Pre-emptive Analgesic Effects of Intravenous Paracetamol Versus Diclofenac in Open Cholecystectomy

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ABSTRACT

INTRODUCTION: Pain is not just a sensory modality but is an unpleasant experience. In order to improve the efficacy of perioperative pain treatment, there are modalities like: pre-emptive analgesia and multimodal pain therapy. Pre-emptive analgesia is reported as an effective management, which pharmacologically induces an effective analgesic state prior to the surgical trauma, thereby significantly reducing post operative analgesic (opioids) requirement.

METHOD: This was a prospective, randomized and double blind study. Fifty two patients of either sex, aged between 20 to 60 years, American Society of Anesthesiologist Physical Status I and II scheduled for open cholecystectomy requiring general anesthesia with endotracheal intubation was included in this randomized double bind study. Patients were divided into two groups. Thirty minutes prior to induction either inj. paracetamol 15 mg/kg (not exceeding 1 gm) or inj. diclofenac 1 mg/kg (not exceeding 75 mg) diluting in 100 ml of normal saline given over 20 minutes. Inj. pethidine 0.5 mg/kg iv was given for analgesia. Induction, maintenance and reversal were standardized in both the groups.

Systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were recorded in intraoperative period. Every patient was evaluated post operatively using pain scores (Numeric pain score 10 cm) in half an hour, 1, 2, 4, 8, 12 and 24 hours. Time duration of first rescue and total pethidine requirement in first 24 hours recorded and compared between the groups.

RESULT: The mean duration of first rescue pethidine in paracetamol group was 46.15±21.25 min whereas in diclofenac group was 35.88±10.13 min (P value 0.031). The mean dose of requirement of rescue pethidine in 24 hours was 109.38±35.22 mg in paracetamol group and 124.19±35.04 mg in diclofenac group (p value 0.135).

CONCLUSION: Pre-emptive iv paracetamol 15 mg/kg is effective than iv diclofenac 1 mg/kg for prolonging the duration of immediate post operative analgesia and reduces (13%) the total pethidine consumption in 24hours.

KEY WORDS: Diclofenac, Paracetamol, Pethidine Pre-emptive Analgesia, Postoperative Analgesia, VAS.

INTRODUCTION

Pain is not just a sensory modality but is a subjective sensation and inevitable experience too. The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in term of tissue damage”. Every surgical procedure produces a tissue trauma with release of potent mediators of inflammation and pain. Post-operative pain is not only an unpleasant experience but also associated with physiological and psychological responses. In addition to the distress and discomfort, poorly managed postoperative pain causes respiratory dysfunction, decreased gastrointestinal motility,
neuroendocrine and metabolic changes. The most common method of managing pain following surgery is the use of opioids and it may result in respiratory depression, post operative nausea vomiting, urinary retention, ileus and addiction. 

Pre-emptive analgesia has been developed as a hypothesis of “preventing pain”. Pre-emptive analgesia is a treatment that is initiated before the surgical stimulus in order to reduce this sensitization. Pre-emptive analgesia helps to alleviate pain, decreases analgesic requirements and decrease morbidity. This promotes early recovery and shortens the length of hospital stay.

Parenteral form of diclofenac and paracetamol are effective analgesics, cost effective and has been used instead of opioids as an adjunctive or pre-emptive. Pre-emptive use of these drugs has shown to reduce up to 30% of post operative opioids consumption and reduction of opioids related adverse effects.

