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A Study on Efficacy of Intravenous Diclofenac and Ketorolac on Post Laparoscopic Cholecystectomy Pain

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Abstract: ***Laparoscopic cholecystectomy is the most common minimal access procedure performed. Incisions of the operative ports are the main cause of abdominal and shoulder tip pain after laparoscopy and are probably caused by gas retained in the peritoneal cavity. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are generally used for management of postoperative pain after laparoscopic cholecystectomy. Materials and Methods: Fifty patients aged 20 – 60 years scheduled for Laparoscopic Cholecystectomy and with ASA physical status I or II were divided into two equal groups. All patients received uniform pre-operative and intra operative medication according to body weight. Patients of Group D received Injection Diclofenac Sodium 75mg IV in 100mL Normal Saline and Group K received Injection Ketorolac 30mg IV in 100mL Normal Saline. The post operative pain score was recorded at 0, 2, 4 and 6 hours. Rescue dose of analgesia was given if VAS score was more than 3 or on demand. Results: VAS scores were not significantly different among the two groups at 0 and 2 hours. At 4th post operative hour, the scores were significantly higher in Group K; 3.28±0.45 vs 3.56±0.50, p= 0.04. The time of rescue analgesia administration in group D was 292 ± 55.56 minutes and group K was 233 ± 34.69 minutes. Conclusion: A single dose of intravenous Diclofenac can be recommended as an effective and safe alternative compared to intravenous Ketorolac for post operative pain relief following laparoscopic cholecystectomy.***

Keywords: Diclofenac, Ketorolac, Laproscopy, Cholecystectomy

1. Introduction

Laparoscopic cholecystectomy is the most common minimal access procedure performed nowadays and is considered as the gold standard and treatment of choice for gallstone disease.[1] Incisions of the operative ports are the main cause of pain after laparoscopic cholecystectomy. Upper abdominal and shoulder tip pain after laparoscopy are probably caused by gas retained in the peritoneal cavity. Carbon dioxide may even take 2 days to get totally absorbed from the peritoneal cavity though it is more soluble than oxygen and nitrogen.[2]

In the postoperative period, pain is the most common complaint seen. If not managed properly it can have detrimental effect over cardiovascular system and respiratory system, due to stimulation of sympathetic nervous system. Thus, multimodal analgesia is used for management of post-operative pain and smooth recovery from general anaesthesia.[3]Different 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 infiltration, intra peritoneal local anaesthetics and preemptive analgesia have also been used for post-operative pain relief.[4]

Diclofenac is a nonsteroidal anti-inflammatory drug of phenyl acetic acid class having antipyretic, anti-inflammatory, analgesic effects. Diclofenac has greater propensity to inhibit COX2 (Cyclooxygenase) enzyme than COX1.[1]Ketorolac acts by inhibiting both Cyclooxygenase and Lipooxygenase enzyme hence prevents synthesis of both Prostaglandin and Leukotrienes, and may enhance Endogenous Opioids release. Because of these properties, Ketorolac is more potent than any other NSAID.[2]This study was performed to compare the efficacy and safety of use of IV Diclofenac vs Ketorolac for management of postoperative pain after laparoscopic cholecystectomy.

2. Materials and Methods

The study was conducted after approval by the Institutional Ethics Committee on 50 patients aged 20 – 60 years, scheduled for laparoscopic cholecystectomy with ASA physical status I or II. Patients inGroup D received Injection Diclofenac Sodium 75mg IV in 100mL Normal Saline and Group K received Injection Ketorolac 30mg IV in 100mL Normal Saline.Patients were excluded if they had any history of allergy to any of the study drugs, if they had a history of severe renal, hepatic, gastric or coagulative diseases, if they had received analgesics during the week prior to surgery and pregnant patients. A thorough pre anaesthetic evaluation was done prior to surgery. Patients were explained about the procedure of Anaesthesia and the Visual Analogue Scale (VAS) Scoring systemto monitor post-operative pain. Patients were kept nil per oral 8 hours prior to surgery and premedicated on the night before surgery with tablet Ranitidine 150mg per oral and tablet Diazepam 5mg per oral.

