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PRE-EMPTIVE USE OF KETOROLAC AND POST-OPERATIVE PAIN AMONG PATIENTS UNDERGOING LAPAROSCOPIC SURGERY

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ABSTRACT

Introduction: Analgesia in the form of pharmacological and non-pharmacological intervention is mandatory to manage pain, so as to limit the neuro-endocrine response to surgery and pain. Inappropriate postoperative pain control has been associated with a number of complications. The sequel of peripheral and central modulation in nociception has given the concept of preemptive analgesia in patients undergoing various kinds of surgeries. NSAIDs like Ketorolac inhibit the (COX) cyclo-oxygenase enzymes, and decrease peripheral central prostaglandin production thus reducing pain. The objective of our study was to understand the efficacy of pre-emptive Ketorolac for post operative pain among patients undergoing operative laparoscopic cholecystectomy. **Methods:** The study was conducted at Cantonment General Hospital, Rawalpindi from Jan 2020 to Dec 2020 over a period of 1 year. A total of 50 patients undergoing laparoscopic Cholecystectomies were enrolled in the study. Patients were randomly divided in group A (n=25) and B (n=25) by consecutive non probability lottery method. SPSS version 17.0 was used to analyze the data. The post-operative pain was assessed by using Visual Analog scale (VAS) graded no pain (0 score) to worst unbearable pain (10 score). Patients complaining moderate to severe pain (pain score 5 or above) in either group at 4 hours or even before postoperatively were given rescue analgesic. **Results:** There were 25 patients in each group. The baseline parameters of all study participants were comparable with no significant differences. Mean age of study patients was 40.6 ± 6.3 years. The mean weight (kg), height (m) and BMI (kg/m^2) of all study patients were 66.4 ± 10.5, 1.57 ± 0.11 and 27.8 ± 3.4 respectively. The mean duration of surgery was 45.7 ± 5.5 min. Overall 48 (96%) patients had either no pain (0 score) or complained of mild pain (1-4 Score) at 4hrs post operatively whereas only 2 (4%) patients had moderate pain. There were no patients with severe post operative pain at 4hrs. **Conclusion:** Pre-emptive use of Ketorolac for the management of post-operative pain especially among patients undergoing laparoscopic cholecystectomy is highly significant. It definitely reduces the pain intensity as well as the duration, thus provides an enhanced recovery after surgery (ERAS).

KEYWORDS: Post-operative pain, Ketorolac, Multi-modal Analgesia.

INTRODUCTION

Post-operative pain is the primary complaint after surgery in all types of operations. Analgesia in the form of pharmacological and non-pharmacological intervention is mandatory to manage pain, so as to limit the neuro-endocrine response to surgery and pain.[1] The prevention, recognition, and early management of postoperative pain is vital in an effective and efficient post-operative outcome. Inappropriate postoperative pain control has been associated with a number of complications such as delay in discharge from the hospital, atelectasis, pulmonary edema, hypoxemia, and cardiovascular system complications.[2,3]

Paracetamol, NSAIDs and Opioids remain the main stay drugs for management of post-surgical pain with each having its pros and cons. Opioids are considered to be the best regimen but fluctuating levels of Opioids in blood may result in sedation or other adverse effects. High blood levels lead to sedation and respiratory depression while low levels can lead to inadequate analgesia before the next injection can be given.[2,4,5,6]

Multimodal and balanced analgesia technique using a combination of analgesic methods throughout the peri-operative period to control postoperative pain is recommended over the use of opioids alone. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the options being easily available, cheap and accessible to reduce postoperative pain and avoid the adverse effects of opioids.[4,5,6] The sequel of peripheral and central modulation in nociception has given the concept of preemptive analgesia in patients undergoing various kinds of surgeries. This type of management induces an effective analgesic state prior to surgery and a very cost-effective way to manage pain. This may involve infiltration of the wound with local anesthetic, central neural blockade, or use of various pharmacological analgesic agents.[7,8] Experimental evidence suggests that preemptive analgesia can effectively attenuate peripheral and central sensitization to pain. Transmission of pain signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways.[9,10,11,12] Pre-emptive analgesia is a treatment that is initiated before the surgical procedure in order to reduce this sensitization.

