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Postoperative Analgesia with Intravenous Paracetamol and Fentanyl and Intravenous Fentanyl Alone in Patients Under Going Laparoscopic Cholecystectomy: A Prospective Randomized Double Blind Study

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ABSTRACT
The aim of our study was to determine the post-operative analgesic effects of pre-emptive intravenous (IV) Paracetamol and the amount of reduction in fentanyl requirement. After approval from institutional ethics committee, 60 patients of ASA PS I and II were enrolled and assigned to 2 groups of 30 each. Group I (fentanyl) and Group II(fentanyl plus Paracetamol) who received either an IV NS or an IV injection of 1g Paracetamol 10 min before induction. Induction and maintenance protocol was similar in both groups. Both groups received IM diclofenac 75 mg 8 hourly. The postoperative pain relief was evaluated by a visual analogue scale (VAS) every two hourly and fentanyl requirement as rescue analgesic in the postoperative period for 24 hrs after surgery was recorded. The incidence of complications including PONV and sedation scores was measured postoperatively. We recorded VAS score was comparable in postoperative period in both groups except during first and second hour of surgery in which group II(receiving paracetamol) was lower. (4.9±1 Vs3.2±0.5 and 4.1±0.3Vs 3.0±0.4) the fentanyl requirement over first 24 hrs was also less in the group II(receiving IV paracetamol) (70.16±43.65 Vs39.33±35.51). The time requirement of first dose of rescue analgesic in the postoperative period was also significantly prolonged in the group receiving IV paracetamol (79.37±64.32 Vs173.33±73.88). There was no difference in the sedation scores and in the incidence of PONV in the two groups. Preemptive iv paracetamol provided effective and reliable pain control after laparoscopic cholecystectomy reducing immediate post-operative pain scores, decrease use of rescue opioid and the time to first request of analgesics.

INTRODUCTION

Although laparoscopy has improved surgical practice and markedly reduced incidence of complications, postoperative pain remains a challenge for anaesthesiologist particularly during first 24 hrs[1,2] Effective postoperative pain management not only improves patient satisfaction but also decreases hospital stay. It also reduces postoperative complications including hypoxemia, atelectasis, pneumonia, deep vein thrombosis, pulmonary embolism, psychological trauma, delay in improvement of bowel function, myocardial ischemia and infarction, urinary retention[3].Although opioid have been used for long period as standard analgesic in perioperative period, greater awareness of opioid related side effects shifted the trend towards using nonopioid analgesic including Paracetamol. Paracetamol not only avoids opioid related side effects but also have safety record with effectively alleviating postoperative pain. Its opioid sparing effect and absence of contraindication makes it more appealing.

So we aimed to study analgesic efficacy of intravenous Paracetamol for postoperative pain, to what extent narcotics requirement is reduced postoperatively and side effects with applying pre-emptive iv Paracetamol if any, in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

It was prospective randomized double-blinded study conducted in tertiary care institute after obtaining approval from institutional ethics committee. A total of 60 patients of ASA physical status I and II of either gender aged 18 to 60 years posted for elective laparoscopic cholecystectomy, who consented, were enrolled in study. Those patients with known allergy to study drugs, psychiatric disorder, liver or kidney disease, drug addiction, those taking steroids or NSAIDS chronically, patient with chronic pain syndrome, surgery duration more than 3 hours and refusal to give consent were excluded.

Computer generated random allocation was done and two groups comprising of 30 patients of each were made. All patients were investigated according to institutional protocol. All patients were visited a day prior to surgery and were explained about Visual Analogue Scale of pain. In the OR ,all standard monitors including ECG, NIBP, temperature probe, SpO2 and EtCO2 were attached and baseline parameters including heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. Documentation of hemodynamic parameters were done every five minutes.

An intravenous line was secured and crystalloid infusion was started. Patients in the group I (Group fentanyl) received 100 mL of normal saline and those in the group II (Group fentanyl plus paracetamol) received 100 mL of Paracetamol IV 10 minutes prior to induction.

After preoxygenation for three minutes, anaesthesia was induced with intravenous fentanyl 2 µg kg^{-1} and intravenous propofol 2.5mg kg^{-1} till the loss of response to verbal commands, orotracheal intubation was facilitated by i.v vecuronium 0.1 mg kg^{-1}. Following induction, a nasogastric tube was placed. Anaesthesia was maintained with 0.6-1% isoflurane and 66% nitrous oxide in oxygen. End tidal capnography ($EtCO_2$) was continuously monitored and mechanical ventilation with minute ventilation adjusted to maintain it between 34-36 mmHG. Supplemental neuromuscular blockade was achieved with intermittent boluses of intravenous vecuronium 0.01 mg kg^{-1}. Tachycardia, hypertension and clinically insufficient analgesia was controlled with supplementary doses of intravenous fentanyl 1 µg kg^{-1}. Intraoperative analgesic requirement were recorded for all patients. All patients were administered injection ondansetron (0.1 mg kg^{-1} i.v.) 20 min before the end of surgery for postoperative nausea and vomiting (PONV) prophylaxis Isoflurane was discontinued after the last skin suture and residual neuromuscular paralysis was reversed with intravenous neostigmine 0.05 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1}. After satisfactory recovery, the patients were extubated and shifted to the post-anaesthesia care unit (PACU).