**METHOD**

This was a prospective, randomized and double blind study. After approval from the Institutional Review Board of National Academy of Medical Sciences, 52 patients were enrolled in the study. The patients enrolled were of aged between 20 to 60 years, ASA I and II and scheduled for elective open cholecystectomy requiring general anesthesia with endotracheal intubation. Patients with allergic to study drugs, surgery duration more than two hours and refused by patient were excluded from the study. Informed written consent was obtained. Patients were divided into two groups, 26 in each group. Randomization was done by lottery method. Group P patients received 15 mg/kg (not exceeding 1 gm) paracetamol in 100 ml of NS and group D patients received 1 mg/kg (not exceeding 75 mg) of diclofenac in 100 ml of NS. Drugs were given over 20 minutes before induction of anesthesia. All patients were premedicated with inj. midazolam 0.04 mg/kg and inj. pethidine 0.5 mg/kg was given for analgesia. Patients were induced with propofol and vecuronium 0.1mg/kg was used to facilitate the tracheal intubation. Anesthesia was maintained with isoflurane, oxygen and vecuronium. Residual effect of muscle relaxant was reversed with inj. neostigmine 0.05mg/kg and inj. glycopyrolate 0.01 mg/kg. SBP, DBP, MAP and HR were recorded throughout the intraoperative period.

For postoperative pain assessment, Numeric pain scale was used (0-10; 0: no pain, 10: worst pain imaginable) and it was measured at 30 minute, 1, 4, 8, 12 and 24 hours after the extubation. Pain score, more than 3 was managed with intramuscular inj. pethidine 1 mg/kg with promethazine 0.5 mg/kg. The duration of time (minutes) from the extubation time to the first rescue of pethidine and total consumption of pethidine in 24 hours were recorded.

Collected data was analyzed by means of statistical software SPSS. Independent t test was used for comparison between two groups for continuous variables like age, weight, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, first dose of rescue analgesic and total analgesic consumption. Chi square test was used for ASA and gender. Continuous variables were presented as mean ± SD. Result were considered statistically significant if P value < 0.05.

**RESULT**

Two groups were comparable in terms of age, gender, weight and ASA status. These demographic data are shown in table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group P (n=26)</th>
<th>Group D (n=26)</th>
<th>Test of significance (P&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>42.15 ± 10.22</td>
<td>42.85 ± 11.47</td>
<td>0.819</td>
</tr>
<tr>
<td>Gender (Male / Female)</td>
<td>4 / 22</td>
<td>5 / 21</td>
<td>0.720</td>
</tr>
<tr>
<td>Weight in kg (mean ± SD)</td>
<td>59.34 ± 8.8</td>
<td>57.92 ± 8.56</td>
<td>0.558</td>
</tr>
<tr>
<td>ASA I/II</td>
<td>24 / 2</td>
<td>23 / 3</td>
<td>0.646</td>
</tr>
<tr>
<td>Duration of surgery (in min)</td>
<td>74.76 ± 22.53</td>
<td>76.23 ± 21.97</td>
<td>0.814</td>
</tr>
</tbody>
</table>

The result of our study showed that intraoperative hemodynamic (SBP, DBP, MAP and HR) changes between the groups were not significant.

Pre-emptive iv paracetamol acts as adjuvant for longer duration of first rescue analgesic than iv diclofenac (46.15±21.25 min versus 35.88±10.13 min) which was statistically significant (p value 0.031). Pethidine consumption in paracetamol group over 24 hours of surgery was 109.38±35.22 mg and diclofenac 124.19±35.04 mg (p value 0.135).
Table 2. Comparison of postoperative analgesic requirement in both groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group of study</th>
<th>Number (n)</th>
<th>Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of first rescue pethidine (in minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>26</td>
<td>46.15±21.25</td>
<td>0.031</td>
</tr>
<tr>
<td>D</td>
<td>26</td>
<td>35.88±10.13</td>
<td></td>
</tr>
<tr>
<td>Total pethidine consumption in 24 hours (in mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>26</td>
<td>109.38±35.22</td>
<td>0.135</td>
</tr>
<tr>
<td>D</td>
<td>26</td>
<td>124.19±35.04</td>
<td></td>
</tr>
</tbody>
</table>

None of the patients had experienced any untoward side effects of paracetamol or diclofenac in this study.

**DISCUSSION**

Postoperative pain causes not only physical suffering but also mental fear and anxiety, affecting the recovery period of the patients by limited exercise, declined respiratory capability, and pulmonary complications. Hence, effective control of postoperative pain can provide a lot of advantages, including a reduction of the complications and early discharge from the hospital. Among them the diclofenac and paracetamol have a growing interest for better control of postoperative pain by administrating pre-emptively. With the use of these drugs it reduces post operative opioid consumption and avoids its adverse effects like respiratory depression, nausea, vomiting, excessive sedation and significant urticaria.

