ORIGINAL ARTICLE

Efficacy of pre-operative Rectal Diclofenac Suppository for Postoperative Pain Management in Laparoscopic Cholecystectomy: A multicenter Prospective Randomized Controlled Trial

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ABSTRACT

Background: Laparoscopic procedures have gained popularity owing to reduction in pain suffered due to large incisions in conventional open procedures, minimally invasive approaches is not absolutely pain free.
Aim: To compare the effectiveness of pre-operative rectal diclofenac suppository (single dose) among patients operated for laparoscopic cholecystectomy (LC).
Methods: 63 patients were randomized into two groups. Single dose 100 mg Diclofenac suppository was placed per rectally at the time of induction and standard 4 –port laparoscopic cholecystectomy was done. Postoperative pain scores were recorded on a visual analogue score and results analyzed.
Results: Both groups were comparable in term of age (36.87±12.52 & 36.93±10.05 years) (p=0.982), BMI (27.63±1.77Kg/m^2 & 27.73±1.73Kg/m^2) and operative time between two groups (P= 0.854). Significant difference in pain score between two groups was observed during zero, three, six, nine and 12 hours of post-operative observation.
Conclusion: Pre-operative use of Diclofenac suppository significantly reduced post-operative pain scores and should be used in all patients planned for laparoscopic cholecystectomy. There is an added benefit that the group can be used safely in patients with acid peptic disease.
Keywords: Laparoscopic cholecystectomy, suppository, pain score

INTRODUCTION

Gall stones surgery is now commonly performed by minimally invasive or laparoscopic technique known as laparoscopic cholecystectomy (LC). The advantage of this technique over the open approach is minimal trauma to the patient that attenuates the surgical stress response and shorten recovery time[1,2]. LC is however associated with some degree of pain and cannot be labelled as an absolutely pain free procedure[2]. Most of the patient complaints of considerable pain in immediate postoperative period. The primary cause of delayed recovery in patients undergoing LC is pain only. Effective analgesia after LC remains a clinical challenge[2].

Only few good controlled clinical trials have been conducted to determine an effective regimen to achieve target for postoperative pain control[1,2,3,4]. Though Opioid group has been recommended for postoperative analgesia; are associated with several side effects specially nausea and vomiting. The risk of opioid overdose and respiratory depression are also well documented. Among other commonly used analgesics diclofenac sodium is an effective and safe analgesic used pre-operatively. Damage to muscle, increasing the bleeding risk and renal toxicity are the important noted adverse effects of intramuscular diclofenac administration whereas giving diclofenac orally in nil per oral patient preoperatively increases the risk of gastrointestinal ulceration and bleeding. Therefore, a great need exists for finding alternative roots of administration[3]. Rectal diclofenac suppositories are available and are proved to be safe for use[6]. The rationale of the study was to determine the effect of change in dosages of opioid analgesia and prevent the harmful effects of this group of analgesia in the peri-operative as well as discharge medication. If proven useful the NSAID group can be declared as a preferable analgesia with a new route which can be administered in perioperative period.

The objectives of this study were to compare postoperative pain score and amount of opioid analgesic required following laparoscopic cholecystectomy with or without use of pre-operative rectal diclofenac suppository.

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MATERIAL AND METHODS

After ethical clearance from Advanced Studies & Research Board (ASRB) of King Edward Medical University, Lahore, Pakistan, this double blinded, controlled randomized clinical trial was conducted at three centers including Mayo Hospital, Lahore Medical and Dental College and Services Institute of Medical Sciences, Lahore from April 2016 to December, 2017. A total of 166 patients with cholelithiasis were enrolled for the study. 42 were excluded due to a second pathology, extension of the port site wounds, extra ports or not patients not consenting for the study (Fig. 1). 124 cases were randomized using computer generated random number table into two comparison groups. Sample size: Sample size of 60 cases in each group were estimated by “Sample Size Determination in Health Studies” software using 1% level of significance and 80% Power of the test with success of avoiding rescue opioids

74% and 20% in the test group receiving pre-operative diclofenac suppository and control group respectively[6].

Inclusion criteria: Patients of any age and gender, with cholelithiasis on ultrasound, Body Mass Index (BMI) ≤30Kg/m^2 and American Society of Anesthesiology Grade I & II undergoing LC were included in this study.

