Journal of Applied Pharmaceutical Research
Volume 11 Issue 2, Year of Publication 2023, Page 06 – 11
DOI: 10.18231/j.joapr.2023.11.2.6.11

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Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR

www.japtronline.com *ISSN: 2348 – 0335*

COMPARISON OF ANALGESIC EFFECT OF PREOPERATIVE INTRAVENOUS PARACETAMOL V/S KETOROLAC IN LAPAROSCOPIC CHOLECYSTECTOMY UNDER GENERAL ANESTHESIA

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Article Information
Received: 13th June 2022
Revised: 19th March 2023
Accepted: 12th April 2023
Published: 30th June 2023

Keywords
Laparoscopic cholecystectomy, intravenous Paracetamol, intravenous Ketorolac, preemptive analgesia.

ABSTRACT
Background: Preemptive analgesia is pain control before inciting a noxious stimulus. Upper abdominal and shoulder tip pain after laparoscopy is probably caused by gas retained in the peritoneal cavity. Pain relievers were given before the incision. **Aim:** The study was planned to compare the Analgesic effect of pre-operative intravenous Paracetamol versus Ketorolac in laparoscopic cholecystectomy under general anesthesia. The difference in the need for first rescue analgesia and total dose of rescue analgesics in 24 hours postoperative period in both groups was assessed. **Methods:** This Hospital Based Double Blinded Randomized Interventional Study was carried out in ASA I and II, aged 18 to 60 years in patients undergoing elective laparoscopic cholecystectomy under general anesthesia. **Group A** received an Intravenous infusion of paracetamol 1gm (100ml) and **Group B** received an intravenous infusion of ketorolac 30mg (1ml) diluted in 99 ml 0.9% normal saline. In both groups, analgesic was given over a period of 30 minutes, 30 min before induction of general anesthesia. The chi-square test and Student's t-test were used for the statistical analysis. **Results:** The time for the demand of the first rescue analgesia was219±81.0 min in group A and 350±175.1min in group B, with a p-value < 0.001. The demand for rescue analgesics was more in Group A in contrast to Group B. **Conclusion:** We concluded with our study, pre-emptive analgesia with 30mg ketorolac is better than 1 gm paracetamol. The time for rescue analgesia is prolonged, the number of rescue analgesics demanded is reduced, VAS score was significantly lower when ketorolac was used.

INTRODUCTION
Laparoscopic cholecystectomy is a minimally invasive procedure that is increasingly performed in the day-care unit. Laparoscopic Cholecystectomy can present pain as visceral, parietal and referred shoulder tip pain. The main sources of pain include pain from incision sites (50-70%), Pneumoperitoneum

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(20-30%), and post cholecystectomy wound (10-20%) within the liver causing visceral pain. Postoperatively commonly pain is felt in the right upper quadrant and port sites [1]. Analgesia given to minimize pain, speed up the healing process and avoid complications related to pain. Early pain management interventions influence long-term outcomes and are an integral component of postoperative care for the patient [2]. A multimodal analgesia regimen, with a combination of opioid and non-opioid analgesic drugs, is often used to target several mechanisms involved in causing post-operative pain [3]. Pre-emptive analgesia assumed to reduce the risk of developing persistent postoperative pain. This term suggests that an analgesic given before a painful stimulus will prevent or reduce subsequent pain. A noxious injury, such as surgery in which tissue damage occurs, causes a hypersensitivity response that initially peaks and then decreases over time. This occurs because of a central change other than the myelinated A-δ and unmyelinated C fibers stimulated by the painful insult. This second mechanism of central sensitization involves a change in the excitability of neurons in the spinal cord. This progressive change in the spinal cord excitability results in a "wind-up" phenomenon [4] that can manifest as a hypersensitivity state that outlasts the duration of the initial injury [3,5].