NSAIDs like Ketorolac inhibit the (COX) cyclo-oxygenase enzymes, and decrease peripheral central prostaglandin production. In addition to reducing the inflammation that accompanies tissue injury, decreasing prostaglandin production alters the response of the peripheral and central components of the nervous system to noxious stimuli.[13,14,15] It can lead to reduced response to pain. ketorolac is an established non-selective NSAID administered in an active form. The efficacy of ketorolac in decreasing postoperative pain following orthopedic surgical procedures including spine surgery has been previously demonstrated.[10,12,13,14] The objective of our study was to understand the efficacy of pre-emptive Ketorolac for post operative pain among patients undergoing operative laparoscopic cholecystectomy.

METHODS

The study was conducted at Cantonment General Hospital, Rawalpindi from Jan 2020 to Dec 2020 over a period of 1 year. The departments of Anesthesia, Surgery, Pain Medicine and Statistics collaborated jointly to gather and process the data. After approval from hospital ethical committee, a total of 50 patients undergoing laparoscopic Cholecystectomies were enrolled in the study. Patients were randomly divided in group A and B by consecutive non probability lottery method. SPSS version 17.0 was used to analyze the data.

Inclusion criteria

ASA – I (normal healthy patient), II (mild systemic disease with no functional limitation). Routine cases booked from OPD based on History, clinical examination and relevant investigations.

Age: Adults, 18-60 years

Elective surgery (Laparoscopic Cholecystectomies)-based on evidence from Ultrasonography (USG).

Exclusion criteria

1. Patient with concomitant co-morbid conditions like diabetes mellitus, hypertension, malignancy, pulmonary, hepatic or renal diseases.
2. Patients having specific NSAIDs contraindications like Bronchial Asthma, Coronary Artery disease, CABG, Gastric/Duodenal Ulcers, Gastritis/ Esophagitis, Anemia and Coagulation disorders, Severe allergies and kidney disorders.
3. Contraindications for using Opioids or NSAIDS (Allergic reactions/hypersensitivity).
4. Patients already taking Ketorolac, GABAergic medications, Opioid analgesics, long term NSAIDS/COX-2 inhibitors or other pain killers.
5. Patients with Chronic Pain conditions, Chronic post-surgical pain (CPSP), Fibromyalgia, Polymyalgia rheumatic, Filed Back Surgery Syndrome (FBSS) or having red/yellow flags of pain.
6. Patients having autoimmune disorders like Rheumatoid Arthritis (RA), Multiple Sclerosis, Amyotrophic Lateral Sclerosis (AML) or Myasthenia Gravis etc.
7. Patients having pain with autonomic disturbances like Complex regional pain syndrome (CRPS) or Diabetic Neuropathy etc.
8. Patients either having Psychiatric/Movement disorders like Anxiety, Depression, Mania, Schizophrenia, Delirium, Parkinsonism, Epilepsy or taking on Antidepressants, anti-psychotics, anxiolytics or antiepileptic.
9. Morbid Obesity (BMI > 35 with Co-Morbid or BMI>40), Obstructive Sleep Apnea or use of BiPAP/CPAP.
10. Contraindication to General Anesthesia or Patient refusal for participation on the study.

All patients were assessed routinely in the outdoor patient department, labeled as procedure fit for Laparoscopic Cholecystectomies and Pre-Anesthesia Consultation was done at least 5 days before surgery to rule out any possible contraindications or complications. Patients were randomly divided in group A and B by consecutive non probability lottery method**.** Group A was planned to use Ketorolac tablet oral dose of 10mg once daily at least for 3 days before surgery while Group B was considered as controls with no Ketorolac use.

After ruling out all contraindications for the use of Ketorolac, Group A was prescribed with tablet Ketorolac 10mg once daily dose to start 3 days before surgery. A day before surgery (at least 8 hours before surgery as preoperative anesthesia re-evaluation procedure on admission to hospital for the surgery), patients were again seen by the anesthesia team and compliance with the use of Ketorolac was ensured during the prescribed duration. Finally, a written informed consent was

obtained for Anesthesia and surgery. Patients were prepared by overnight fasting.

