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# COMPARISON OF INTRAVENOUS PARACETAMOL AS PREEMPTIVE AND PREVENTIVE ANALGESIC IN PATIENTS UNDERGOING PYELOLITHOTOMY: A PROSPECTIVE, RANDOMISED DOUBLE BLIND, COMPARATIVE STUDY

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## ABSTRACT

**Aim and objectives:** Aim of this study is to compare the effects of intravenous paracetamol as: Pre-emptive analgesic and Preventive analgesic as regards to hemodynamics, pain control and duration of analgesia in patients undergoing pyelolithotomy under general anaesthesia. **Patients and methods:** 60 patients randomised in two groups undergoing pyelolithotomy under general anaesthesia. In Group Pe, intravenous paracetamol, 1 g was administered over 15-20 minutes, 30 minutes prior to induction of anaesthesia as pre-emptive analgesia and 100 ml NS (placebo) was given over 15-20 minutes, 30 minutes prior to completion of surgery. In Group Pv, 100 ml NS (placebo) was given over 15-20 minutes, 30 minutes prior to induction of anaesthesia and intravenous paracetamol, 1 g was administered over 15-20 minutes, 30 minutes prior to completion of surgery as preventive analgesia. Intraoperative vitals, intraoperative fentanyl, postoperative vitals and VAS score was noted and compared. **Results:** Pre-emptive paracetamol contributed to intraoperative analgesia leading to better control of hemodynamics in intraoperative period and it also provided early postoperative analgesia (around 1.25 hr). Preventive paracetamol is better in terms of providing longer duration of postoperative analgesia (around 4 hr), but it requires additional opioid administration during intraoperative period to supplement analgesia for better hemodynamic stability. **Conclusions:** In our opinion, iv paracetamol should be better administered pre-emptively, because of its advantage of providing analgesia during intraoperative as well as early postoperative period.

**KEYWORDS:** Pyelolithotomy, Paracetamol, Pre-emptive analgesic, Preventive analgesic.

## INTRODUCTION

Post operative pain is a subject receiving an increasing amount of attention. Poorly controlled post operative pain can lead to serious complications like longer hospital stays, increased use of medications, delayed recoveries. Opioid analgesic[1] such as tramadol, fentanyl, morphine, pethidine, pentazocine, remifentanil although provides strong analgesic effect but their use is associated with many side effects such as sedation, nausea, vomiting, respiratory depression, gut disturbances like constipation. Paracetamol[2] is devoid of risks related to opioids. IV Paracetamol is now-a-days available as 100 ml infusion solution. It has both analgesic and antipyretic effects similar to aspirin and it is devoid of many side effects of NSAID's such as gastrointestinal ulceration, impaired platelet function and adverse cardio-renal effects.[3]

IV Paracetamol was found to provide postoperative analgesia when given prior to induction (pre-emptive)[4,5] or prior to closure (preventive)[6,7] as compared to control groups in various studies. However there is limited number of studies till date which have investigated the comparison of i.v paracetamol given in these two different modes (pre-emptive versus preventive) in providing perioperative analgesia.

Therefore we conducted present study to evaluate the comparative efficacy of i.v paracetamol when administered pre-emptively (before induction) versus preventive (before closure) for perioperative analgesia in patients undergoing pyelolithotomy under general anaesthesia.

## MATERIAL AND METHODS

After taking approval from hospitals ethical committee and written and well informed consent from patient and their relatives the present study was conducted in a tertiary care teaching hospital in Udaipur (Raj.) India.

### *Sample size*

Based on prior experience we hypothesized that preemptive and preventive paracetamol would result in a difference of atleast 20% in the duration of analgesia to be clinically significant therefore, a sample size of 30 patients in each group was calculated to detect a significant difference of 20% or more in duration of analgesia with a power of 90% two tailed and a significance level of 5% (alpha of 0.05) corresponding to level of confidence 95%.

### *Exclusion criteria*

American Society of Anaesthesiologists (ASA) scores III and IV**,** Patient refusal**,** history of allergic reactions to paracetamol or fentanyl**,** chronic alcoholism, disease of liver and kidney**,** cardiovascular system illness, endocrine disease, bleeding diasthesis, pregnancy, neurological disorders and psychiatric illness.

### *Randomization*

To conduct the study patients were randomly allocated in two groups using computer generated randomised table. To make the study double blind the 100 ml bottles of Paracetamol and Normal saline were wrapped by black paper by a junior anaesthesiologist and handed over to the anaesthesiologist conducting the case and making the observations with clear instructions to use the bottles in a chronological order using number 1 and 2. Bottle 1 was given 30 min before induction and bottle 2 was given 30 min before closure but the researcher did not know whether bottle is of paracetamol or saline to ensure double blindness.

