0.660 (SNSD)   |
| Induction     | 85.1   | 84.2   | 84.6 | 0.482 (SNSD)   |
| 5 min         | 84.1   | 82.3   | 83.2 | 0.065 (SNSD)   |
| 15 min        | 88.7   | 79.2   | 81.5 | <0.001 (SSD)   |
| Extubation    | 86.2   | 82.4   | 85.9 | <0.001 (SSD)   |
| 15 min        | 82.7   | 78.6   | 82.4 | <0.001 (SSD)   |
| 1 hr          | 80.2   | 75.5   | 79.9 | <0.001 (SSD)   |
| 4 hr          | 82.7   | 75.2   | 75.7 | <0.001 (SSD)   |
| 8 hr          | 81.1   | 75.1   | 79.0 | <0.001 (SSD)   |

SNSD: Statistically non-significant difference SSD: Statistically significant difference

Values are expressed as mean and statistically significant if p value of < 0.05.
Table 4: Comparison of temperature (°C) at different time period of the studied groups.

| Time Interval | Gr-P20 | Gr-P40 | Gr-D | P-value (ANOVA) |
|---------------|--------|--------|------|-----------------|
| Base Line     | 98.12  | 98.38  | 98.56| 0.225 (SNSD)    |
| Induction     | 98.43  | 97.69  | 98.16| 0.027 (SSD)     |
| 5 min         | 98.36  | 97.43  | 97.87| 0.004 (SSD)     |
| 15 min        | 97.63  | 96.97  | 97.72| 0.005 (SSD)     |
| Extubation     | 97.54  | 97.02  | 97.86| <0.001 (SSD)    |
| 1 hr           | 97.18  | 96.87  | 97.7 | 0.003 (SSD)     |
| 4 hr           | 97.92  | 97.32  | 98.28| <0.001 (SSD)    |
| 8 hr           | 99.1   | 98.5   | 98.8 | 0.006 (SSD)     |

SNSD: Statistically non-significant difference  SSD: Statistically significant difference  
Values are expressed as mean and statistically significant if p < 0.05.

Table 5: TPPPS score of the studied groups.

| Time Interval       | Gr-P20 | Gr-P40 | Gr-D | P-value(ANOVA) |
|---------------------|--------|--------|------|----------------|
| 15 min after extubation | 0.74   | 0.13   | 0.92 | <0.001 (SSD)   |
| 1 hr                 | 0.26   | 0.08   | 0.09 | <0.001 (SSD)   |
| 4 hr                 | 1.92   | 0.04   | 0.03 | <0.001 (SSD)   |
| 8 hr                 | 1.71   | 0.05   | 1.93 | <0.001 (SSD)   |

SSD: Statistically significant difference  
Values are expressed as mean. P value of < 0.05 is considered statistically significant.

Table 6: Time of First Dose of Analgesia Required in postoperative period.

| Time Interval       | Gr-20 | Gr-P40 | Gr-D | P-value (ANOVA) |
|---------------------|-------|--------|------|-----------------|
| Time of first analgesic demand in minutes | 294.5 | 646.3  | 501.0 | <0.001 (SSD)   |

SSD: Statistically significant difference  
A p value of < 0.05 is considered as statistically significant.

Table 7: Mean Of Total dose of paracetamol (mg) consumed in within 24 hours in groups.

| Time Interval       | Gr-P20 | Gr-P40 | Gr-D | P-value (ANOVA) |
|---------------------|--------|--------|------|-----------------|
| Total Paracetamol consumed in mg | 316.2  | 175.9  | 213.6 | <0.001 (SSD)   |

SSD: Statistically significant difference  
A p value of < 0.05 is considered as statistically significant

Mean value of total paracetamol (mg) consumed in each group is depicted as: Group P 20– 316mg, Group P40 – 175mg, and Group D – 213mg. (mean value of total doses received by all patients in each group in post operative period after first demand of analgesia).

Figure 1: Distribution of patients on the basis of various surgeries performed.

There were no statistically significantly differences between the three groups in respect of age/gender/ASA status/weight/ [Table 1]. Majority of patients (41%) belonged to inguinal hernia repair followed by tonsillectomy (24%) and hypospadias (17%) [Figure 1].