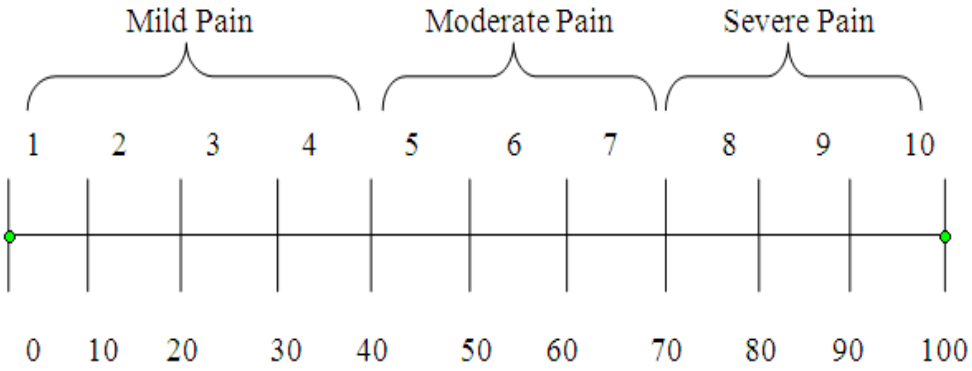
Intravascular access with an Intravenous cannula was established in the pre-operative room before arriving in the operation theater. After arrival in Operation Theater, Standard AAGBI/ASA monitoring included Electrocardiography (ECG), Pulse oximetry, noninvasive blood pressure (NIBP) was attached and the base line heart rate and blood pressure were noted.

General anesthesia was administered with 1-2 ug/kg Fentanyl, 2-3 mg/kg Propofol, 0.6-0.9 mg/kg Rocuronium, 0.1mg/kg Dexamethasone for induction and intubation. After intubation, anesthesia was maintained with 40-60 % Oxygen, Air and 1.0 - 1.2% Isoflurane Volatile anesthetic agent. Paracetamol 15-20 mg/kg was administered per operatively along with Ondansetron 0.1 mg/kg as antiemetic. Vitals monitoring and appropriate interventions were done accordingly at regular intervals of 5 minutes as per standard guidelines.

Patients were reversed with injection Neostigmine 0.04 mg/kg and 0.005-0.01 mg/kg Glycopyrrolate after completion of surgery. All the anesthetic administration was performed by the registrar level anesthetist who was blinded about the drug so as to eliminate bias factor.

At the end of surgery, patients were extubated and shifted to the post-anesthesia care unit (PACU) for monitoring, where the control of post-operative pain was strictly monitored. The pain score was measured at 4 hours postoperatively by the researcher team.

The post-operative pain was assessed by using Visual Analog scale (VAS) graded no pain (0 score) to worst unbearable pain (10 score). Patients complaining moderate to severe pain(pain score 5 or above) in either group at 4 hours or even before postoperatively were given rescue analgesic (Tramadol 50mg slow intravenous injection), and the pain score measured at that point (Time interval) was considered end point for that patient regardless of the fact that 4 hours have been passed.



VAS Pain Scale

RESULTS

A total of 50 patients were included in the study. There were 25 patients in each group. The baseline parameters of all study participants are given in Table 1. Mean age of study patients was 40.6 ± 6.3 years. The mean weight (kg), height (m) and BMI (kg/m^2) of all study patients were 66.4 ± 10.5, 1.57 ± 0.11 and 27.8 ± 3.4 respectively. The mean duration of surgery was 45.7 ± 5.5 min. Overall 48 (96%) patients had either no pain (0 score) or complained of mild pain (1-4 Score) at 4hrs post operatively whereas only 2 (4%) patients had moderate pain. There were no patients with severe post operative pain at 4hrs.

Table 1: Baseline Parameters Of All Study Participants.

Parameter		**Mean ± SD**
Age		40.6 ± 6.3 Years
Weight		66.4 ± 10.5 KG
Height		1.57 ± 0.11 Met
BMI		27.8 ± 3.4 Kg/m2
Duration of Surgery		45.7 ± 5.5 Min
		No. of patients (Frequency)
Gender	Male	20 (40%)
	Female	30 (60%)
Pain Score	0	10 (20%) ……No Pain
	1	22 (44%)
	2	09(18%)
	3	04 (8%)

	4	03 (6%)
	5	02 (4%)
Pain Category	No Pain or Mild Pain	48 (96%)
	Moderate	02 (4%)
	Severe	0 (0%)

Table 2: Baseline Comparison of the two groups.

