Comparative Efficacy of Pre-emptive Analgesic Effects of Intravenous Paracetamol and Intravenous Ketorolac in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract

Introduction: Accurate management of pain is one of the most important challenges of health care providers and one of the most important concerns of the patients in postoperative period. This study aims to compare the pre-emptive analgesic effects of intravenous paracetamol with intravenous ketorolac in patients undergoing laparoscopic cholecystectomy under general anesthesia.

Methods: This study was conducted atWestern Regional Hospital, Pokhara Academy of Health Sciences and adult patients undergoing laparoscopic cholecystectomy under general anesthesia were included in our study. Seventy patients were divided into two groups of 35 each:group P – Paracetamol group, where patients receivedintravenous paracetamol andgroup K – where patients received intravenous ketorolac as pre-emptive analgesia 30 minutes before induction of anesthesia. The incidence of pain in post-operative period was assessed using Numerical Rating Scale (NRS).

Results: There was no significant difference in demographic and hemodynamic variables,the incidence of mild pain was greater and moderate pain was lesser in post-operative period in group paracetamol than group ketorolac but these differences were statistically not significant except at 30 minutes after surgery (p=0.04).NRS score of pain was significantly lower in paracetamol group {median (interquartile range) – 2(1,3)} than in ketorolac group {3(2,3), p=0.006}. The consumption of pethidine in post-operative period between the two groups was comparable (p=0.269)

Conclusion: Pre-emptive analgesia with injection paracetamol provides better analgesia than injection ketorolac in first 24 hours of post-operative period in patients undergoing laparoscopic cholecystectomy but these were statistically not significant except at 30 minutes after the end of surgery.

Keywords: Ketorolac, laparoscopic cholecystectomy, paracetamol, pre-emptive analgesia

Introduction

Pain is not just a sensory modality but is a subjective sensation and inevitable experience too.[1] 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. Between one third and half of all surgical patients experience significant post-operative pain.[2]

Post-operative pain is not only an unpleasant experience but is also associated with physiological and psychological

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responses. In addition to the distress and discomfort, poorly managed postoperative pain causes respiratory dysfunction, decreased gastrointestinal motility, neuroendocrine and metabolic changes.[3] The stress response to surgery aggravates catabolism. Adequate post-operative analgesia is associated with less physiological derangement which results quicker recovery and ambulation.[4] The pre-operative administration of opioids, NSAIDs. and local infiltration of the surgical area with local anesthetic markedly decrease the degree of postoperative pain.[5]

Transmission of pain signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways. Sensitizations of these pathways cause amplification of post-operative pain and may lead to development of chronic pain.[6] Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce this sensitization.[7] Pre-emptive analgesia helps to subside pain, decreases analgesic requirements and decrease morbidity. This promotes early recovery and shortens the length of hospital stay.[8]

The most common method of managing pain following surgery is the use of intramuscular (IM) opioids and it may result in respiratory depression, post-operative nausea vomiting (PONV), urinary retention, ileus and addiction. Local anesthetics can cause systemic and localized toxic reactions usually as a result of accidental intravascular or intrathecal injection or administration of an excessive dose.[9]

Intravenous Ketorolac and Paracetamol are effective analgesics, cost effective and have been used instead of opioids, adjunctively or pre-emptively to reduce opioid consumption, with the aim of reducing opioids related adverse effects. Non-steroidal anti-inflammatory (NSAIDs) drugs act by inhibiting the cyclooxygenase enzymes, and by decreasing the 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 ideal drugs to use in a pre-emptive fashion.[10]

Ketorolac acts by inhibiting both cyclooxygenase and lipooxygenase enzyme hence prevents synthesis of both prostaglandin and leukotriene's, and may enhance endogenous opioids release. [10]

Paracetamol is a non-opioid agent, active metabolite of phenacetin. It primarily acts upon the central nervous system by way of central cyclooxygenase inhibition, and has an indirect influence on the serotoninergic system. Paracetamol is an effective analgesic which easily passes through the brain barrier. It is metabolized in the liver by conjugation and hydroxylation to inactive metabolites and it is excreted from kidney.[11]

This study has not done in hospital settings and if encouraging results come from this study, it supports to decrease the notorious side effect associated with narcotic by decreasing its consumption in postoperative period. Our study was done to compare the pre-emptive analgesic effects of intravenous paracetamol with ketorolac in patients undergoing laparoscopic cholecystectomy in Western Regional Hospital, Pokhara Academy of Health Science.