Exclusion criteria: Patients with following confounding factors were excluded from the study.

- Previous abdominal surgery – Identified in history or multiple adhesions on diagnostic laparoscopy.
- Body mass index more than 30Kg/m^2 – Calculated by taking height and weight and dividing weight by square of height in meter. Readings >30Kg/m^2 were excluded.
- Choledocholithiasis – Excluded by ultrasound study of common bile duct.
- Any known malignancy – Identified in history. Any positive history excluded the case as it might alter the pain threshold of the patient.
- ASA grade III or above – American Society of Anesthesiology (ASA) grading was done for the patients during pre-anesthetic evaluation. Grade III or more was excluded from the study.
- Hepatitis B & C – Positive cases were excluded after screening serology.
- Pregnancy – Identified in history.
- Patient with history of bleeding, mass, discharge, pain or pruritus per anum suggestive of anorectal disease who are unfit for rectal diclofenac suppository were also excluded from the study.
- Complicated cholecystectomy like conversion to open procedure and prolonged duration of the procedure (more than 2 hours) and laparoscopic cholecystectomy done by other than consultants were dropped out and excluded from this study.

METHODOLOGY

Cases of cholelithiasis, diagnosed by consultant surgeon at outpatient department with evidence of gall stone in ultrasonography, fulfilling inclusion criteria of the study and with complete pre-operative investigation were admitted at South Surgical Unit, Mayo hospital, Lahore one day prior surgery. After pre anesthetic evaluation and getting fitness for general anesthesia from the department of anesthesia, sample cases were listed in elective operation list with consent for operation and study. Patients were kept nil by mouth for 6 hours prior surgery. Rectal diclofenac suppository of 100mg was inserted per rectum 60 minutes before induction in the intervention arm. No other analgesic premedication was given to patient before surgery. Demographic information of the patients was recorded in case report form pre-operatively along with age, gender, height, and weight and body mass index. Observer recording those parameters was blind to the study.

All the patients were anesthetized with standard general anesthesia protocol with same inducing agent and same per-operative analgesic. All the surgeries in this study were performed by consultant surgeons well trained for the procedure using four port approaches and were blinded of the intervention or the control arm. Time of first incision to insert umbilical port was noted and duration of surgery was calculated from this point to application of final suture to repair port sites. Patients during recovery from anesthesia were monitored and the time of first verbal response was noted, which was taken as the zero hour of postoperative assessment of pain score. The observer recording duration of the surgery and time of first verbal response was blinded to the study. A single dose of 10mg Nalbuphine Intravenous was administered to all patients in both groups at zero hour.

Postoperative pain score was measured for 12 hours of postoperatively. Pain score was assessed by surgical resident trained to use the Visual Analogue Scale. Intravenous opioid (Nalbuphine) was given as rescue analgesic if the VAS score was more than 50mm. Total dose of opioid required was calculated at 12 hours on hourly basis. All the data were collected using case report form.

Data was analyzed using SPSS version 20. Normality of the data was calculated . Continuous quantitative variables including age, weight, height, BMI, duration of surgery and total dose of opioid (Nalbuphine) consumed were compared using the Unpaired Student's t test. Gender was compared using Chi-Square test. Repeated measure ANOVA test was used to compare for mean pain scores at pre-specified intervals. p value less than 0.05 was considered as statistically significant.

RESULTS

A total of 63 cases were included in the study. There was no significant difference between two groups in term of baseline characteristics of the patients; two groups were comparable statistically. One case from the study group was dropped out due to incidental finding of small paraumblical hernia, repair of whose lengthened the procedure time and two cases from the control group were dropped out because of conversion into open cholecystectomy due to massive adhesion and phlegmon formation. Mean age of the patients in diclofenac suppository group was 36.87±12.52 years ranging from 20 to 60 years and that of control group was 36.93 ± 10.05 years ranging from 19 to 60 years. (p=0.982)

There was no significant difference in gender distribution of the patients (p=0.353). 83.33% of the patients in the study group were female and 16.67% were male. Whereas 90% were female and 10% male in the control group.