In Group Pe, intravenous paracetamol, 1 g (100ml infusion) was administered over 15-20 minutes, 30 minutes prior to induction of anaesthesia as pre-emptive analgesia and 100 ml NS (placebo) was given over 15-20 minutes, 30 minutes prior to completion of surgery.

In Group Pv, 100 ml NS (placebo) was given over 15-20 minutes, 30 minutes prior to induction of anaesthesia and intravenous paracetamol, 1 g (100ml infusion) was administered over 15-20 minutes, 30 minutes prior to completion of surgery as preventive analgesia. Paracetamol used in study was inj. Neomol* 100 ml (10 mg/ml) containing 1000 mg of paracetamol. (Neon laboratories India).

The day prior to surgery all patients underwent a pre-anaesthetic evaluation with special consideration to elicit a history of hypertension, dyspnoea, chest pain, cough, wheezing, convulsions and diabetes mellitus as well as previous anaesthetic history and drug sensitivity. Information was collected including weight, nutritional status and airway assessment by the Mallampatti scoring system. A detailed examination of the respiratory, cardiovascular and central nervous system was performed in all patients including preoperative routine investigations such as haemoglobin, hematocrit, total lymphocyte count, differential lymphocyte count, platelet count, serum electrolytes, blood group/Rh typing, blood urea nitrogen, serum creatinine, fasting blood sugar, chest radiography and electrocardiogram. Patients were advised to fast the night prior to surgery and received tablet alprazolam 0.5 mg and tablet ranitidine 150 mg orally on the previous night and day of surgery. On arrival in operating room standard monitoring (pulse oximeter, noninvasive blood pressure and ECG) was applied and the baseline vital parameters pulse rate, systolic BP (SBP), diastolic BP (DBP) and SpO2 of all the patients was recorded. Two peripheral intravenous lines were secured via 20G cannula. Study solution 1 was administered in one iv line 30 minutes prior to the induction of anaesthesia over a period of 15-20 min. Ringer lactate (RL) was started in another iv line to administer 10 ml/kg over the same period.

After completion of solution 1, before induction vital parameters were noted and this time was considered as zero (0) for further data recording. Then premedication was given to patients with inj. glycopyrrolate 0.2mg, inj. Ondansetron 4mg, inj. Midazolam 1mg, inj. Fentanyl 2mcg/kg. After pre-oxygenation for 3 minutes anaesthesia was induced using inj. Thiopentone sodium 5 mg/kg and succinylcholine 2 mg/kg to facilitate tracheal intubation. The HR, SBP, DBP and $SpO_2$ were recorded at the beginning of induction of anaesthesia, at 5 min, 10 min, 15 min, thereafter at 15 minutes interval till completion of surgery. Maintenance of anaesthesia was done with 66% nitrous oxide in $O_2$, 0.8-1.0% isoflurane and vecuronium 0.08mg/kg followed by maintenance doses. Fluid and blood were given intraoperatively as per need.

Vitals were maintained within $\pm$25% of baseline value and Inj. Fentanyl 1mcg/kg i.v. was administered to patients if hemodynamic parameters rise more than 25% of baseline value. 30 min before closure solution 2 was administered over 15-20 min. At the end of surgery anaesthesia was reversed by inj. Neostigmine 2.5mg and inj. Glycopyrrolate one fifth of neostigmine dose. Postoperatively, patient vitals and VAS score were recorded in immediate postoperative period and then 1 hourly till patient demanded rescue analgesia. Rescue analgesia was given to patient when they themselves complained of pain or when their VAS was >3 and time to rescue analgesia was noted. This was end point of study.

Visual Analogue Score (VAS) 0-10 cm was used postoperatively for assessment of severity of pain.
Any adverse effect if occurred were noted perioperatively.

**STATISTICAL ANALYSIS**

Categorical data were presented as number (proportion) and compared with chi square test. Results on continuous measurements were presented as Mean ± SD (Min-Max) and compared using t-test. $p< 0.05$ was considered as statistically significant. The Statistical software SPSS 15.0 was used for the analysis of the data and Microsoft word and Excel were used to generate graphs, tables etc.