Postoperatively, all patients received routine analgesic i.m Diclofenac 75 mg 8 hourly and rescue analgesic (i.v fentanyl 1 µg kg^{-1}). Patients were explained preoperatively about the 10-point visual analogue scale (VAS) with which the severity of postoperative pain was determined 0 corresponding to "no pain" and 10, corresponding to "worst imaginable pain". Ramsay sedation score was used to asses degree of sedation postoperatively where 1 is Anxious, agitated, or restless state while 6 indicates no response to a light glabellar tap/loud auditory stimulus. VAS score and sedation score was assessed postoperatively every 2 hrs for 24 hrs. Haemodynamic parameters were recorded at 0, 15, 30, 45 min, 1st hrs, 2nd hrs and thereafter every second hourly till 24 hrs in postoperative period. Postoperatively, all patients received routine analgesic i.m diclofenac 75 mg 8 hourly. Time for first dose of rescue analgesic in postoperative period and total rescue analgesic requirement in 24 hrs were recorded. Patients were given i.v fentanyl as rescue analgesic when their VAS pain score was more than 3, (1 µg kg^{-1}) if VAS <5 and 1 mcg kg^{-1} for VAS $\geq$5). The maximum pain scores at different time intervals (0, 15, 30, 45min, 1st hrs, 2nd hrs and there after every second hourly till 24 hrs in postoperative period) for each patient were recorded. At the end of the study, all data were compiled and tabulated and were analysed using SPSS software version 17 (SPSS Inc., Chicago) for Windows. The results of the quantitative variable were presented as mean and standard deviation while categorical variables were analysed as an absolute number and percentage. Sample size calculations were based on a previous study. Assuming an α value of 0.05 and power value of 80%, 28 patients were required, for better results, and in view of dropouts from the study, we took 60 patients (30 in each group). Data were reported as mean±SD. Statistical assessment included analysis of variance (ANOVA) and student's t-test for continuous data and VAS pain data. Fisher's exact t-test and chi-square test was used to analyse nominal data, $p<0.05$ was considered statistically significant.

RESULTS

Patients were screened and enrolled in study and all of them completed study without any dropout. Demographic parameters were comparable in both groups with respect to age, weight, sex, ASA physical status and duration of anaesthesia and surgery (Table 1). In group I, 6 patients required fentanyl in dose of 1 $\mu g\ kg^{-1}$ (Table 2). Although mean VAS score was almost similar in both groups, however it was less in group II after 2and 4 hrs of surgery which was significant (Table 3). The total dose of rescue fentanyl in recovery room was significantly higher in Group I than in Group II (Table 2) and the time to first rescue analgesic dose postoperatively was significantly less in Group I than in Group II (Table 2). Although number of patients requiring rescue dose of fentanyl was higher in group I compared to group II, this difference was not significant statistically (Table 2).

Hemodynamic parameters including heart rate, systolic blood pressure and diastolic blood pressure were comparable in both groups. Incidence of complications including postoperative nausea and vomiting as well as sedation was comparable in both groups (Table 2).

DISCUSSIONS

Perioperative pain can be of multiple subtypes and includes neuropathic, nociceptive, psychogenic, mixed or idiopathic pain depending on type of surgery[4]. Pain after laparoscopic surgery can also be of complex having multifactorial in origin which includes somatic pain of incision to visceral pain. Hence pain management perioperatively should have multimodal analgesia as suggested by Kehlet and Dahl[5]. It not only standardizes analgesia regimen but also provides flexibility in management based on individual patient's requirement considering allergy, previous analgesia experience, patient comorbidities and medications. (Paracetamol is considered safe and highly effective component of multimodal analgesia. It's opioid sparing effect as well as absence of any contraindication except, in severe liver disease makes it more appealing[6-8].

In present study, IV Paracetamol 1 gm was used as pre-emptive analgesic in laparoscopic cholecystectomy and its effectiveness was assessed based on intraoperative analgesic requirement, post-operative analgesia, post-operative fentanyl consumption, time for first rescue analgesic and frequency of side-effects. We found Paracetamol having opioid sparing effect when used as part of multimodal regimen prior to induction as pre-emptive analgesia. This is consistent with findings of previously conducted studies[9,10].