Nonsteroidal anti-inflammatory (NSAIDs) drugs act by inhibiting the cyclooxygenase enzymes, and by decreasing peripheral and central prostaglandin production. They not only reduce the inflammation that occurs due to tissue injury and decrease prostaglandin production but also attenuate the response of the peripheral and central components of the nervous system to noxious stimuli, leading to lesser peripheral and central sensitization. These properties seem to make NSAIDs an ideal drug to use in a pre-emptive fashion [6]. The action of paracetamol is largely unclear. A central anti-nociceptive effect, inhibition of a central nervous system COX-2, inhibition of a putative central cyclooxygenase 'COX-3' that is selectively susceptible to paracetamol, and modulation of inhibitory descending serotonergic pathways can be the potential pathways. It also prevents prostaglandin production at the cellular transcriptional level, independent of cyclooxygenase activity. Paracetamol is therefore an effective postoperative analgesic, with potency slightly less than a standard dose of morphine or the NSAIDs yet important differences exist; notably, paracetamol displays weak anti-inflammatory activity, few or no gastrointestinal, and only a small dose-dependent alteration of platelet function [7]. Ketorolac like most NSAIDs has anti-inflammatory/ antipyretic/analgesic effects by the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX). It is a non-selective cyclooxygenase inhibitor and mainly acts peripherally than centrally [8].

MATERIAL AND METHODS

The present study was carried out in a tertiary care institute after obtaining permission from the ethics committee (180/MC/EC/2020) and review board and a written consent form from the patient obtained. It was a prospective, randomized, interventional study wherein subjects were allocated in 2 groups of 30 pts each (N=60) by sealed enveloped method. A minimum sample size of 30 each was taken by convenience sampling technique. Patients who underwent elective laparoscopic cholecystectomy under general anesthesia, of ASA Class I and II, of either sex, age group from 18-60 years with bodyweight ranges between 50-70kg were to be included. Patients unwilling to participate, H/O Bleeding diathesis, chronic pulmonary disease, cardiovascular, renal disorder, and psychological disorder, and history of study drugs allergy, were excluded.

The study protocol, procedure and likely complications were explained to the patients in the pre-anesthetic check-up and written informed consent was taken. In the pre-operative room, baseline vital parameters, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), oxygen saturation (SpO2), and temperature were recorded. Intravenous access with 18G was secured and infusion of the study drug i.e. paracetamol or ketorolac was given intravenously over 30 min. The study drugs were prepared by an anesthesiologist and their identity was kept hidden to the observer (the anesthetist who collects the study data). Total volume 100ml each of drug samples were used for the study in both the groups. The patient shifted to the operation theatre [9]. The patient was pre medicated with inj. metoclopromide 0.1mg/kg, inj. glycopyrrolate 10ug/kg, inj. midazolam 0.1mg/kg and inj. fentanyl 2µg/kg. IV fluid RL was given according to the rule of 4-2-1 throughout the procedure with correction of fasting deficit. Anesthesia was induced with inj propofol 2mg/kg and inj. succinyl choline 1.5mg/kg and tracheal intubation was done. Anesthesia was maintained with 1-2% sevoflurane and N2O:O2 (60%-40%). Inj Atracurium 0.5mg/kg loading dose and its maintenance dose of 0.1mg/kg were given when required. End-tidal CO2 (ETCO2) was maintained between 35-45 mm of Hg. Vitals were maintained within a 20% variation of pre-operative values. At the end of the surgery, anaesthetic agents were stopped, and Inj. Ondansetron 0.1mg/kg iv given. Thorough oropharyngeal suction was done before extubation. Residual muscle relaxation reversed with Inj. neostigmine 0.05mg/kg and Inj. glycopyrrolate 0.01mg/kg IV. After fulfilling the extubation criteria, the patient was extubated. The patient was shifted to post anaesthetic care unit wherein hemodynamic parameters, VAS Score, and side effects {post-operative nausea, vomiting} were monitored. Inj. Tramadol 50mg iv was given as rescue analgesic. The time for the first dose of rescue analgesic with the total number and dosage of rescue analgesic in 24 hours noted.

ANALYSIS OF DATA

Obtained data were entered in the excel spread sheet and variables were coded accordingly. Statistical analysis was performed with the SPSS (Statistical Package for the Social Science), version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). All the qualitative data were analyzed using the chi-square method and the quantitative method by unpaired t test. Results obtained in Mean ± SD. P values < 0.05 were as statistically significant and < 0.001 were taken as highly significant.