Methods

This hospital based cross sectional study was conducted for 4 months between March 2023 to June 2023 at Western Regional Hospital, Pokhara Academy of Health Sciences. Sample size was calculated by using the formulas n=2(Zα +Zβ)2× SD 2/ d2, Where n= number of sample, Zα = 1·96 (type 1 error 0·05) ,Zβ = 0.842 (power of 80%)Based on the previous study conducted SD as 5.14, Difference in mean as 4.[12] The sample size was 25.92 in each group. To empower the study 30 patients in each group was taken into consideration. We initially calculated the required sample size to be 60. However to account for potential non response and ensure robust statistical power, we decided to increase the sample size to 70. This adjustment was made to mitigate the risk of data loss due to non-responders and maintain the integrity of our result. A total number of 70 adult patients between the age of 15 to 60 years, American Society of Anesthesiologists (ASA) status I and II who were scheduled to undergo elective laparoscopic cholecystectomy under general anesthesia, with duration of surgery less than 120 minutes and kept in postoperative ward for 24 hours after surgery were included in our study. Patients who had history of allergic reactions to paracetamol or ketorolac, pregnant females and patients who refused to give consent were excluded from our study. The written informed consent was taken from the participants. Seventy patients were randomly allocated into two groups of 35 patients each, according to simple randomization with computer-generated random numbers using Microsoft Excel 2013, group P- Paracetamol group, and group K - Ketorolac group. Group P patients received 15mg/kg (not exceeding 1gm) of Paracetamol and group K Patients received 0.5 mg/kg (not exceeding 30mg) of Ketorolac in 100 ml of saline and wasgiven intravenously in 30 minutes before inductionof anesthesia.

After arrival to the operation theatre (OT), pulse oximetry, electrocardiography (ECG), end tidal carbon dioxide ($ETCO_2$) monitoring and non-invasive blood pressure (NIBP) monitoring were started in the patient. Hemodynamic parameters - heart rate and mean arterial pressure were recorded 5 minutes before induction of anesthesia (baseline) and at 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes after induction of anesthesia. The time interval between first surgical incisions to closure of incision was noted as 'duration of surgery.

For post-operative analgesia, injection paracetamol 1 gm 6 hourly and injection ketorolac 30 mg 8 hourly were given intravenously to all the patients. Numerical Rating Scale(NRS) for pain was used for post-operative pain assessment.Patients had to rate their pain on a defined scale of 0 to 10, where 0 is 'no pain' and 10 is the 'worst pain imaginable'. Pain was classified as 'no pain' (NRS score 0), 'mild pain' (NRS score 1-3), 'moderate pain' (NRS score 4-7) and 'severe pain' (NRS score 8-10.NRS scores for pain of the patients were recorded in the post-operative period at 15 minutes, 30 minutes, 1 hour, 4 hours,12 hours and 24 hours after completion of surgeryand if patient complained of moderate to severe pain, they were treated with injection pethidine 1 mg/kg with promethazine 0.5 mg/kg given intramuscularly. Total consumption of pethidine in 24 hours was recorded.

The duration of time from the end of surgery to administration ofpethidine for the first timein post-operative period was recorded.

The collected data were analyzed by means of statistical software SPSS version 23 (SPSS, Chicago, IL, USA).Normality of quantitative data was determined using Shapiro Wilk test. Student t test was used for comparison ofnormally distributed quantitative variables like age, weight, heart rate and mean arterial pressure and they were presented as mean ± standard deviation. Non parametric test like Mann Whitney test was used for comparison of non-normally distributed quantitative data like NRS score for pain,total amount of pethidine consumption and time for first dose of rescue analgesic in post-operative in the two groupsand they were presented as median (inter quartile range). Comparison of categorical variables like gender, ASA status and pain category at various time points between the two groups was done using Chi square test or Fisher's exact test. The p-value of less than 0.05 was taken as statistically significant.

Results

There was no significant difference in the demographic variable like age, weight, gender distribution and ASA status between the two groups (table 1).

Table 1: Demographic data in two groups

Demographic Variables	Group P (n=35)	Group K (n=35)	P value
Age (years)	45.03±10.81	44.54±12.16	0.860
Sex			
Male	7 (20.0%)	13 (37.1%)	0.112
Female	28 (80.0%)	22 (62.9%)	
Weight (kg)	61.60±13.01	66.54±10.99	0.091
ASA status			0.314
I	21 (60.0%)	25 (71.4%)	
II	14 (40.0%)	10 (28.6%)	

Data presented as mean±SD or number (percentage)

Comparison of hemodynamic variation of heart rate and mean arterial pressure at baseline and various time points after induction of anesthesia between the two groups demonstrated no statistically significant difference (table 2).

