Original Research Article

Pre-emptive analgesic effects of paracetamol infusion versus intramuscular ketorolac in patients undergoing elective laparoscopic cholecystectomy: A comparative study

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Abstract

Background: Minimally invasive surgery has displayed advantages over open surgery but still causes mild to moderate post-operative pain. Preemptive analgesia is one of the strategies of pain management which has beneficial effects on the occurrence and intensity of postoperative pain. **Method:** A total of 120 patients, aged 19-59 years with ASA grades of I/II were scheduled for elective laparoscopic cholecystectomy under general anaesthesia. They were randomized into two equal groups of 60 patients each. Group A received intravenous Paracetamol infusion (1gm) and group B received intramuscular Ketorolac (30 mg) 15 minutes before surgery. The two groups were compared statistically in terms of demography, intraoperative hemodynamics, postoperative pain (VAS), and need for rescue analgesic with tramadol. **Results:** Demographic profile and hemodynamic parameters were comparable in both the groups. The Mean VAS scores on the intergroup comparison post-operatively at 30 minutes, 1 hour, 3 hours and 6 hours were found to be lower for intramuscular ketorolac group and was statistically significant (p-value<0.05). Rescue analgesic when required was seen within 3-6 hours post-operatively and was used much earlier in paracetamol group. **Conclusion:** Pre-emptive intramuscular ketorolac (30 mg) is more effective in reducing postoperative pain scores (VAS) after laparoscopic cholecystectomy in the first 6 hours as compared to 1 gm intravenous paracetamol infusion.

Key Word: Intravenous paracetamol, Intramuscular ketorolac, Postoperative analgesia, preemptive analgesia, Laparoscopic cholecystectomy.

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INTRODUCTION

Laparoscopic cholecystectomy is the current gold standard for the treatment of gall stone disease[1]. Laparoscopic surgery has displayed advantages over open surgery, including less postoperative pain, smaller incisions, shorter postoperative ileus, reduced blood loss, reduced length of hospital stay, faster recovery, as well as earlier return to preoperative activity and work[2,3]. Studies have shown that laparoscopic surgery too causes postoperative pain in at least one-third of the patients and these patients have been seen taking more analgesics to alleviate pain[4]. The type of pain after laparoscopy differs from laparotomy which results mainly in parietal pain. Patients undergoing laparoscopy complain more of visceral pain[5]. Incisions of the operative ports also contribute to pain after laparoscopic cholecystectomy. Upper abdominal and shoulder tip pain after laparoscopy are probably caused by gas retained in the peritoneal cavity which may even take up to two days to get totally absorbed from the peritoneal cavity [6]. Different

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treatments have been proposed to relieve pain after laparoscopy. The choice of different drugs, the timing and route of their administration as well as the dosages are variable. Opioids and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are generally used for management of postoperative pain after laparoscopic cholecystectomy. Use of port site and intra peritoneal local anaesthetics have also been used for post-operative pain relief[7]. Preemptive analgesia is one of the strategies of pain management and is defined as an analgesic intervention before the surgical noxious stimulus arises, which has beneficial effects on the occurrence and intensity of postoperative pain[8]. The physical injury generates a complex stress response that contributes to the experience of postoperative pain. To cope the injury, the release of neurotransmitters, peptides, endocannabinoids, cytokines, and hormones occur, all of which operate interdependently through various nervous, endocrine, and immune processes[9]. Hence, preemptive analgesia partially decreases these influencing factors, which in turn, prevents the sensitizing effects of the surgical noxious stimuli. Paracetamol is the most commonly prescribed analgesic for the treatment of acute pain. Its major advantages over NSAIDs are its lack of interference with platelet function and safe administration in patients with a history of peptic ulcers or asthma[10]. Paracetamol(PCM) is considered to act as the inhibition of cyclooxygenase (COX) especially COX-2. NSAIDs act by inhibiting the cyclooxygenase enzymes, and by decreasing the peripheral and central prostaglandin production[6]. The onset of analgesia after intravenous paracetamol occurs within 5 minutes, peaking at 40–60 minutes, and lasting 4–6 hours[10]. Ketorolac acts by inhibiting both cyclooxygenase and lipo-oxygenase enzyme hence prevents synthesis of both prostaglandin and leukotrienes, and may enhance endogenous opioids release. When given intramuscular, the bioavailability of ketorolac approaches 100% and the time to peak concentration (Cmax) is 45-50 minutes[11]. Pain after laparoscopic cholecystectomy is treated optimally with local anesthetics, paracetamol, NSAIDs, and opioids if required[12]. This study was performed to compare the efficacy and safety of preemptive use of intravenous paracetamol and intramuscular ketorolac for management of postoperative pain after laparoscopic cholecystectomy.