We did not observe any difference in analgesia amongst two groups as assessed by VAS scores although median pain score at 2 and 4 hrs interval postoperatively , as assessed by VAS score, was significantly lower in group II(Fentanyl plus Paracetamol group). Similarly time for dose of rescue analgesia was significantly lower in group I(Fentanyl only group) than in group II. This is likely because of initial loading dose of Paracetamol which provided higher plasma concentration. Study conducted by PIguet *et al.*[11] demonstrated correlation between higher plasma concentration of Paracetamol and its analgesic efficacy in healthy volunteers. Similar efficacy was also demonstrated by Juhl *et al.*[12] in patients following dental extraction. Our results are consistent with these results. (We found additive analgesic effect of Paracetamol and fentanyl combination with improved postoperative analgesia and decrease in opioid consumption. Having different sites of action ie Paracetamol on prostaglandins inhibition and opioids on opioid receptor may compliment analgesic effect of each other and make them an important part of multimodal analgesia[13].

Remy *et al.*[14]. in a metaanalysis concluded that paracetamol reduces post-operative morphine usage after major surgery. Few meta-analyses demonstrated efficacy of IV paracetamol in decreasing rescue opioid consumption and pain scores in patients undergoing total knee and hip arthroplasty[15,16] and bariatric surgery[17] Although paracetamol could reduce opioid consumption but average pain scores did not decrease significantly for joint replacement surgeries, as demonstrated by Guo *et al.*[18]in a meta-analysis. Toygar *et al.*[19] demonstrated effective use of paracetamol 1 g iv preoperatively , intraoperatively and every 6 h for 24 hrs in patients of lumbar discectomy surgery may provide a better postoperative analgesia compared to control group, will extend the time of the post-operative first opioid request and reduce post-operative use of total opioid.

Study conducted by Choudhari *et al.*[20] demonstrated usefulness of intravenous paracetamol for pre-emptive analgesia as adjunct to fentanyl for the

Table 1: Demographic and other characteristics of the patients

Variable	Group I(fentanyl) n = 30	Group II(Fentanyl plus Paracetamol) n = 30
Age (years) (Mean±SD)	36.06±9.39	37.36±11.69
Gender (male female)	17(56.67%):13(43.33%)	14(46.67%):16(53.33%)
Weight (in kg) (Mean±SD)	58.13± 6.08	58.10± 6.47
ASA physical status	17(56.67%):13(43.33%)	14(46.67%):16(53.33%)
Duration of anaesthesia (in hrs) (Mean±SD)	1.46±0.39	1.49±0.36
Duration of surgery(in hrs) (Mean±SD)	1.20±0.40	1.26±0.36

Table 2: Intraoperative and postoperative analgesia with side effects

Parameter	Group I (fentanyl) n = 30	Group II (fentanyl plus paracetamol) n = 30	Significance
Number of Patients requiring fentanyl (1µ kg^{-1}) intraoperatively	06	00	p = 0.009(significant)
Time of First dose (in min) (Mean±SD)	79.37±64.32	173.33±73.88	p = 0.0001(significant)
Number of doses required in 24 hrs (Mean±SD)	2.10±1.24	1.23±1.07	p = 0.0053 (significant)
Total amount fentanyl required in 24 hrs (in µ) (mean±SD)	70.16±43.65	39.33±35.51	0.0039 (significant)
Number of patients requiring rescue analgesia	24	18	0.09 (NS)
Incidence of PONV	09 (30%)	03(10%)	0.054 (NS)
Incidence of Sedation postoperatively	03 (10%)	00(0%)	0.083 (NS)

Table 3: Mean VAS score postoperatively at various time intervals (mean±SD)

Duration in hrs	Group I (fentanyl) n = 30	Group II (fentanyl plus paracetamol) n = 30
2	4.9±1	3.2±0.5*
4	4.1± 0.3	3.0±0.4*
6	3.2±0.5	3.0±0.2
8	2.8±0.3	2.5±0.5
12	2.7±0.3	2.4±0.4
24	2.4±0.4	2.4±0.3

*Indicates p<0.05

postoperative pain after laparoscopic cholecystectomy. They found decreased fentanyl consumption as well as decreased VAS score in immediate postoperative period although mean VAS score for pain was almost similar in both group. Findings of our study was similar to this study. We could not demonstrate decrease in incidence of side effects including PONV and sedation as one may expect following reduction in opioid requirement.

CONCLUSIONS

The result of our study suggested iv Paracetamol used for pre-emptive analgesia might be valuable medication to reduce opioid consumption and improving postoperative analgesia after laparoscopic cholecystectomy. IV Paracetamol provides satisfactory analgesia particularly in immediate postoperative period and reduces opioid consumption which may be particularly useful in patients prone to opioid-related complications .However, this was small scale study and larger better-designed studies are necessary to be able to make more definite recommendations.

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