Table 2: Hemodynamic variables: Heart Rate and MAP between the two groups

Heart Rate	Group P (n=35)	Group K (n=35)	P value
Baseline (5 minutes before induction of anesthesia)	83.71±16.71	83.69±14.37	0.994
After induction of anesthesia			
At 5 minutes	83.69±14.12	88.00±12.83	0.184
At 10 min	82.63±15.16	84.06±11.03	0.654
At 15 min	80.8±14.12	85.80±14.82	0.155
At 30 min	84.74±15.39	83.23±12.30	0.654
At 45 min	84.51±16.812	86.34±13.34	0.616
At 60 min	81.68±15.21	84.64±9.72	0.397
At 75 min	81.18±11.44	82.64±9.72	0.733
At 90 min	86.50±11.31	81.00±8.78	0.317
At 105 min	93.80±9.73	84.40±10.92	0.189
At 120 min	89.50±6.64	76.50±15.16	0.167
Mean arterial pressure (MAP)			
Baseline (5 minutes before induction of anesthesia)	95.57±14.21	94.94±15.19	0.859
After induction of anesthesia			
At 5 min	89.49±17.57	92.11±16.88	0.525
At 10 min	86.31±19.31	86.03±15.07	0.946
At 15 min	88.86±13.63	90.60±15.64	0.621
At 30 min	90.79±14.24	90.34±12.26	0.888
At 45 min	91.09±21.41	90.83±10.24	0.949
At 60 min	91.52±14.96	92.82±11.87	0.714
At 75 min	87.92±18.55	96.36±15.21	0.214
At 90 min	89.38±13.85	83.75±11.35	0.389
At 105 min	91.40±7.96	80.75±11.35	0.141
At 120 min	97.00±14.07	85.33±17.24	0.307

Data presented as mean±SD

The incidence of mild pain was greater and moderate pain was lesser in group P than group K at 15 minutes, 30 minutes, 1 hour, 4 hours, 12 hours and 24 hours after surgery but these differences were statistically not significant at all-time points except at 30 minutes after surgery (p=0.04). The incidence of moderate pain was least (5.7%) at 30 minutes and 24 hours post-surgery in group P and 8.6% at 24 hours post-surgery in group K.

Table 3: NRS score for pain category in two groups

Pain category in post-operative period	Group P (n=35)	Group K (n=35)	P value
At 15 Minutes			
1-3(Mild pain)	30 (85.7%)	29 (82.9%)	0.743
4-7(Moderate pain)	5 (14.3%)	6 (17.1%)	
At 30Minutes			
1-3(Mild pain)	33 (94.3%)	27 (77.1%)	0.040*
4-7(Moderate pain)	2 (5.7%)	8 (22.9%)	
At 1 Hour			
1-3(Mild pain)	31 (88.6%)	28 (80.0%)	0.324
4-7(Moderate pain)	4 (11.4%)	7 (20.0%)	
At4 Hours			
1-3(Mild pain)	28 (80.0%)	24 (68.6%)	0.274
4-7(Moderate pain)	7 (20.0%)	11 (31.4%)	
At 12 Hours			
1-3(Mild pain)	31 (88.6%)	30 (85.7%)	>0.05
4-7(Moderate pain)	4 (11.4%)	5 (14.3%)	
At 24 Hours			
1-3(Mild pain)	33 (94.3%)	32 (91.4%)	>0.05
4-7(Moderate pain)	2 (5.7%)	3 (8.6%)	

Data presented as number (percentage), *Statistically Significant

The NRS pain score was significantly higher in ketorolac group than paracetamol group at 30 minutes after the end of surgery (median (IQR) – 3(2,3) in ketorolac groupand 2(1,3) in paracetamol group, p=0.006) (table 4).

Table 4: Distribution of NRS score of pain in two groups

NRS score of pain in post-operative period at	Group P (n=35)	Group K (n=35)	P value
1. 15 minute after surgery	2 (1,3)	2 (0,3)	0.778
2. 30 minute after surgery	2 (1,3)	3 (2,3)	0.006*
3. 1 hour after surgery	2 (2,3)	3 (2,3)	0.071
4. 4 hours after surgery	3 (2,3)	3 (2,4)	0.443
5. 12 hours after surgery	2 (1,3)	2 (1,3)	0.525
6. 24 hours after surgery	2 (2,3)	2 (1,3)	0.680

Data shown as median (IQR). * Statistically significant

The dose of pethidine given for moderate to severe pain in post-operative period was similar in the two groups (table 5).