MATERIALS AND METHODS

The prospective study was conducted at a peripheral Sub District Hospital in Kashmir, JandK, India from January 2017 to February 2019 and included a total of 120 patients scheduled for elective laparoscopic cholecystectomy under general anaesthesia. Age of the patients ranged between 19-59 years with body weight of 50-70 kg. The study was done on patients with American Society of Anesthesiologists grade I and II. Enrolled patients were divided into two equal groups (A and B) of 60 each by computer generated randomization. Exclusion criteria included acid peptic disease, pregnancy and lactation, known allergy to paracetamol or ketorolac, chronic analgesic dependency, significant coronary artery disease or ischemic myocardial disease, drug or alcohol abuse, chronic pulmonary disease, renal failure, hepatic dysfunction, hemorrhagic disorder, psychological disorder and those with acute cholecystitis. Group A (n=60) comprised of patients who received intravenous paracetamol infusion (1g) and group B (n=60) patients received intramuscular ketorolac (30 mg) 15 min before surgery. A day before surgery all the patients were explained details of Visual Analogue Scale (VAS of 0-100). Tab alprazolam 0.5 mg and tab. pantoprazole 40 mg were given orally night before surgery. In the operation theatre, intravenous line was established with 18G cannula and Ringer Lactate solution was started at the rate of 60-80 ml/h. Preoperative recording of heart rate (HR), noninvasive blood pressure (Systolic/Diastolic/Mean) and arterial oxygen saturation (SpO2) was carried out. All patients were premedicated intravenously with, midazolam (0.02 mg/kg). After being preoxygenated with100% oxygen for 3 minutes, patients were induced with intravenous propofol (1%) in dose of 2 mg/kg followed by atracurium 0.5 mg/ kg to facilitate the laryngoscopy and tracheal intubation. In addition to above mentioned monitoring end tidal carbon dioxide (ETCO2) monitoring was done intraoperatively. Anesthesia was maintained with isoflurane, nitrous oxide 60% in oxygen, and Atracurium in incremental dosages of 0.02 mg/kg when needed. Laparoscopic cholecystectomy was done using four standard ports at conventional sites (Umbilical 10mm, Epigastric 10mm, Right subcostal 5mm and Right lumbar 5mm). Surgery was completed in all the patients. A small 14 Fr tube drain was placed in sub-hepatic region in all the patients. Ports were removed under vision and port sites closed. A few minutes before the completion of surgery, inj. ondansetron 0.1mg/kg was given to patient for prevention of PONV. At the conclusion of surgery residual muscle paralysis was reversed with inj. neostigmine 50 µg/kg and inj. glycopyrrolate 10 µg/ kg intravenously. The patients were extubated following return of regular, rhythmic respiration when reasonably awake, after a gentle oral suction. Patients were transferred to post anesthesia care unit to monitor hemodynamic parameters, and any other adverse events such as nausea, vomiting and bleeding. Pain intensity was measured based on a 10-point Visual Analogue Scale (VAS; 0-10 cm; 0= no pain and 10= worst imaginable pain) at 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours and 24 hours post-operatively. Initial

dose of analgesic (Paracetamol intravenous infusion 1gm or intramuscular Ketorolac 30 mg) was given to the patients in the postoperative period when the pain intensity, as observed on the VAS, showed a score >4. Thereafter, Paracetamol 1g intravenous infusion or Ketorolac 30 mg intramuscular was given every 6 hours. If the VAS score was >4, rescue analgesia with intravenous tramadol 2mg/kg body weight was given to the patients. At the end of 24 hours, the total amount of patients requiring rescue analgesic and its timing in each group was noted. At the end of the study the data was collected and analyzed statistically. Chi-square test was used as a test of significance for data and a p-value of < 0.05 was considered significant.

