Oral versus Intravenous Paracetamol for Perioperative Analgesia in Patients Undergoing Total Abdominal Hysterectomy - A Randomised Double-Blind Controlled Trial

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ABSTRACT

BACKGROUND

Paracetamol has been commonly used for perioperative pain management. The perceived benefits of IV paracetamol (PCM) over oral are few if oral PCM is given sometime before surgery. We wanted to compare the effects of oral and intravenous paracetamol on perioperative pain management in patients undergoing total abdominal hysterectomy under general anaesthesia.

METHODS

Sixty-four female patients of American Society of Anesthesiologists (ASA) I / II, in the age group of 18 - 70 years, weighing 40 - 80 Kg, undergoing total abdominal hysterectomy (TAH) were randomised using computer-generated random number table, into two groups. They received oral dispersible 1 g PCM tablets (group PO) at least 45 minutes prior to surgery or intravenous (IV) PCM 1 g (group PI) after induction of anaesthesia. VAS pain scores were recorded and rescue analgesia with tramadol was provided postoperatively.

RESULTS

The primary outcome measure, time to first rescue analgesic, was statistically similar in both groups. The secondary outcome measures i.e., pain scores, postoperative 24 hours tramadol requirements, patient satisfaction scores and complications were also comparable.

CONCLUSIONS

Considering the similar efficacy and side effect profile but a much lower cost of oral PCM, routine administration of oral PCM 45 minutes before induction of anaesthesia may be an acceptable alternative to routine intraoperative IV PCM infusion.

KEY WORDS

Paracetamol, Intravenous, Oral, VAS Pain Score, Analgesia

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BACKGROUND

Paracetamol has been widely used for over a century as an effective analgesic and antipyretic agent with an established efficacy and tolerability.[1-4,5] It is currently the most commonly used drug for the treatment of postoperative pain as mono-therapy or as a part of multimodal therapy.[6] The consumption of opioids, other analgesics and their related side effects have been shown to be reduced with the use of PCM.[7,8,9] Paracetamol has the advantage of being available in oral, intravenous and rectal formulations.

Intravenous PCM has been very commonly used in perioperative period for providing pain relief due to its multiple advantages in terms of safety, efficacy, rapid onset of action, predictable pharmacokinetics and few clinically significant drug interactions.[5,10,11,12] IV PCM in standard equivalent doses provides analgesia comparable with nonsteroidal anti-inflammatory drugs (NSAIDs) and tramadol with minimal side effects.[10,13] However, IV preparations are significantly more expensive and their administration is also more complex. Oral PCM preparation is very cheap and its administration is also simple. It is completely absorbed from the proximal small intestine with a peak plasma concentration achieved in 30 to 60 minutes which is facilitated by the fasting status of the patient. The bioavailability of oral PCM is time, dose and age dependent.[14,15]

There is an evidence of efficacy of oral PCM for acute pain management and it has been suggested that its role in perioperative pain management needs to be further explored.[16,17,18] To our knowledge, there has been no study comparing the intravenous and oral routes of paracetamol administration for perioperative pain relief in female patients undergoing total abdominal hysterectomy. Therefore, we conducted a randomised controlled trial to compare the analgesic efficacy of paracetamol via oral and intravenous routes in patients undergoing total abdominal hysterectomy under general anaesthesia (GA).

METHODS

The present randomised, double blind controlled trial was undertaken after approval from the institutional ethics committee–human research and obtaining written informed consent from each patient. The trial was prospectively registered at Clinical Trials Registry–India. The study was carried out in 64 ASA grade I / II patients, aged between 18 – 70 years, weighing 40 - 80 Kg undergoing abdominal hysterectomy with Pfannenstiel incision under general anaesthesia. The study was conducted from November 2014 to April 2016 in the Department of Anaesthesiology & Critical Care and the Department of Obstetrics & Gynaecology, University College of Medical Sciences & Guru Teg Bahar Hospital, Delhi. Patients with history of daily intake of analgesics, intake of any analgesic in preceding 24 hours of surgery, history of convulsive disorders, those on antiepileptic treatment, or having liver and kidney dysfunction were excluded. The patients were randomly allocated into two groups 'PI' and 'PO' using computer generated random number tables. A sealed envelope technique was used to maintain allocation concealment. To maintain blinding, double dummy technique was used. An anaesthesiologist not involved in the study prepared the drug with their placebo in a separate area. All patients received premedication in the form of tab alprazolam 0.25 mg in the night and 2 hours before surgery. In the preoperative room, the patients were explained and instructed about the pain assessment using visual analogue scale (0 - 100; 0 - no pain, 100 - worst imaginable pain). According to group allocation, to group 'PO', oral dispersible PCM 1g tablets were given approximately 45 min before the induction of anaesthesia and 100 ml of normal saline after induction of anaesthesia; whereas Group 'PI' patients received oral dispersible placebo tablet in the preoperative period and IV PCM 1 gm after induction of anaesthesia. Drugs were given by the staff not involved in the study.