Paracetamol and diclofenac has an important role in balanced analgesia. Pre-emptive iv paracetamol and diclofenac has shown to have significant opioids sparing effect in post operative patients. Paracetamol intravenous 1 gm has analgesic activity in moderate to severe post operative pain similar to those have shown by diclofenac 75 mg.

The mean duration of pain free time after surgery was 46.15±21.25 minutes in paracetamol group where as the diclofenac group was 35.88±10.13 minutes (p < 0.05). Goel p et al performed a comparative study, pre-emptive analgesia with iv paracetamol and iv diclofenac sodium in patients undergoing various surgical procedure. They found that the duration of analgesia was 4.27+ 1.26 hours in paracetamol group while 4.86+1.55 hours in diclofenac group (p<0.05). Prolong duration of analgesia in this might be due to use of nitrous oxide for maintenance of anesthesia, less traumatic and short duration of surgical procedures. Yasmin R et al compared pre-emptive effect of paracetamol 50 mg/kg (Gr P50), 25mg/kg (Gr P25) and diclofenac 1mg/kg (GrD) per-rectally half an hour before surgery. Total duration of analgesia in group P50 was (657±9.94) min and in group D (502± 10.63) min and in group P25 (288±23.17) min. High dose of paracetamol and diclofenac used in the study along with inj.fentanyl for pain management and use of nitrous oxide for maintenance of anesthesia, might explain the disparity of time duration of first rescue analgesia with our study. Choudhuri AH et al compared pre-emptive effect of 1gm iv paracetamol and placebo in laparoscopic cholecystectomy. The time requirement of first dose of rescue analgesic in the postoperative period was also significantly prolonged in the group receiving iv paracetamol compared with placebo (76±24.7 min vs. 48±15.8 min). Arslan M et al compared pre-emptive efficacy of iv 1 gm paracetamol with placebo in laparoscopic cholecystectomy. They found that patients who received 1 gm iv paracetamol pre-emptively experienced a longer interval (153 min) post operative analgesics compared with those patients who did not receive pre-emptive drug (33.7 min). Longer duration of pain free interval than in our study might be due to laparoscopic operation which is less painful compared to open cholecystectomy.

The total mean requirement of rescue analgesic (pethidine) in 24 hours was 13% less in paracetamol group compared to diclofenac group (109.38±35.22 mg versus 124.19±35.04 mg) but statistically it was not significant (p value 0.135). Gurbet A et al compared pre-emptive analgesic effect of iv paracetamol with placebo in patients undergoing abdominal hysterectomy. They also found that pre emptive administration of iv paracetamol reduces postoperative opioids (morphine) consumption and its adverse effects. Cobby TF et al compared the pre-emptive effect of 1.3 gm paracetamol, 50 mg diclofenac and placebo per-rectally. They have also found that mean morphine consumption was less in patient who received pre-emptive 1.3 gm rectal paracetamol than patient who received 50 mg rectal diclofenac and placebo. Choudhuri AH et al compared pre-emptive effect of 1gm iv paracetamol and placebo in laparoscopic cholecystectomy. They
also found that fentanyl consumption over first 24 hours in post operative period was significantly less in patient receiving pre-emptive iv paracetamol. Afhami MR et al\(^1\) compared pre-emptive efficacy of oral paracetamol with placebo. They found that patients who received single dose of 325 mg oral paracetamol as pre-emptive analgesic was effective in acute postoperative pain relief and reduces post operative opioids consumption. Arslan M et al\(^2\) compared pre-emptive iv paracetamol 1 gm with placebo in patients undergoing cholecystectomy. Similar to our study, they also found that, pre-emptive 1 gm iv paracetamol reduces opioids consumption in first 24 hours of surgery in paracetamol group compared to placebo. 

CONCLUSION

Pre-emptive intravenous paracetamol is more effective than diclofenac for prolonging the duration of post operative analgesia and requires less amount of rescue pethidine.

REFERENCES