**RESULTS**

In our study mean age, weight, ASA status [Table.1], type and duration of surgeries [Table.2] of patients in group Pe and group Pv were statistically comparable. Intraoperatively heart rate was significantly higher in Group Pv as compared to Group Pe at 10, 15, 30 and 45 min ($p < 0.05$) and for rest of time intervals both the groups were comparable ($p > 0.05$) [Fig.1].

**Table 1. Demographic and ASA parameters**

| Data | Group Pe (n=30) | Group Pv (n=30) | p value |
|---|---|---|---|
| Age (years) (Mean ±SD) | 40.60±11.04 | 41.50±11.28 | 0.756 |
| Weight (kg) (Mean ±SD) | 58.90±6.17 | 60.23±7.73 | 0.463 |
| **ASA** | | | |
| 1 | 21 (70.0%) | 22 (73.3%) | - |
| 2 | 9 (30.0%) | 8 (26.7%) | - |
| Total | 30 (100%) | 30 (100%) | - |

**Table 2. Duration of surgery and Duration of analgesia (in minutes)**

| Duration of surgery (min) | Group Pe | Group Pv | p value |
|---|---|---|---|
| Mean ± SD | 70.17±8.46 | 68.50±6.45 | 0.394 |
| Range | 50-90 min | 60-90 min | |
| **Duration of analgesia(min)** | | | |
| Mean ± SD | 77.50±10.48 | 220.00±10.83 | 0.000 |
| Range | 60-90 min | 200-240 min | |

Postoperatively heart rate was significantly higher in Group Pe as compared to Group Pv during immediate postoperative period ($p < 0.05$) and for rest of time interval both the groups were comparable ($p > 0.05$) [Fig.1].

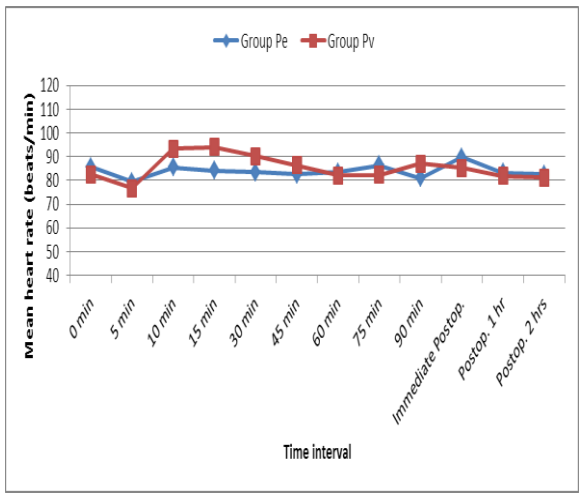


**Fig. 1 Perioperative mean heart rate**

Intraoperatively systolic blood pressure was significantly higher in Group Pv as compared to Group Pe at 10, 15, 30 and 45 min ($p< 0.05$) and for rest of time interval both groups were comparable ($p > 0.05$) [Fig.2].

Postoperatively systolic blood pressure was significantly higher in Group Pe as compared to Group Pv during immediate postoperative period ($p < 0.05$) and for rest of time interval both groups were comparable ($p > 0.05$) [Fig.2].

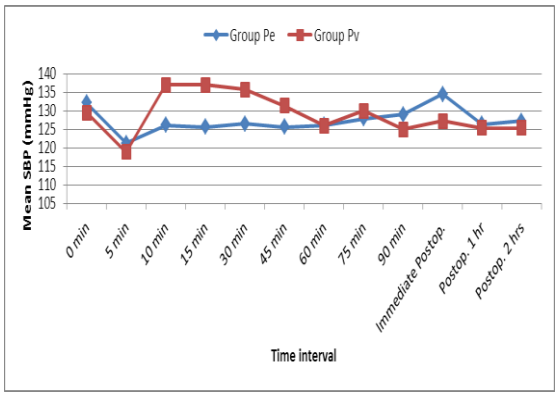


**Fig.2 Perioperative mean systolic blood pressure**

Intraoperatively diastolic blood pressure was significantly higher in Group Pv than in Group Pe at 10, 15, 30 and 45 min ($p < 0.05$) and for rest of time interval both groups were comparable ($p > 0.05$) [Fig.3].

Postoperatively diastolic blood pressure was significantly higher in Group Pe than in Group Pv during immediate postoperative ($p < 0.05$) and for rest of time interval both groups were comparable ($p > 0.05$) [Fig.3].