Baseline heart rate [Table 2] were not significantly different in all the three groups but varied significantly at induction (P <0.001), at 5 min. after inductions (P<0.001), at 15 min. after induction (P<0.001), at extubation (P<0.001), 15 min. after extubation (P<0.001), 4 hours after extubation (P<0.001), and at 8 hours after extubation (P<0.001)

Base line mean blood pressure were not significantly different (P=0.0660) in all the three groups. But varied significantly 15 min. after induction (P<0.001), at extubation (P<0.001), 1 hour after

RESULTS

There were no statistically significantly differences between the three groups in respect of age/gender/ASA status/weight/ [Table 1]. Majority of patients (41%) belonged to inguinal hernia repair followed by tonsillectomy (24%) and hypospadias (17%) [Figure 1].

Baseline heart rate [Table 2] were not significantly different in all the three groups but varied significantly at induction (P <0.001), at 5 min. after inductions (P<0.001), at 15 min. after induction (P<0.001), at extubation (P<0.001), 15 min. after extubation (P<0.001), 4 hours after extubation (P<0.001), and at 8 hours after extubation (P<0.001)

Base line mean blood pressure were not significantly different (P=0.0660) in all the three groups. But varied significantly 15 min. after induction (P<0.001), at extubation (P<0.001), 1 hour after
extubation (P<0.001), 4 hours after extubation (P<0.001), 8 hours after extubation (P<0.001) [Table 3].

Change of temperature (\(c^0\)) base line temperature changes were not significant (P=0.225) but varied significantly at 5 min. after induction (P=0.027), 15 min. after induction (P=0.004), at extubation (P=0.005), 15 min. after extubation (P=0.001), 1 hour after extubation (P=0.003) 4 hours after extubation (P<0.001), 8 hours after extubation (P=0.006) [Table 4].

Pain intensity of the three studied groups was assessed by TPPPS. TPPPS of the three studied groups varied significantly at 15 min. after extubation (P<0.001), at 1 hour after extubation (P<0.001), at 2 hours after extubation (P<0.001) and at 8 hours after extubation (P<0.001) there were significant interaction between the groups [Table 5].

Time of first demand of analgesic in all three groups were significant (P=0.001) [Table 6]. Mean of total paracetamol consumed in all three groups were also significant (P=0.00) [Table 7]. The recovery status was evaluated by “modified Steward Coma Scale” at five minutes and ten minutes after extubation [Table 8].

Group 1: (Grp20) out of 20 patients 3 obtained score of seven at 5 min. and remaining 17 after 10 min.

Group 2: (Grp40) out of 20 patients 15 obtained score of 7 at 5 min. and remaining 5 after 10 min. of extubation.

Group 3: (GrpD) out of 20 patients 14 obtained score of 7 after 5 min. and remaining 6 after 10 min. of extubation.

**DISCUSSION**

Pre-emptive analgesia is an antinociceptive treatment that prevent establishment of altered central processing of afferent input from sites of injury.[14] The most important condition for establishment of effective pre-emptive analgesia are the establishment of an effective level of antinociception before injury and the continuation of this effective analgesia level into the post injury period to prevent central sensitization during the inflammatory phase. The concept of pre-emptive analgesia was formulated by Crile at the beginning of previous century on the basis of clinical observation.[12]

The recommended daily dose for paracetamol in children in 90 mg/kg given 4 to 6 hourly.[13,14] Although the optimum paediatric dose for anti-pyretic is 20 mg/kg,[14,16] this dose should only be used as a loading dose if repeated administration is envisaged dose in the range of 10-15 mg/kg[15] is used, although there is increasing evidence that a single rectal loading dose of 35-45 mg/kg results in more desirable plasma paracetamol concentrations.[15] Concern about hepatotoxicity has result in cautious preoperative dosing regimens, but both pharmacokinetic and pharmacodynamic data have shown these to be inadequate.[11]

In our present study, we have used 20 mg/kg and 40 mg/kg body weight of paracetamol per rectum which were within the recommended dose suggested by Brian Anderson, Frank and Coulthard, Temple and Wilcon et al.[13,15,17] In the present study, we have also used Diclofenac sodium, a dose of 1 mg/kg body weight per rectum. Although diclofenac sodium is an excellent analgesic but it has the side effects like gastrointestinal bleeding, depression of platelet function, increase in bleeding time, hepatotoxicity, decreased renal and splanchnic perfusion.[18,19] Diclofenac sodium therefore have greater risks in tonsilslectomy where bleeding from tonsil bed is likely to be large.[20] In our study, we also used paracetamol in two doses Gr. P20-20 mg/kg body weight per rectum Gr. P40-40 mg/kg body weight per rectum. It was found that, Gr. P40 patients have duration of analgesia (646±9.94) minutes on the other hand Gr. P20 patients had duration of analgesia (294±23.17) minutes and Gr. D patients had duration of analgesia (501±10.63) minutes.