In operating room, standard monitoring in the form of continuous electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP) and pulse oximetry (SpO_2) was started. Baseline vitals were recorded. IV cannula was secured, and ringer lactate infusion started. Haemodynamics were monitored during intraoperative as well as post-operative period.

Standard anaesthetic technique for general anaesthesia was followed in all the patients. Anaesthesia was induced with inj. morphine 0.1 mg / Kg and inj. propofol 2 mg / Kg followed by inj. vecuronium 0.1 mg / Kg to facilitate orotracheal intubation. Anaesthesia was maintained with oxygen, nitrous oxide, isoflurane and top-up doses of vecuronium. At the end of surgery, infiltration of skin incision was carried out with 0.25 % plain bupivacaine and ondansetron 4 mg IV was given to all the patients. Neuromuscular blockade was reversed using neostigmine 0.05 mg / Kg and glycopyrrolate 0.01 mg / Kg. The durations of surgery and anaesthesia were recorded.

Pain was assessed using VAS pain score on arrival in the post anaesthesia care unit (PACU), then every 30 min interval for initial 2 hours, then at 4, 8, 12 and 24 hours in the postoperative period. Rescue analgesia was provided with tramadol 1 mg / Kg by slow IV injection whenever VAS pain score was > 30 mm. This time was noted as the time to first analgesic requirement. Same dose was repeated if pain relief was inadequate with the initial dose. In the ward, analgesia was provided with inj. tramadol 1 mg / Kg whenever VAS pain score was > 30 mm. If pain relief was not adequate with tramadol 1 mg / Kg, inj. diclofenac 75 mg by slow IV infusion was given. Intravenous PCM 1 g was given if adequate pain relief could not be achieved even after giving diclofenac. The total analgesic requirement was calculated in terms of tramadol consumption, considering diclofenac 75 mg and IV PCM 1 g equivalent to IV tramadol 100 mg.[19,20] Any episode of nausea, vomiting or hypotension was managed and recorded. Patient's satisfaction with the pain relief was asked and graded as 'good', 'average' or 'poor'.

The primary outcome measure was time to first rescue analgesic; whereas, secondary outcome measures were pain scores, postoperative 24 hours analgesic requirements and patient satisfaction score.

Sample Size

Considering a standard deviation of 38 min for time to rescue analgesia in patients undergoing total abdominal hysterectomy under general anaesthesia,[21] 29 patients in each group were needed to detect a difference of 30 min in time to

rescue analgesia with a power of 80 % at 5 % significance level. However, to compensate for any attrition in data, 10 % of this number was added so as to give a final sample size of 32 patients in each group.

Statistical Analysis

Statistical analysis was performed using Statistical Package for SPSS version 20.0. Unpaired Student's t-test was used to compare mean age, weight, time to first rescue analgesic and postoperative 24 hours analgesic requirement. Repeated measures ANOVA was used to perform inter-group comparisons for VAS pain scores. Fisher's exact test or chi-square test was used to compare ASA grade, patient satisfaction score and complications. Post hoc analysis was done with Tukey's test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Demographic profile was comparable among both the groups as shown in Table 1.

Demographics and Patient Characteristics	Group PI (N = 32)	Group PO (N = 32)	P-Value
Age (years)	42.4 ± 6.0	42.8 ± 9.3	0.823
Weight (Kg)	57.1 ± 10.04	53.69 ± 10.07	0.185
ASA I / II	23 / 9	18 / 14	0.297
Duration of surgery	129.3 ± 42.2	135.1 ± 43.7	0.592
Duration of anaesthesia	149.3 ± 42.6	154.8 ± 43.2	0.606
Time of tablet before induction (min)	54.7 ± 7.5	56.8 ± 10.2	0.341
Time of infusion from induction (min)	16.6 ± 9.7	12.2 ± 6.1	0.032

Table 1. Demographic Profile and Other Patient Characteristics

In the present study, analgesic efficacy of oral and IV PCM was studied in terms of time to first analgesic requirement (TFR), 24 hours analgesic requirement and VAS pain scores.