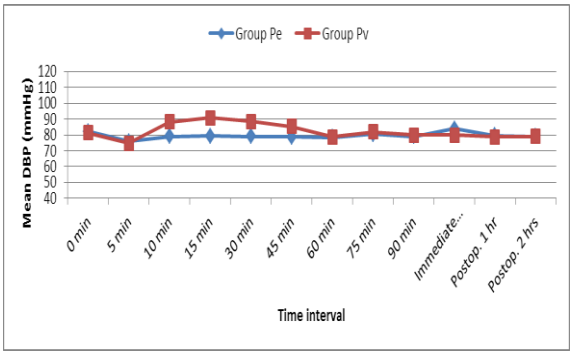


**Fig. 3 Perioperative mean diastolic blood pressure**

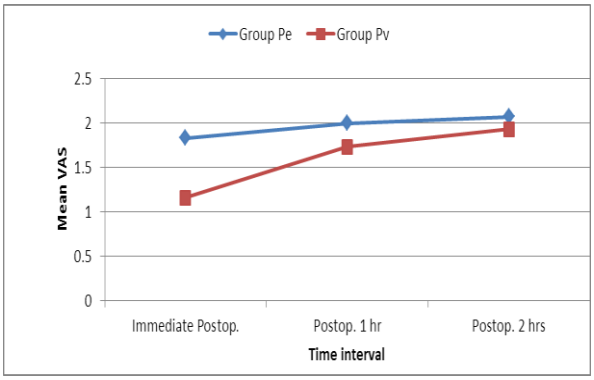


**Fig.4 Mean VAS score in postoperative period**

$SpO_2$ was above 98% in both groups at all time intervals in all patients. Intraoperatively $SpO_2$ was comparable in both groups ($p > 0.05$). Postoperatively $SpO_2$ was significantly higher in Group Pv during immediate postoperative, at 1 and at 2 hrs ($p < 0.05$) but this difference was of around 1% between two groups which has no clinical significance.

We measured duration of analgesia from end of surgery to the time when VAS score was more than 3. It was 77.50±10.48 minutes in Group Pe and 220.00±10.83 minutes in Group Pv and the difference was statistically significant (p = 0.00) [Table.2].

In our study pain intensity using VAS score was significantly higher in Group Pe than in Group Pv at immediate postoperative period (1.83±0.834 vs 1.16±0.379, p=0.000) and at 1 hr postoperatively (2.0±0.426 vs 1.73±0.432, p=0.023). At 2 hr postoperatively VAS was higher in Group Pe (2.07±0.271) than in Group Pv (1.93±0.257) but it could not reach statistical significance (p=0.051). In group Pv VAS score at 3 hr was 1.93±.185 and at 4 hr was 2.53±.508. At these time intervals VAS score in group Pe were not available because study was completed after rescue analgesia administration between 1 to 2 hr in group Pe while it completed between 3 to 4 hr in group Pv. [Tab.3, Fig.4].

**Table 3. Comparison of VAS score at various time intervals**

| Time interval | Group Pe | Group Pv | p value |
|---|---|---|---|
| Immediate Postop. | 1.83±0.384 | 1.16±0.379 | **0.000** |
| Postop. 1 hr | 2.00±0.462 | 1.73±0.432 | **0.023** |
| Postop. 2 hrs | 2.07±0.271 | 1.93±0.257 | 0.051 |
| Postop. 3 hr | -- | 1.96±0.185 | -- |
| Postop. 4 hrs | -- | 2.35±0.508 | -- |

Intraoperatively, in Group Pv, 2 (6.67%) patients showed > 25% rise in heart rate for which intraoperative fentanyl 1 µg/kg was administered. None of the patients in Group Pe required fentanyl. In immediate postoperative period, analgesia was adequate in all patients of both groups (VAS <3 in all) therefore none of the patients received rescue analgesia (iv tramadol) at this point of time. Postoperatively in Group Pe, 3 (10%) patients achieved VAS >3 within 1 hour so rescue analgesia was administered. Remaining 27 (90%) patients achieved VAS> 3 between 1 to 2 hrs and received rescue analgesia therefore study was declared complete at 2 hrs in Group Pe. Postoperatively in Group Pv, all patients achieved VAS >3 between 3 to 4 hrs so rescue analgesia was administered and study was declared complete in Group Pv at 4 hrs.

None of the patients in both groups had any side effects like PONV, respiratory depression and urinary retention or any other at any time interval during postoperative period.

## DISCUSSION

Surgical procedures invariably cause tissue damage along with presence of drains, tubes and post operative complications resulting in pain.

In our study demographic data (mean age, weight, ASA status, type and duration of surgeries) of patients in group Pe and group Pv were statistically comparable.