On the day of the surgery, after arrival at the Operating Room, standard monitors were connected and baseline vitals noted. An 18G intravenous peripheral line was secured and all patients were hydrated with 10ml/kg of appropriate intravenous fluid. All patients received uniform pre-operative and intra operative medication. They were premedicated with injection Glycopyrolate 0.2mg IV and injection Fentanyl 2mcg/kg IV. After preoxygenation, general anaesthesia was induced with injection Propofol 2mg/kg IV. Intubation was facilitated by administration of Succinylcholine 2mg/kg with appropriate size oral endotracheal tube. Anaesthesia was maintained with 60% Nitrous Oxide and 40% Oxygen and

1% Isoflurane. Injection Vecuronium was administered at a dose of 0.1mg/kg as neuromuscular blocking agent. Ventilation was controlled aiming to attain end tidal Carbon Dioxide between 35-45mmHg. Maintenance doses of Vecuronium was given as per requirement. Intra peritoneal pressure was maintained between 12 to 14 mmHg. About 15 minutes prior to completion of surgery, the test drug was administered over a period of 5 minutes. Injection Ondansetron was administered at a dose of 0.1mg/kg. At the completion of surgery, neuromuscular blockade was reversed using injection Neostigmine 0.05mg/kg and injection Glycopyrolate 0.01mg/kg and then extubated once extubation criterias were met.

The post-operative pain score was recorded at 0, 2, 4 and6 hours. Rescue dose of analgesia was given if VAS score was more than 3 or on demand. VAS score and demand for rescue analgesia in the first 6 hours following surgery were used to determine the efficacy of the two drugs with respect to post-operative pain relief.Post-operative sedation profile was noted and patients were questioned about nausea and vomiting. Sedation was assessed using a sedation scale (wide awake=0; mildly sleepy and responsive to verbal command=1; moderately sleepy and responsive to nociceptive stimulation=2, extremely sleepy and unrousable to nociceptive stimulation=3). Duration of effective analgesia will be measured as the time from drug administration to the first administration of rescue analgesic or VAS 4. Injection Paracetamol 1gm IV was given as rescue analgesic.Post-operative heart rate and mean arterial pressures were monitored at 0, 2, 4 and 6 hours.

Data was analyzed using SPSS (Statistical Package for Social Sciences) version 16. P value was calculated by using Student's t test. A value of $p< 0.05$ was considered to be statistically significant.

3. Results

The demographic data as shown in table 1 was comparable between the two groups.

Table 1: Demographic data

Demographic data		Group D	Group K	P value
Age		36.9 ± 6.3	36.1 ± 7.6	>0.05
Sex (M/F)		55%	45%	>0.05
Weight		60.8 ± 7.6	61.1 ± 5.5	>0.05
ASA	I	18 (72 %)	16 (64 %)	>0.05
	ii	7 (28 %)	9(36 %)	>0.05
Duration of Surgery		45.5 ± 15.6	50.6 ± 22.4	>0.05

Table 2 shows VAS taken for post-operative pain assessment and it was not significantly different among the two groups at 0 and 2 hours. However, at 4thpost operative hour, the scores were significantly higher in Group K($p = 0.04$).

Table 2: VAS pain score

	VAS SCORE			
	0 hour	2 hours	4 hours	6 hours
Group D	1±0	1.56±0.50	3.28±0.45	3.16±0.62
Group K	1.12±0.33	1.88±0.83	3.56±0.50	2.88±0.92
P value	0.08	0.10	0.04	0.21