Analgesic Requirement at Various Time Points	Group PI (N = 32)	Group PO (N = 32)	P-Value
TFR induction (min)	227.3 ± 96.7	215.5 ± 87.0	0.608
TFR reversal (min)	80.4 ± 91.2	74.2 ± 94.5	0.792
Total tramadol requirement in 24 hours (mg)	230.4 ± 70.8	195.6 ± 91.7	0.094
Total analgesic requirement in 24 hours (mg)	260	209	0.093

Table 2. Time to First Rescue Analgesia and Analgesic Requirement

TFR was noted from the time of induction as well as reversal. There was no statistically significant difference in TFR from induction and reversal between the groups as shown in Table 2. In group 'PI', nine patients received inj. diclofenac and two patients received diclofenac and inj. PCM in addition to tramadol whereas in 'PO' group, nine patients received inj. diclofenac and one patient received diclofenac as well as PCM in addition to tramadol in the postoperative period, Figure 1a & 1b. The total tramadol as well as total analgesic requirement in 24 hours was found to be lower in PO group; however, the difference was statistically not significant. Figure 2 shows, the postoperative VAS pain scores were also comparable in both the groups at various time points.

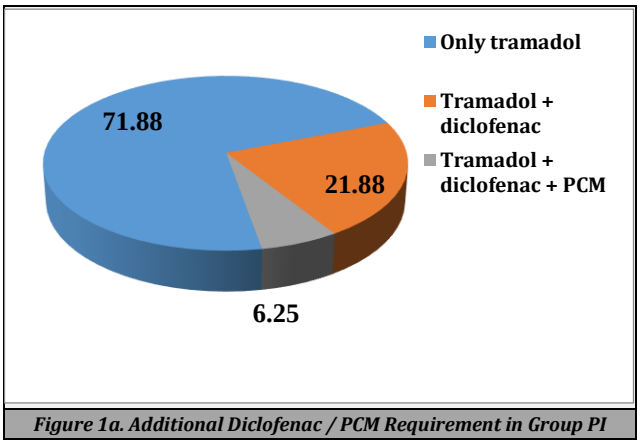

Figure 1a. Additional Diclofenac / PCM Requirement in Group PI

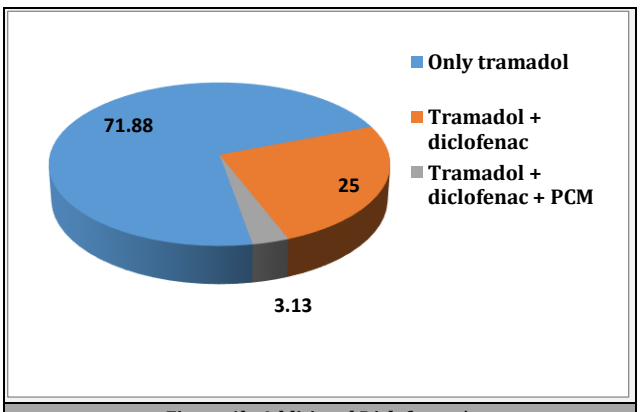

Figure 1b. Additional Diclofenac / PCM Requirement in Group PO

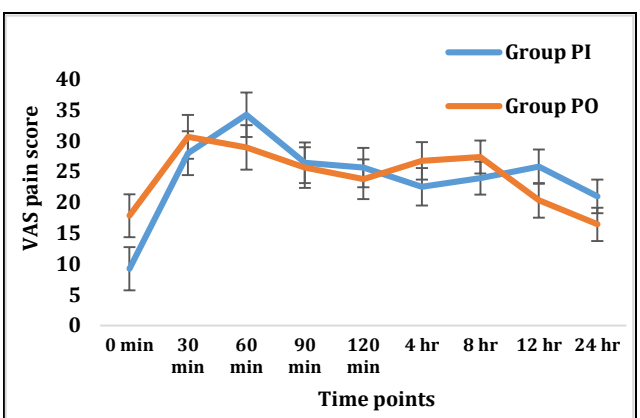

Figure 2. VAS Pain Scores at Various Time Points in the 24 Hours Postoperative Period

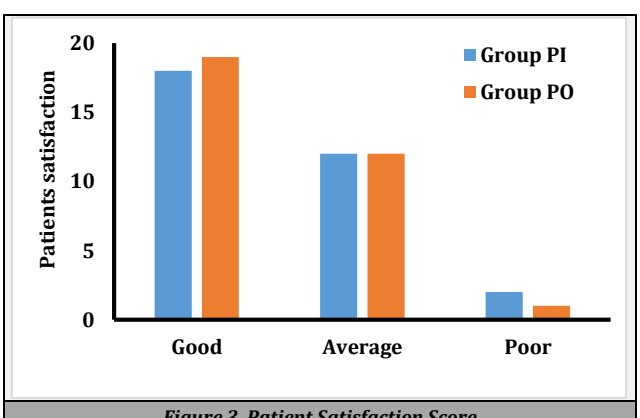

Figure 3. Patient Satisfaction Score

Two patients in group PI while four in PO group developed nausea and vomiting in the postoperative period after inj. tramadol, which was treated with inj. dexamethasone. The incidence of bradycardia, hypotension and postoperative nausea vomiting (PONV) were found to be similar between the groups. Also, the baseline, intraoperative and postoperative haemodynamic parameters were comparable in both the groups.