Table 5: Comparison of post-operative pethidine requirements in two groups

Variables	Group P	Group K	P value
No of patients requiring pethidine as rescue analgesic in post-operative period	17 (48.6%)	21 (60%)	0.337
Consumption of pethidine in post-operative period (in mg)	0 (0,50)	50 (0,50)	0.269
Time for administration of first rescue pethidine in post-operative period (hours)	3.5 (1.4, 6.88)	4.40 (2.63, 10.88)	0.167

Data presented as frequency (percentage), median (IQR)

Discussion

Pain is the one of the commonest complications seen in patients after laparoscopic cholecystectomy surgery.[12] Different etiological factors like chemical peritoneal irritation, injury in the incisions site of the trocar insertion and abdominal distention due to CO_2 were found to cause pain after laparoscopic cholecystectomy. Opioid is one of the most frequently used analgesics after laparoscopic cholecystectomy, however it has side effects like respiratory depression, postoperative nausea and vomiting.[13] Pre-emptive analgesia given before surgery can help in relieving intra and post-operative pain and reduce the use of opioid analgesicsin post-operative period in patients undergoing laparoscopic cholecystectomy. Paracetamol and non-steroidalanti-inflammatory drugs like ketorolaccan be used as pre-emptive analgesia and they can reduce pain produced by stretched nerve during pneumoperitoneum by CO_2insufflation.[14,15] Paracetamol and ketorolac have the advantage of easy availability and cost effectiveness as well. Our study was done to compare the pre-emptive analgesic effect of paracetamol and ketorolac in patients undergoing laparoscopic cholecystectomy.

In our study, no significant difference was observed in demographicand hemodynamic variables between the two groups.Similar findings were obtained in a study conducted by Rastogi et al.[10] We found that the incidence of mild and moderate pain and the NRS score of pain was similar at 15 minute, 1 hour, 4 hour, 12 hour and 24 hours after surgery in the two groups. However, the incidence of moderate pain and the NRS score for pain after 30 minutesin post-operative period was significantly lower in the paracetamol group compared to ketorolac group. A similar finding was observed by Arslanetal.[16] who found that pre-emptive intravenous paracetamol 1 gram given 10 minute before cholecystectomy reduced the post-operative pain scores.In contrast to our study, Boccaraetal.[17] found better post-operative analgesia with ketoprofenthan proparacetamolfor providing analgesia after laparoscopic cholecystectomy. The result of study by Watcha et al. was also different. They summarized that preoperative administration of oral ketorolac provides better postoperative analgesia than acetaminophen or placebo but this study was done in children undergoing bilateral myringotomy. Rastogi et al. also had suggested single dose of intravenous ketorolac to be superior to intravenous paracetamolin providing analgesia in early post-operative period after laparoscopic cholecystectomy.[10]

The number of patients requiring pethidine as rescue analgesic for moderate pain in the two groups was similar in the two groups (p=0.337). The consumption of rescue pethidine in patients of paracetamol group was lower than ketorolac group implying the incidence of moderate pain to be lower in paracetamol group but this difference was notstatistically significant.Arslanetal.[16] also had found reduced use of opioids in post-operative period in pre-emptive paracetamol group. However, the time required for administration of first rescue pethidine in the post-operative period was earlier in paracetamol group than ketorolac group in our study. In contrast, Arslanetal.[16] had found increased time to first request of tramadol in post-operative period in patients undergoing cholecystectomy.

The hemodynamic parameters like heart rate and mean arterial pressure were similar in the first 120 minutes after induction of anesthesia in paracetamol and ketorolac groups. There was also no significant hemodynamic variation in heart rate and mean arterial pressure in the first 60 minutes after intubation in paracetamol and ketorolac group in a study done by Rastogietal.[10]

Hyllested et al. had found NSAIDs to be better analgesics than paracetamol in some surgeries like dental and orthopaedic surgeries. But they also found paracetamol to be a good alternative in high risk patients and suggested combination of NSAIDs and paracetamol for better analgesia.[18]Our study was done in a single center in patients undergoing laparoscopic cholecystectomy. In the future, we could include greater number of patients, in multiple centers, undergoing surgeries other than laparoscopic cholecystectomy as well to determine the effectiveness of pre-emptive analgesic drugs in controlling pain and reducing the dose of rescue opioids in post-operative period.

Conclusion

Pre-emptive analgesia with injection paracetamol provides better analgesia than injection ketorolac in first 24 hours of post-operative period in patients undergoing elective laparoscopic cholecystectomy under general anesthesia in Western Regional Hospital but these were statistically not significant except at 30 minutes after the end of surgery.

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