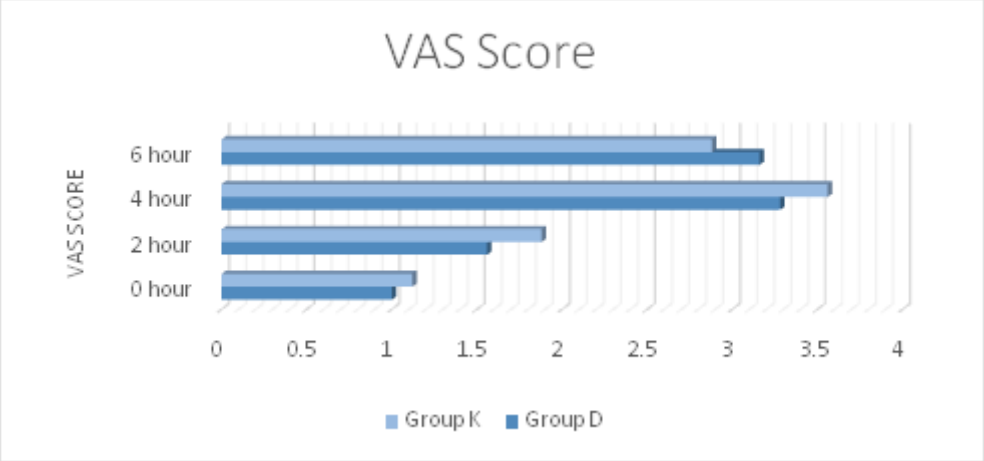

Figure 1: VAS scores at various time intervals across the two groups

Figure 2 shows that the time of rescue analgesia administration was significantly earlier in group K with a p value of <0.001. The time of rescue analgesia administration in group D was 292 ± 55.56 minutes and group K was 233 ± 34.69minutes.

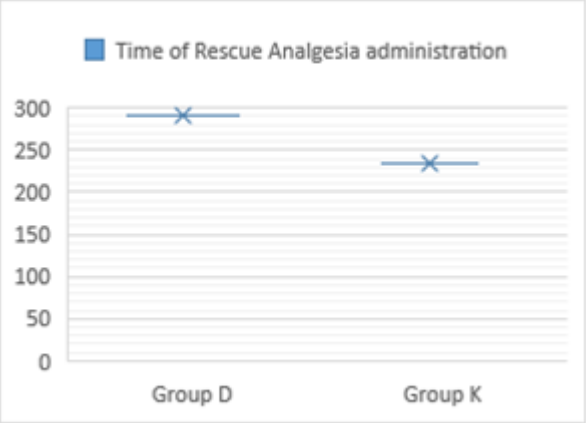

Figure 2: Time of rescue analgesia administration

The requirements of rescue analgesia (grams)during the first 6 post-operative hours is shown in figure 3. The requirement at 4th hour was significantly higher in group K and was not significantly different between the two groups at 6th hour.

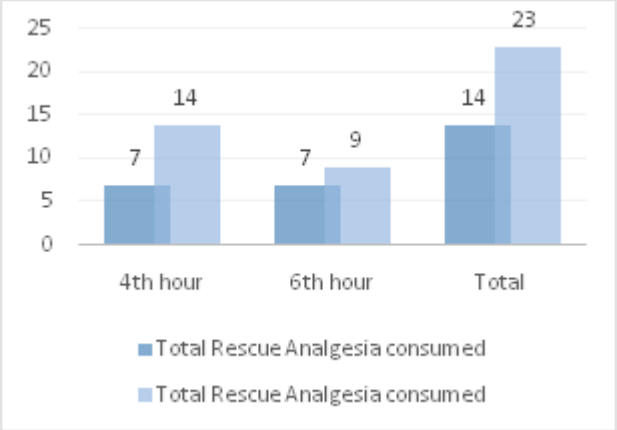

Figure 3: Consumption of rescue analgesia across the two groups at various time intervals

There was no significant difference in incidence of side effect among the two groups.