In our study we found that intra-operative hemodynamic parameters (HR, SBP, DBP) were significantly higher in group Pv at 10,15,30,45 min (p value <0.05) as compared to group Pe. Though they were within 15% of baseline at all time intervals in both groups, signifying acceptable intraoperative analgesia and hemodynamic stability. It was noteworthy that HR increased to > 25% of baseline in 2 (6.67%) patients in group Pv, for which supplemental analgesia in form of fentanyl 1mcg/kg was administered. It shows that when paracetamol 1 gm was administered pre-emptively that is 30 min before induction; it added to intraoperative analgesia hence better hemodynamic stability was observed in group Pe intraoperatively. Postoperatively hemodynamic parameters (HR, SBP, DBP) were significantly higher in

group Pe ($p<0.05$) as compared to group Pv, in immediate postoperative period. In rest of postoperative time intervals they remained higher in group Pe though could not reach statistically significance ($p>0.05$). This shows that when paracetamol was given 30 min before closure (preventive), postoperative analgesia was significantly better as compared to when used pre-emptively (30 min before induction), therefore better hemodynamic stability in postoperative period was observed in group Pv as compared to group Pe.

Similar to our study, Hassan et al (2014)[8] conducted a study to compare between administration of intravenous paracetmol as preemptive and preventive analgesia in group I and group II respectively in elective caesarean section surgeries under general anaesthesia. They observed that there were significantly higher HR, SBP and DBP in patients of group II than group I from intubation time till delivery of the baby ($p<0.001$) but Group I showed significantly higher HR, SBP and DBP than Group II in immediate postoperative period ($p<0.001$). There were no statistically significant differences between both groups as regards to HR, SBP and DBP preoperative, after induction, intraoperative (after delivery of baby) and 1 h and 2 h postoperative ($p > 0.05$). Their study also showed that I.V. paracetamol when used as pre-emptive analgesia 30 min. before induction produced significantly better control of hemodynamics in the most stressful period before delivery of the baby. There were more significant reductions of HR, SBP and DBP in intraoperative period in pre-emptive group when compared with preventive analgesia by paracetamol given 30 min before the end of procedure. However, better control of hemodynamic parameters in postoperative period was observed when iv. Paracetamol was administered before end of surgery as compared to when it was used pre-emptively. These results were in accordance to our study.

In our study pain intensity using VAS score was significantly higher in Group Pe than in Group Pv at immediate postoperative period (1.83±0.834 vs 1.16±0.379, p=0.000) and at 1 hr postoperatively (2.0±0.426 vs 1.73±0.432, p=0.023). At 2 hr postoperatively VAS was higher in Group Pe (2.07±0.271) than in Group Pv (1.93±0.257) but it could not reach statistical significance (p=0.051). In group Pv VAS score at 3 hr was 1.93±.185 and at 4 hr was 2.53±.508. At these time intervals VAS score in group Pe were not available because study was completed after rescue analgesia administration between 1 to 2 hr in group Pe while it completed between 3 to 4 hr in group Pv.

Hassan et al. (2014)[8] observed similar results. They found that Group I (pre-emptive) patients had extremely higher pain scores than patients in preventive Group II (3.9 ± 0.3 and 3.3 ± 0.4 immediately and 2.8 ± 0.2 and 2.6 ± 0.36 at 1 hour postoperatively) $P < 0.01$.

Semih Arici et al. (2009)[9] observed that when the VAS scores of the patients in Group III (control group) were compared with Groups I (pre-emptive) and II (preventive), they were found to be significantly higher at all time points. But they reported higher pain scores in group II than in group I postoperatively.

## CONCLUSION

We conclude that:

- IV paracetamol is a safe and effective analgesic when administered either before induction (pre-emptive) or before closure (preventive), as a part of multimodal analgesia for pyelolithotomy surgeries conducted under general anaesthesia. However, both regimes (pre-emptive versus preventive) have their own advantage and disadvantage, and it is discretion of anaesthesiologist which regime they want to prefer.
- Pre-emptive paracetamol contributed to intraoperative analgesia leading to better control of hemodynamics in intraoperative period and it also provided early postoperative analgesia (around 1.25 hr).
- Preventive paracetamol is better in terms of providing longer duration of postoperative analgesia (around 4 hr), but it requires additional opioid administration during intraoperative period to supplement analgesia for better hemodynamic stability.
- In our opinion, iv paracetamol should be better administered pre-emptively, because of its advantage of providing analgesia during intraoperative as well as early postoperative period.

**ACKNOWLEDGEMENT –** Nil.

**Conflict of Interest -** Nil.

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