Mean height of the patients in the study group was 1.64±0.054m ranging from 1.5 to 1.73m and that of the control group was 1.65±0.052m ranging from 1.54 to 1.74m. Mean weight of the patients in the study group was 74.57±6.81Kg ranging from 52 to 86Kg and that of the control group was 75.1±6.49Kg ranging from 56 to 88Kg.

There was no significant difference in BMI of the patients between two groups (P = 0.834), BMI being 27.63±1.77 Kg/m^2 and 27.73±1.73 Kg/m^2 for the study and the control group respectively. 70% of patients in the study groups had ASA Grade I and 30% had ASA Grade II. The proportion was similar for the control group also, 73.3% under ASA I and 26.7% under ASA II (P = 0.5).

Mean operative time in the study group was 80.23±7.70 minutes (65 to 92 minutes) and that of the control group was 80.60±7.70 minutes (66 to 95 minutes). (p= 0.854). Significant difference in pain score between two groups was observed during zero, three, six, nine and 12 hours of post-operative observation

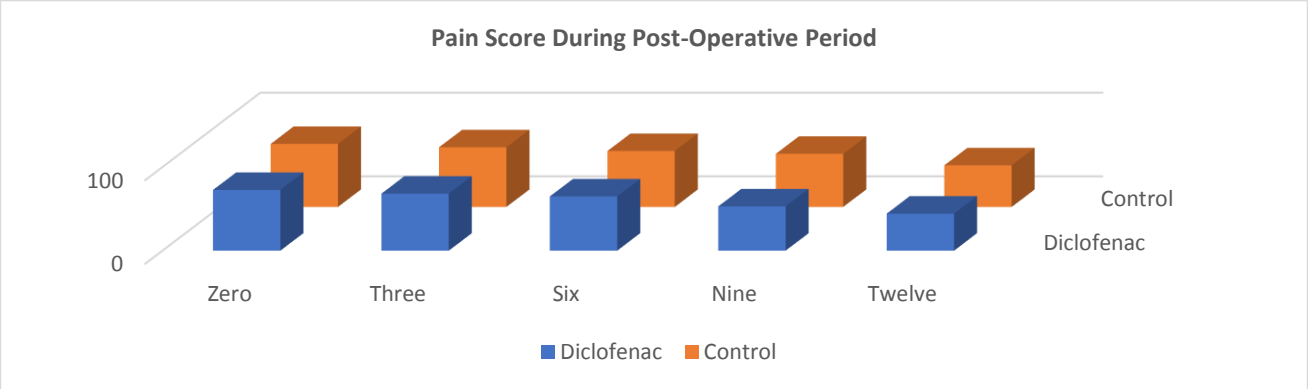

Table-1: Pain scores during post-operative period

Time	*Group-A*	*Group-B*	*P value*
0 hour	72.57 ± 3.97	75.30 ± 3.37	0.006*
3 hours	68.20 ±3.28	71.30 ± 4.47	0.003*
6 hours	64.83 ± 2.91	66.90 ± 4.31	0.034
9 hours	52.93 ±3.79	63.50 ± 5.03	<0.001*
12 hours	44.23 ± 9.90	49.70 ± 5.15	0.009*
N	30	30	

Group-A= Diclofenac Suppository Group, Group-B= Control Group, * Statistically significant (p=< 0.05)

Results showed statistically significant reduction in frequency and dosage of rescue analgesia in diclofenac suppository group when compared to the control group (p= <0.001); 24 patients in control group (80%) required rescue analgesia whereas only 7 patients (23.33%) in the study group. Similarly, the mean dose of Nalbuphane in the study group (1.53±2.91) was statistically lower than that in control group (4.8±2.44) with P value less than 0.001.

DISCUSSION

Narcotic analgesics are the most potent and effective group of pain killers which can be used postoperatively but are associated with PONV and respiratory depressions. Use of PCA reduces both these side effects but PCA pumps are not available in most centers in the low and the low middle-income countries. According to a survey in Kigali, Rwanda done by global Surg® collaborative group Opiod analgesia are out of reach of common patients in public sector hospitals in LMICs (expensive, drug control regulations, PCA pumps cost or tedious hospital paper work being a few factors.). Diclofenac Suppositories are not associated with any such side effects and are widely available in most of the LMICs[9].