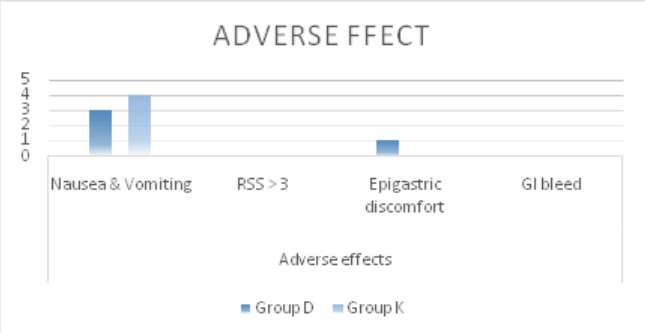

Figure 4: Incidence of Adverse effects

The heart rate and mean arterial pressure values were comparable between the two groups throughout the study period.

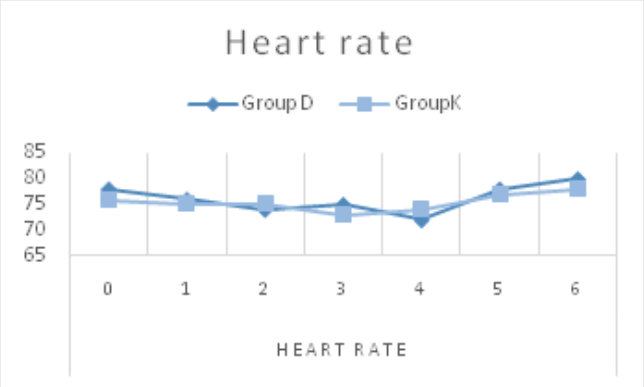

Figure 5: Heart rate across the two groups between 0-6 post operative hours

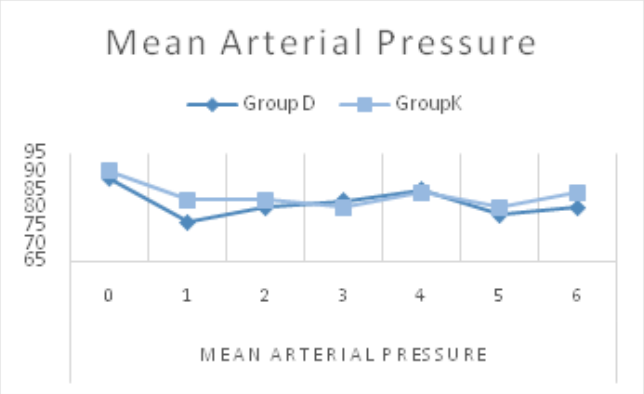

Figure 6: Mean arterial pressure across the two groups between 0-6 post operative hours

4. Discussion

Good postoperative pain management is an important component of perioperative care. Peri operative pain is a common reason for fear and anxiety associated with surgery. If analgesia is not adequate, postoperative pain can not only cause physical suffering but can also have detrimental effect on various systems. The analgesics commonly used for post-operative pain control are either opioids or NSAIDS or both. Laparoscopic cholecystectomy is the gold standard treatment for the management of symptomatic gallbladder.[5]

Pain after laparoscopic cholecystectomy is visceral in nature and said to be due to CO_2 insufflation which leads to traction of nerves and also the result of release of inflammatory mediators which cause pain. This pain occurs early in the postoperative period and its intensity decreases by24 hours. NSAIDS are the preferred agents probably because the pain is dependent on the release of inflammatory mediators. This pain is not intensified by mobilization as this only requires movement of abdominal muscle. However, cough causes liver and visceral displacement resulting in pain.[6]

Opioids are the most potent analgesics used for pain relief both and intra and post-operatively. The adverse effects associated with opioids like nausea, vomiting, excessive sedation and respiratory depression limits their use under most circumstances.[4]

The principal action of NSAIDs or COX-2 inhibitors is modulation of the local inflammatory response by inhibiting cyclooxygenase in the spinal cord and periphery to reduce Prostanoid synthesis.[7]

Diclofenac sodium is the most extensively used NSAID for this purpose. It has got analgesic, anti-inflammatory and antipyretic effect. Diclofenacis a phenylacetic acid derivative that inhibits prostaglandin synthesis and is relatively more COX-2 selective.[1]The opioid sparing effects of NSAIDs or COX-2 inhibitors and acetaminophen are in the range of 20–30%.[8]