RESULTS

The two groups were comparable based on demographic and hemodynamic parameters. The mean of 1st time of rescue analgesia was significantly higher in group B as compared to group A 219±81.0min vs i.e 350±175.1min group B is better than group A with p-value < 0.001. The total dose of rescue analgesia consumed was significant higher in group A than in group B. Occurrence of postoperative nausea and vomiting was higher in group A than in group B. Visual Analog Score (VAS) was significantly higher in Group A as compared to Group B at extubation,2hr,12hr and highly significant at 4hr, except at 6 hours the VAS score was high in group B with a P value of 0.001 (highly significant) but there was no significant difference observed further. Nausea was observed in 10% of cases in Group A null at group B (P=0.236 NS) and Vomiting was observed significantly more in group A as compared to group B (23.33% vs 0%).

Table 1: Comparison of demographic parameters of both groups

Demographic Parameter	Group A	Group B	p value
Age (Years)	41±11.80	38.50±11.87	0.417 NS
Gender (M:F)	4: 26	8:22	0.333 NS
Weight (kg)	57.33±6.95	55.47±5.07	0.239 NS
Duration of surgery (min)	49.57±9.04	48±8.23	0.486 NS

(Mean±SD)

DISCUSSION

The most predominant complaint following laparoscopic procedures, in the early postoperative period, is pain. The cause of pain might be because of chemical irritation of the peritoneum, distension of the abdomen, soft tissue injury, or incisional trauma at the trocar entry sites. In an attempt to decrease the severity of pain following laparoscopic procedures, many techniques have been adopted for adult patients such as using low inflation pressure, local anaesthetics infiltration of port sites, and intraperitoneal instillation.

Table 2: Comparison of the hemodynamic parameters of both groups

Hemodynamic Parameters	Group A (Mean±SD)		Group B (Mean±SD)	
	MAP (mm of hg)	HR (bpm)	MAP (mm of hg)	HR (bpm)
Baseline	95.55±6.67	82.53±7.45	95.4±7.65	83.67±8.57
Intraoperative	102.77±6.42	88.73±9.11	99.93±7.12	91.47±9.99
At Extubation	101.97±6.82	94.73±8.03	102.56±6.57	96.33±7.88
2 hours	88.6±5.78	80.47±7.4	91.03±6.14	81.97±4.49
4 hours	88.23±6.53	81.27±5.81	89.23±5.44	77.13±15.07
6 hours.	92.19±7.95	78.47±6.4	89.64±5.72	80.83±4.79
12 hours	92.42±7.95	78.6±5.33	91.91±6.7	77.33±4.3
18 hours.	90.78±6.23	77.13±4.48	91.04±6.96	78.43±5.76
24 hours	92.17±7.82	74.47±5.08	91.49±6.95	76.27±4.46

SD- Standard Deviation, MAP-Mean arterial pressure, HR-Heart rate, bpm-beats per minute

Table 3: Comparison of the VAS at different follow up between the groups

VAS SCORE	Group A			Group B			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P value
At extubation	30	0.93	0.98	30	0.43	0.50	0.016S
2 hours	30	2.07	1.11	30	1.40	0.56	0.005S
4 hours	30	3.50	1.53	30	1.77	0.43	<0.001S
6 hours.	30	1.77	1.36	30	3.67	1.42	<0.001S
12 hours	30	3.10	1.75	30	1.83	1.66	0.018S
18 hours.	30	1.27	1.44	30	0.77	0.86	0.107NS
24 hours	30	0.37	0.56	30	0.30	0.47	0.617NS

Table 4: Distribution of the cases according to analgesic requirement

Need for rescue analgesic	Group A (n = 30)	Group B (n = 6)	P value
Time for need of first rescue analgesic (min) Mean ± SD	219±81.0	350±175.1	<0.001(S)
Mean consumption of rescue analgesics (mg of tramadol) in 24 hours	2250	1450	<0.001(S)

Table No.5 Distribution of the cases according to Side effects

Side effects	Group A		Group B		Total		p value
	N	%	N	%	N	%	
Nausea	3	10	0	0	3	5	0.236 NS
Vomiting	7	23.33	0	0	7	11.67	0.016 S