OBSERVATIONS AND RESULTS

In our study, both the study groups were comparable in terms of mean age, weight, sex ratio and operative time (Table 1).

Table 1: Demographic characteristics of patients in two groups

Parameter	PCM Infusion	Intramuscular Ketorolac	P-value
Mean Age (Years)	42.81	40.97	0.7631
Sex Ratio (M: F)	27:33	26:34	0.5645
Mean Weight (Kg)	59.85	61.03	0.8769
Mean Operative Time (Minutes)	58.20	57.66	0.6892

[P < 0.05: Significant]

Baseline heart rate (HR) and mean arterial pressure (MAP) were comparable between the two treatment groups pre-operatively, just after intubation, at 5 min, 15 min, 30 min, 45 min, at the end of surgical procedures as well as at extubation (Table 2). No statistically significant difference was found between two groups (p-value>0.05). In the paracetamol and ketorolac groups, laparoscopic cholecystectomies were done in a mean operative time of 58.2 and 57.6 minutes respectively (Range 31-108 min).

Table 2: Preoperative and Intraoperative hemodynamic parameters.

Time	Mean Heart Rate (b/min)			M A P (mmHg)		
	PCM Infusion (n=60)	Intramuscular Ketorolac (n=60)	p-Value	PCM Infusion (n=60)	Ketorolac IM(n=60)	p-Value
Preoperative	81	83	0.9192	85	87	0.8987
Intubation	101	103	0.9223	105	106	0.9982
5 minutes	102	105	0.8768	100	101	0.9991
15 minutes	93	91	0.8665	92	93	0.9879
30 minutes	87	86	0.9811	87	86	0.9811
45 minutes	82	81	0.8874	86	85	0.9781
Extubation	109	112	0.8183	106	104	0.9541

[P < 0.05: Significant]

All patients were monitored for VAS in the post-operative period which was found to be persistently higher in paracetamol group as compared to ketorolac group. The Mean VAS scores on the intergroup comparison post-operatively at 30 min, 1 hour, 3 hours and 6 hours were found to be statistically significant (p-value< 0.05), however at 12 and 24 hours the difference was insignificant. [Table 3]

Table 3: Mean Visual analogue scale (VAS) pain scores in the two groups undergoing Laparoscopic Cholecystectomy.

Post-Op Time	Mean VAS (PCM Infusion)	Mean VAS (Intramuscular Ketorolac)	P-value
30 minutes	3.2	1.5	< 0.0001
1 hour	4.6	2.1	< 0.0001
3 hours	4.5	2.8	< 0.0001
6 hours	2.8	2.5	0.0393
12 hours	1.1	0.8	0.7291
24 hours	0.6	0.5	0.5631

[P < 0.05: Significant]

In our study, 49 (81.6%) patients in paracetamol group and 16 (26.6%) patients in the ketorolac group required a single dose of rescue analgesic most commonly within 3-6 hours post-operatively. The rescue analgesia was used much earlier in paracetamol group (Mean 108 minutes) as compared to the ketorolac group (Mean 227 minutes) and the duration of analgesia was longer with a single preemptive dose of intramuscular ketorolac than with paracetamol infusion (p-value < 0.05). None of our patients in both groups had any significant side effects and did not require any additional dose of rescue analgesia.