Ketorolac was the first parenteral NSAID for clinical analgesic use introduced in the United States. The analgesic effect occurs within 30 minutes with maximum effect between 1 and 2 hours and duration of 4–6 hours. Ketorolac acts by inhibiting both cyclooxygenase and lipooxygenase enzyme hence prevents synthesis of both prostaglandin and leukotrienes, and may enhance endogenous opioids release. Because of these properties, Ketorolac is more potent than any other NSAID.[2]

Fredman B et al[9] conducted a comparative study of Ketorolac and Diclofenac on post-laparoscopic cholecystectomy pain. They observed improved pain scores in both the Ketorolac and Diclofenac groups compared with the saline group. PCA demands and post-operative morphine requirements were similar in the Ketorolac and Diclofenacgroups(Saline :12.2 mg +/- 5.0; Ketorolac : 8.6 mg +/- 5.2; Diclofenac : 8.9 mg +/- 4.8).

S P Sinha et al[10] assessed the efficacy of Tramadol V/s Diclofenac in Management of Post Laparoscopic Cholecystectomy Pain. They suggested that tramadol reduces pain more effectively than Diclofenac following elective laparoscopic cholecystectomy. There was a significant difference in VAS scores at 12 hourpost-operative (p= 0.0007) with tramadol being more efficacious but having increased incidence of nausea and vomiting.

Smith CH et al[11] compared tramadol with Diclofenac in post caesarean patients and found that the mean time to rescue dose of Diclofenac was much shorter at 55 minutes compared to tramadol at 113 minutes.

Safina Tahir et al[4]studied the analgesic effects of Pre-emptive use of paracetamol infusion versus intramuscular Ketorolac in patients undergoing elective laparoscopic cholecystectomy. The mean VAS scores at various time intervals were found to be lower for intramuscular Ketorolac group and statistically significant. Therefore Ketorolac 30 mg is more effective in reducing postoperative pain scores after laparoscopic cholecystectomy in the first 6 hours as compared to 1 gm intravenous paracetamol infusion.

RH Khan et al[12]compared pre-emptive use of Diclofenac, Ketorolac and tramadol for post-operative pain in laparoscopic cholecystectomy. The time of 1st rescue dose of pethidine in Diclofenac group was at 1.8±0.11 hour, in Ketorolac was 2.2±0.12 hour and in tramadol was 2.3-0.10 hour. They concluded that postoperative pain can be managed by pre-emptive use of Diclofenac, Ketorolac, and tramadol for the first 24 hours with little or no supplementation of low dose IV pethidine. The analgesic efficacy of Ketorolac and tramadol is same and better than Diclofenac.

Rastogi et al[2] compared postoperative analgesia after laparoscopic cholecystectomy by pre-emptive use of intravenous paracetamol or Ketorolac. VAS scores in the Post-operative period were higher in paracetamol group. Allpatients in paracetamol group and 8 patients in Ketorolac group required rescue analgesic within 6 hrs of study time. Total tramadol consumption was much higher (2250 mg) in paracetamol group as compared to 400 mg in Ketorolac group.

Chowdhary et al[13] compared intravenous Tramadol vs Diclofenac for Postoperative Pain Management in Laparoscopic Cholecystectomy. They concluded that Pain relief was better in a significantly higher number of patients in the Tramadol group than Diclofenac.

M Wadhwani et al [14]compared the efficacy of intravenous paracetamol and Diclofenac for post-operative analgesia in laparoscopic surgeries and concluded that Paracetamol appears to be equally safe and effective analgesic for postoperative pain like Diclofenac. It is hemodynamically stable and does not cause respiratory depression. Paracetamol is devoid of any serious side effects and can be used for both intra and postoperative analgesia.

5. Conclusion

A single dose of intravenous Diclofenac can be recommended as an effective and safe alternative compared to intravenous Ketorolac for post operative pain relief following laparoscopic cholecystectomy.

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