We have managed immediate postoperative pain by tramadol 1 mg/kg IV as rescue analgesic. Only 5 children of group P20 received tramadol 1 mg/kg IV as rescue analgesic for immediate post operative pain relief. Mean consumption of paracetamol in post operative period up to 24 hour period by each patient was significantly lower in Group P40 (175mg±14.25) than Group P20 (316mg±26.39) and Gr. D (213mg±25) respectively. That is mean dose/average consumed by each patient in each group in post operative period post first demand of analgesia. It was lower in Gr P40 as demand for first dose of analgesia post operatively was delayed in them. Hence, they required less number or no dose of analgesia in first 24 hr of post operative period. This was in contrast to other two groups particularly in Gr P20.

Post operative pain scoring was done by TPPPS. (Toddler preschooler postoperative pain scale). TPPPS varied significantly in 15 min after extubation (P=0.00), at 1hr after extubation (P=0.0), at 4 hr after extubation (P=0.00) and at 8 hr after extubation (P=0.00) in Group P40 in favour of group P40. Findings were in accordance with finding of Schmidt and his group who reported that pre-operative rectal diclofenac offers no advantage over paracetamol with respect to pain score and the postoperative pethidine consumption in patients undergoing tonsilslectomy.[21] Similarly, Rømsing and his colleagues demonstrated that diclofenac was no more effective than high-dose paracetamol for analgesia inpatients following tonsilslectomy.[22] Viitanen et al. demonstrated that the total morphine used was significantly less in groups receiving paracetamol, ibuprofen or their combination compared to those receiving placebo for paediatric...
adenoidectomy. Morton and O’Brien demonstrated that concurrent administration of diclofenac sodium in children receiving patient-controlled analgesia (PCA) morphine has a highly significant morphine sparing effect. Our study finding were in contrast with finding of Baer and his colleagues that demonstrated that children receiving preoperative rectal diclofenac sodium needed fewer supplementary doses of postoperative pethidine compared to those who received pre-operative rectal paracetamol.

Paracetamol is an effective antipyretic at plasma concentration of 0.866-0.130 mmol/L. In our study, body temperature of children also had decreased significantly in Gr. P40 & Gr. D. This may be due to paracetamol or diclofenac used in the study. It may also be due to general anaesthesia, cold ambient temperature in the operating room, or unwarmed intravenous fluid used, although the patient’s body temperature had been reduced but not to the extent of hypothermia, even of mild variety. It is also observed that time of first demand of analgesic was delayed in Gr. P40 than Gr-D and Gr-P20. Total duration of analgesic was also greater in Gr-P40 than Gr-D and Gr-P20. El-fattah et al also demonstrated in post-tonsillectomy paediatric patient that postoperative pain measure scores of control group children were significantly higher within the first 3 post-operative days (p = 0.000), with a greater percentage of children experiencing significant pain and requiring more analgesia then study group who received pre-emptive analgesia.

Acute pain results in sympathetic over activity which is manifested by increase in heart rate, blood pressure, peripheral resistance and cardiac output. In this present study, heart rate and blood pressure remained stable throughout the study period in Gr. P40 and Gr. D. Irinia et al. also demonstrated in their study decreasing levels of stress hormones by pre-emptive analgesia with rectal paracetamol thus providing appropriate levels of post operative analgesia after neurosurgical operations in children. Similarly Srivishu et al noted in their study that combination of paracetamol and diclofenac administered per rectum is more effective than paracetamol alone in providing postoperative analgesia in children thus again emphasizing the role of pre-emptive analgesia in management of post operative pain.

CONCLUSION

So, it can be concluded from the study that, high dose rectal paracetamol (40 mg/kg body weight) when used as pre-emptive analgesic appears to be more effective than low dose rectal paracetamol (20 mg/kg) and diclofenac sodium (1 mg/kg) suppository for controlling post operative pain in children undergoing paediatric surgeries. It also provides better recovery score. High dose paracetamol can be used as part of multimodal analgesic helping in decreasing the dose of opioids used and thus their side effects, without any serious side effect of its own.

Limitations

Our study included pediatric patients undergoing various surgical procedures, hence we could not rule out the influence of type and duration of surgery on the outcome.

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