Use of Diclofenac suppository as a constituent part of pain medication in the perioperative period significantly reduces need for opion analgesia in patients undergoing laparoscopic procedures. Use of Diclofenac suppository has been associated with sustained relief of pain after 2 -3 hours after surgery when the effect of local anesthetist injected in the trocar sites wear off[6].

This route has not been investigated as a standard of care for patient being operated for gall stone disease laparoscopically. Use of Diclofenac group is preferred over simple paracetamol where studies have reported significant differences in use of narcotics as PCA in group of patients being administered Paracetamol or Diclofenac group[5].

Relieving suffering by preserving and restoring health is the task of medicine. Understanding of pain is essential to achieve this goal. Pain is universally understood as a signal of disease and is the most common symptom a physician encounters. Furthermore, it is the obligation to the physician for providing rapid and effective pain relief. Thus pain management has always been a dynamic topic, search for whose better way has been evergreen topic for researchers[1-9].

Physicians strive to provide the best quality of patient care possible and above all to do no harm. But, even the most benign therapy has unwanted side effect. There has been a recent focus to deal with the problems of opioid crisis in high income countries (10). Whereas many of the middle and low middle income either do not have an adequate supply or have major legislative issues with administration of these medications to achieve analgesia. The devices used for delivery of perioperative safe dosages are not available in majority of health care facilities. Moreover, opioids have been associated with adverse effects like nausea & vomiting, drowsiness and respiratory depression especially in higher doses which limits physicians for its adequate use.

NSAIDs have established their efficacy in management of postoperative pain, either alone or in combination with opioids/local anesthetics. Enormous volumes of literatures documenting the effective use of NSAIDs are available[7]. However, most of the previous studies evaluated the parenteral or intramuscular administration of NSAIDs in this specific group of patient and reported a good outcome[8]. Use of Ketorolac alone as well in combination with diclofenac has been studied, and is proven to be useful when used in combination[7].

Per rectal route of administration of Diclofenac suppository excludes the reported adverse effects of muscle damage, increased risk of bleeding and acute kidney injury (intramuscular route) or increased risk of gastrointestinal ulceration and bleeding (oral route) with additional benefit of eliminating the first pass effect[6]. Several studies have proven the effectiveness of rectal diclofenac suppositories in postoperative analgesia in

various procedures are available. The modality has successfully been used in repair of cleft palate, ERCP, elective C-sections, herniotomy as well as hemorrhoidectomy[12-18]. These studies reported a significant relief of acute postoperative pain and marked reduction in need of opioid analgesia. In two studies at least the opioid sparing effect of rectal diclofenac following total abdominal hysterectomy or C-section showed that rectal diclofenac reduces morphine consumption, improves postoperative analgesia and reduces the incidence of adverse effects such as sedation and nausea[14,15]. Jodie M. et al (2004) showed that the use of rectal non-steroidal anti-inflammatory drug suppositories is a simple, effective and safe method of reducing the pain experienced by women following perineal trauma within first 24hrs after childbirth.

Administration of diclofenac rectally is a safe and convenient approach which results in complete absorption and sustained release of medicine to provide early onset and durable post-operative analgesia. Transmission of pain signals evoked by tissue damage leads to sensitization of the peripheral and central pain pathways. Result in this study showed the effectiveness of pre-operative rectal diclofenac suppository in postoperative analgesia in laparoscopic cholecystectomy. Mean pain scores in patients receiving preoperative rectal diclofenac are significantly lower than that in control group. The study also showed the incidence of requirement of opioid as rescue analgesia along with its dose is significantly lower with the use of diclofenac suppository. The result is similar to Arab M. et al. (2013) who concluded diclofenac rectal suppository as simple and safe analgesic in laparoscopic cholecystectomy[2,3].

The study is a simple comparative study undertaken on a small population. The results however are very encouraging and a high-quality randomized control trial with a larger sample size bundled with application of local anesthetists may change practices for management of perioperative pain in minimally invasive surgery. The study did not include patient views for using this new route for administration of medication. The acceptability of this rectal route may be a problem in certain cultures specially in the low- and middle-income countries.

CONCLUSION

Rectal suppository of diclofenac is suited for a preemptive approach of pain management and is efficient drug to reduce consumption of opioids in the postoperative period following laparoscopic cholecystectomy.

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