The patients' satisfaction with pain relief was graded as good / average / poor. In both PI and PO patient's satisfaction scores were comparable as shown in Figure 3.

DISCUSSION

The analysis of results across the groups in terms of time to first rescue analgesic, total analgesic requirements, VAS pain scores and patients' satisfaction does not show statistically significant difference with oral and i.v. paracetamol for the relief of pain in patients undergoing total abdominal hysterectomy. Many earlier studies have compared efficacy of oral and I.V. PCM during different types of surgical procedures; however, ours is the first study comparing these two routes of PCM administration in females undergoing total abdominal hysterectomy.

Intravenous paracetamol is very commonly prescribed for peri-operative pain relief. It provides onset of pain relief within 5 to 10 minutes after administration due to high bioavailability. However, IV preparation is expensive and needs to be given as infusion. Oral PCM is very cheap and more convenient than intravenous medication. Its pre-operative administration has been found to be effective to provide post-operative analgesia. The time to achieve maximum concentration with oral PCM has been reported to be one hour.[22] Therefore in the present study, it was decided to give oral PCM at least 45 min before and IV PCM after the induction of anaesthesia.

Westhuizen et al. found maximum median plasma concentration of 19 mg / L with IV PCM and 13 mg / L with oral PCM.[23] Although plasma concentration was higher with IV preparation, the difference was less marked after 150 minutes. The systemic availability of IV dose is almost 100 % compared to oral PCM which is quoted as 69 - 84 %. However, the area under the absorption / time curve in healthy subjects is equivalent to that with IV PCM. Similarly, Langford et al. in their study observed that the difference in peak plasma concentrations was not statistically significant after one hour with oral and intravenous paracetamol administration.[19]

Our study results are in concordance with the results of some earlier studies. Fenlon et al. compared oral and IV PCM for lower third molar extraction, they demonstrated that oral PCM given at least 45 minutes before surgery was not inferior to IV PCM for providing postoperative analgesia.[24] Pettersson et al. compared the analgesic efficacy of oral and IV PCM in terms of its opioid-sparing effect in patients who had undergone coronary artery bypass surgery.[25] The use of opioid was significantly lower in the patients receiving IV PCM than in the oral PCM group; however, no difference was observed in pain scores on VAS scale at any time. In another study, there was no evidence of differences in pain or opioid consumption after receiving oral or IV PCM in patients undergoing laparoscopic cholecystectomy.[26] A systematic review and meta-analysis was conducted to compare the efficacy and safety of intravenous and oral acetaminophen as adjunct to multimodal analgesia regimens for pain control after total knee and hip arthroplasty. Authors observed that pain relief and opioid consumption was similar among both the groups and no increased risk of postoperative pulmonary complications were seen. However, the evidence quality for each outcome was moderate as only 2 randomised controlled trails (RCT's) were studied involving 120 participants in the experiment group and 116 participants in the control group. Therefore, higher quality of RCTs are required for further research.[27]

A recent systematic review by Mallama et al. suggested that route of paracetamol administration does not affect pain or any other postoperative outcomes. However, there was an insufficient evidence to exclude important clinical effects and overall, the quality of evidence was poor due to inadequate sample size. The studies included in this systematic review were carried out in hip and knee arthroplasties, laparoscopic cholecystectomy, hernia, varicose veins, ENT surgeries, dental surgery, coronary artery bypass, and Caesarean section. No study till now has involved patients undergoing hysterectomy.[28]

CONCLUSIONS

Efficacy of oral PCM 1 g administered about 45 min before induction is comparable to IV PCM 1 g infused after induction with respect to time to first rescue analgesic, postoperative pain scores, postoperative 24 hours analgesic requirements, patient satisfaction scores and side effects in patients undergoing total abdominal hysterectomy. Considering the similar efficacy and side effect profile, but at a much lower cost of oral PCM, routine administration of oral PCM 45 min before induction may be an acceptable alternative to routine intraoperative IV PCM infusion.

Limitations of the Study

It was decided to give oral PCM at least 45 min before and IV PCM after induction of anaesthesia. These timings of drug administration could not be accurately controlled. However, the difference in timings of drug administration was clinically as well as statistically insignificant.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.
Financial or other competing interests: None.
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