DISCUSSION

Despite many advances in laparoscopic cholecystectomy, postoperative pain is still a problem, and in most reports, up to 80% of patients ask for analgesics after laparoscopic cholecystectomy[13].Pain after laparoscopic surgery may vary in different individuals in quality and localization and is reported in several trials to be incisional, visceral, or referred. Visceral pain apart from arising due to tissue dissection, also occurs due to rapid distension of peritoneum because of CO2 insuffation which leads to traumatic traction of nerves and causes release of inflammatory mediators. This visceral pain occurs early in the postoperative period and its intensity decreases after first 24 hours[14]. Although opioids are the main choice for acute postoperative pain control, many side effects have been reported for them. NSAIDs and paracetamol have been used extensively as alternatives, and it seems that they are more effective for minor to moderate pain control postoperatively when have been used alone or in combination with opioids[15]. In the present study, a comparison of the efficacy and safety of preemptive use of intravenous infusion of paracetamol and intramuscular injection of ketorolac for management of postoperative pain after laparoscopic cholecystectomy was assessed. Both the study groups were comparable in terms of demographic characteristics and hemodynamic parameters (Tables1and2). Preemptive analgesia prevents the onset of the noxious stimulus, prevents central sensitization and therefore may have a role in reducing acute postoperative pain. In the present prospective randomized study preemptive use of intramuscular ketorolac was more effective in reducing postoperative pain scores at 30 minutes, 1 hour, 3 hours and 6 hours as compared to paracetamol infusion which was not as much effective. No significant difference was found between the two groups at 12 and 24 hours of surgery. All the patients who required rescue analgesia (65 in both groups) did so within first 6 hours of surgery, however it was used much earlier in paracetamol group (Mean 108 minutes) as compared to the ketorolac group (Mean 227 minutes) and the duration of analgesia was longer with a single preemptive dose of intramuscular ketorolac than with paracetamol infusion. Clinically, paracetamol has analgesic efficacy comparable to aspirin but it is less effective than other NSAIDs[16]. Rastogi B *et al.* compared the efficacy of preemptive intravenous paracetamol versus intravenous ketorolac for post-operative analgesia after laparoscopic cholecystectomy and concluded that ketorolac exerted superior postoperative analgesia in comparison to paracetamol without any significant side effect[6]. These results are consistent with our study even though the route of ketorolac administration in our study was intramuscular and that in study by Rastogi B *et al.* was intravenous. The reason for this consistent analgesic effect despite the different route of its administration is that ketorolac is highly protein bound, has a limited volume of distribution, and has a terminal half-life of approximately 5-6 hours regardless of the route of administration[17]. When given intramuscular, the bioavailability of ketorolac approaches 100% and the time to peak concentration (Cmax) is 45-50 minutes [11]. Khan MR *et al.* studied the effect of preemptive dose of ketorolac, diclofenac and tramadol in laparoscopic cholecystectomy patients for postoperative pain and hemodynamic changes. They concluded that postoperative pain can be managed by preemptive use of diclofenac, ketorolac, and tramadol for the first 24 hours with little or no supplementation of low dose intravenous pethidine. The analgesic efficacy of ketorolac and tramadol is same and better than diclofenac. There was no significant complication in using the drugs[18]. Boccara *et al*. compared preemptive use of proparacetamol and ketoprofen for providing analgesia after laparoscopic cholecystectomy and concluded that preoperative administration of NSAIDS such as ketoprofen has better postoperative analgesia after laparoscopic cholecystectomy as compared to proparacetamol and postoperative use of both these drugs[19]. Recently, operative grading system for laparoscopic cholecystectomy was proposed by Surgrue M *et al*., to classify difficult cholecystectomy on the basis of intraoperative predicators. The scoring system (Score 0-10) incorporates key operative findings including appearance of the gall bladder, presence of gall bladder distension, ease of access, potential biliary complications and time taken to identify cystic duct and artery to classify the difficult cholecystectomy from mild to extreme[20]. A number of studies report that NSAIDs have better postoperative analgesic effect after laparoscopic cholecystectomy as compared to paracetamol or its prodrug[6,15,18,19]. The flaw in most of these studies including in the present study is that the operative difficulty scores were not corelated with the postoperative VAS scores. It cannot be ruled out that the cases with difficult internal anatomy demanding excessive dissection of tissues have higher VAS scores and require a rescue analgesic.

CONCLUSIONS

Pre-emptive intramuscular ketorolac (30 mg) is more effective in reducing postoperative pain scores (VAS) after laparoscopic cholecystectomy in the first 6 hours as compared to intravenous paracetamol infusion (1 gm). However both regimes were equally effective in doing so at 12 hours and thereafter. Intramuscular ketorolac is

better than paracetamol infusion in reducing the need and prolonging the time for need of a rescue analgesic.

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