The use of parenteral opioids provided adequate analgesia, but the amount of drug required was higher, which was resulting in complications like respiratory depression, postoperative nausea and vomiting, constipation, and pruritus that need adequate postoperative monitoring thereby increasing the hospital stay. Planning for postoperative pain management should begin in the preoperative period. Patient education regarding the degree of pain that they expect, the pain assessment tools, and the modalities of pain management that are utilized should reduce the patient's anxiety and the fear of unrelieved pain. Reduced patient anxiety reduces the incidence of postoperative pain. In addition, patients have to be made aware of the importance of communicating their analgesic needs. Pre-emptive analgesia prevents the onset of the noxious stimulus and prevents central sensitization. Therefore, the concept of pre-emptive analgesia may have a role in reducing not only acute postoperative pain but also chronic pain. NSAIDs are helpful in the management of the postoperative pain after laparoscopic cholecystectomy which is mainly visceral experienced due to rapid distension of the peritoneum because of CO_2 insufflation which leads to traumatic traction of nerves and causes the release of inflammatory mediators which cause pain [10]. This visceral pain occurs early in the postoperative period and its intensity decreases after the first 24 h. NSAIDs were found the best alternative non-opioid agents for pain relief after laparoscopic cholecystectomy by Boccara et al. [10] and Bhawana et al.[9] may be because the pain in this surgery is mostly dependent on the release of inflammatory mediators. As shown in table 1, age group of the patients was 18 to 60 year similar to Bhawana et al.[9] Medina et al. [11], and Heo et al.[12] In our study in both group number of female cases were more than male similar to Heo et al.[12], male cases were more in Medina et al.[11] and almost equal in number in a study by Bhawana et al.[9].

The hemodynamic parameters were comparable in both groups with no statistically significant difference preoperatively, at extubation, 2,4,6,12,18 and 24hour [Table 2].

As shown in Table 3, VAS scoring done for 24hrs and the results were significant until 18hrs. Pain assessment in Bhawana et al.[9] done till 6hr after surgery, and till 24hr in Medina et al and Bong et al. similar to our study but time points were different. The rescue analgesic opioid used was tramadol in study by

Bhawana et al. [9] similar to our study (Table 4) but was fentanyl PCA by Heo et al.[12] and morphine in Medina et al. [11]. In our study, the time of need to give first rescue analgesia was significantly ($p < 0.001$) less in paracetamol group (219 min) compare to the ketorolac group (350 min) similar to the study conducted by Bhawana et al. [9] but lesser in both groups may be due to longer duration of surgery in their study. Contrary to these results, time of need to give rescue analgesia was similar in both study groups in study by Medina et al.[11] and Heo et al. [12].

Mean consumption of rescue analgesics was significantly higher in paracetamol group (2250 mg) than ketorolac group (1450 mg), results were similar to study by Bhawana et al. [9]. Contrary to this consumption of rescue analgesia was comparable in both groups in studies by Medina et al.[11] and Heo et al. [12].

Patients with side effect like nausea and vomiting was more in paracetamol compare to ketorolac group similar to Bhawana et al. [9] as shown in table 5. In the present prospective randomized double-blind study pre-emptive use of IV ketorolac was effective in reducing postoperative pain scores and amount of rescue analgesic in immediate postoperative period after laparoscopic cholecystectomy whereas IV paracetamol was not much effective in doing so. The difference in results in comparison to other studies may be due to use of local anaesthetic infiltration at port site by medina et al. use of large dose of studied agents with fentanyl PCA by Heo et al.[12]. A different route or dosage of analgesic drug administered, different intra-operative analgesic used, different inflation pressures, duration of surgery, nature of surgery, intra-abdominal spillage of bile, different sample size, and methodology, etc.

CONCLUSION

We conclude that preemptive use of intravenous ketorolac 30mg is better as compare to intravenous paracetamol 1g for post-operative pain relief for patients undergoing laparoscopic cholecystectomy. Ketorolac was found to be better analgesic when compared to intravenous paracetamol with reduced use of rescue analgesia and side effects. The limitation of our study were that we did not evaluate sedation score, recovery time and satisfaction score after surgery. Furthermore, our sample size was small and inclusion of a particular surgery make it difficult to impose outcome results on different type of surgery. Side effect nausea can also be due to postoperative pain and use of tramadol.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Dr. Mahipal and Dr. Budhram planned the study, did the literature survey and collected the data. Dr. Manisha and Dr. Chetali helped in designing the manuscript and collecting the data. All the authors helped in proofreading and reviewing the final manuscript.

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