Gender		Group A (n=25)	Group B (n=25)	P value
	Males	11 (44%)	09 (36%)	0.1
	Females	14 (56%)	16 (64%)	
Age (yrs)		41.2 ± 5.3	40.3 ± 6.8	0.3
Weight (kg)		66.9 ± 11.5	68.7 ± 8.3	0.2
Height (m)		1.55 ± 0.11	1.54 ± 0.10	0.6
BMI (kg/m2)		27.3 ± 4.2	26.8 ± 4.7	0.5
Duration of Surgery (min)		45.3 ± 6.5	46.5 ± 5.1	0.5
Pain Score at 4hrs		1.5 ± 0.3	3.8 ± 0.8	**0.0001**

Table 3: Comparison Of Different Visual Analogue Score.

Visual Analogue Scale Pain Category	Group A	Group B
0	10 (20%)	0
1	22 (44%)	0
2	5 (10%)	4 (8%)
3	1 (2%)	3(6%)
4	0	3 (6%)
5	0	2 (4%)
Chi square: p= 0.0001		

Table 4: Comparison of Different Pain Categories.

Visual Analogue Scale Pain Category	Group A	Group B
NO PAIN	10 (20%)	0
MILD (1-4 Score)	28 (56%)	10(20%)
MODERATE	0	02 (4%)
SEVERE	0	0
Chi square p value 0.004		

The pain score in group A who received Ketorolac was significantly lower than group B which was controlled group. Thus, the study significantly showed difference in pain scores while using Ketorolac.

DISCUSSION

Opioids like morphine and its derivatives have been extensively used to treat postoperative pain since long due to quick and efficient pain relief. But the opioids carry their own side effects and sometimes contraindicated in addition to their deleterious side effects. NSAIDs despite their drawbacks remain available easily with cost effectiveness.[16,17,18]

The use of these drugs especially through the natural enteral route makes a very compliant and justified method for management of pain especially if used as pre-emptive analgesia for post operative pain.

Ketorolac is a non-selective COX inhibitor. It is considered as a first-generation NSAID. The primary mechanism of action responsible for ketorolac's anti-inflammatory, antipyretic, and analgesic effects is the inhibition of prostaglandin synthesis by competitive blocking of the enzyme cyclooxygenase (COX).

Ketorolac is used to relieve moderate to severe pain, usually pain that occurs after an operation or other painful procedure. Ketorolac is not a narcotic and thus dependence or tolerance risk is minimal. It will not cause physical or mental dependence, as narcotics can.[18,19,20] However, ketorolac is sometimes used together with a narcotic to provide better pain relief than either medicine used alone. Ketorolac has side effects that can be fatal. The risk of having a serious side effect increases with the dose and duration of ketorolac use. Therefore, ketorolac should not be used for more than 5-7 days.

Postoperative pain is experienced by the majority of patients undergoing surgical procedures. Control of postoperative pain plays vital role in facilitating a patient's recovery to normal function (ERAS) and reduces the incidence of adverse physiologic and psychological effects.[18,19,20] Postoperative pain control is achieved by variety of mechanisms labelled as multimodal analgesia regimen based on WHO pain ladder scheme.

Postoperative pain control is a complex entity requiring interprofessional participation that should begin in preoperative phase and continue till the time when patient recovers. A thorough preoperative assessment of the patient by the primary team, anesthesia team and the pain physician can aid in identifying patient risk factors and comorbidities that may influence the severity of postoperative pain, recovery and discharge from the hospital.[19,20,21] These all factors necessitate the use of a proper analgesic agent like NSAIDs or opioids or combination of all to provide adequate post operative analgesia.

CONCLUSION

Pre-emptive use of Ketorolac for the management of post-operative pain especially among patients undergoing laparoscopic cholecystectomy is highly significant. It definitely reduces the pain intensity as well as the duration, thus provides an enhanced recovery after surgery (ERAS).

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