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Comparative Study of Post-Operative Analgesic Effects of Intramuscular Versus Transdermal Route of Diclofenac Sodium in Laparoscopic Cholecystectomy.

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Abstract
BACKGROUND*: Transdermal patch of Diclofenac is as effective as intramuscular Diclofenac in relieving mild to moderate post-operative pain of elective laparoscopic cholecystectomy. However, transdermal route is non-invasive and with lower incidence of systemic adverse effects as compared to oral or parenteral routes.*
PATIENTS AND METHODS*: In this prospective randomized clinical study, 60 patients of either sex with ASA-1 and ASA-2, undergoing elective laparoscopic cholecystectomy were randomly allocated to two groups, each of 30 patients. Group-1 patients received 75mgs (I/M) of Diclofenac sodium post incision and Group-2 patients received 100 mgs of Diclofenac transdermal patch, 6 hours prior to surgery. Post-operative analgesia was assessed using Visual Analogue Scale (VAS) and consumption of rescue analgesia. Additionally, Post-operative sedation was assessed by Ramsay sedation score (RSS) and Aldrete scoring. The data was statistically analyzed using various statistical tests and p- value of <0.005 was considered as statistically significant.*
RESULTS*: Post-operative Visual Analogue Scale (VAS) at various time intervals, consumption of rescue analgesia using Tramadol (no. of boluses and dose) were compared among two groups, which were almost same in both groups and were statistically insignificant.*
CONCLUSION*: The non-invasive route of transdermal patch of Diclofenac is as effective analgesic as intramuscular Diclofenac for mild to moderate post-operative pain of elective laparoscopic cholecystectomy.*
KEY WORDS: Transdermal, Intramuscular, Diclofenac, Post-operative, Analgesia.

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I. Introduction

Pain is derived from Latin word-*poena,* which means penalty or punishment. Pain is no longer considered as penalty or punishment. It is a protective mechanism designed to alert the body to potentially injurious stimuli. Pain is the fifth vital sign, says *Joint Commission on Accreditation of HealthCare Organization.* The *International Association for Study of Pain* has defined pain as – an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1]

Post-operative pain following laparoscopic cholecystectomy is less as compared to open cholecystectomy.[2] Early post-operative pain is the most common complaint after elective laparoscopic cholecystectomy.[3] In 17.41% of the patients, pain is the main reason for staying overnight in the hospital on the day of surgery and pain is the dominating complaint and the primary reason for the prolonged convalescence.[4-9]

Effective post-operative pain control is an essential component of care of the surgical patients. Various types of drugs are used for post-operative analgesia, of which narcotics and NSAIDs are the most important ones. Narcotics are known to cause drowsiness, constipation, urinary retention, hemodynamic and respiratory disturbances as compared to minimal side effects by NSAIDs. Diclofenac is one of the most commonly used NSAIDs. Oral administration is the route of choice in daily practice but it becomes impracticable in the peri-operative period in view of fasting requirement in peri-operative period. Its parenteral preparation is irritating and hence it is very painful at the site of administration. Development of skin, subcutaneous and even muscle tissue necrosis (Nicolau Syndrome), abscess formation etc are rare but serious complications of intramuscular injection of NSAIDs.[10] As the understanding of pain pathophysiology and management is increasing, new routes of drug delivery are being discovered with the objective of attempting to block pain at peripheral sites, with maximum active drug and minimum systematic effects. Topical (transdermal) preparations are the result of such experimentation which is expected to be free of drawbacks of oral, parenteral Diclofenac. Administration is also

very simple, non- invasive and offering the advantage of sustained drug delivery with reduced incidence of systemic side-effects due to lower plasma concentration.[11-12]

II. Material And Methods

After getting the study protocol approved by the institutional ethical committee and informed consent from each patient for incorporating into the study, 60 patients of either sex in the age group of 18-60 years and belonging to ASA-1 and ASA-2, who were scheduled to undergo elective laparoscopic cholecystectomies, were randomly allocated to one of the two groups (each having 30 patients).

A detailed history, physical examination and laboratory investigations were performed in all patients. On the evening before surgery, the visual analogue scale (VAS) scoring system was explained to all patients.

All patients were premedicated with oral diazepam (10 mgs) administered on night prior to surgery as night sedation. On the day of surgery, all patients were premedicated with injection Pantoprazole (40 mgs IV) and Midazolam (1 mg IV) in the holding up area before transferring the patient to operating room and baseline hemodynamic parameters viz; HR, NIBP, SpO_2 and ECG (standard chest leads) are recorded.

All patients were induced and maintained with standard anesthetic technique i.e. induced with fentanyl (1-1.5µgs/kg) and Propofol (2-3 mgs/kg) and tracheal intubation was facilitated with Atracurium (0.4- 0.5 mgs/kg). The anesthesia in all patients was maintained with oxygen in nitrous oxide (50% each) with Isoflurane (0.5-1.0%) supplementation. The muscle relaxation was maintained by incremental doses of Atracurium (0.1mgs/kg) as and when required.

Immediately after intubation a nasogastric tube was introduced and stomach was deflated prior to tilting of the patient and nasogastric tube was removed just before extubating the patient.

For post-operative analgesia, the patients were randomly allocated into two groups.

GROUP-1 received 75 mgs (1ml) of Diclofenac sodium intramuscularly (intragluteal) post-incision.

GROUP-2 received 100mgs Diclofenac sodium transdermal patch applied on the anterior chest wall 6 hours before surgery.

Pain was assessed using Visual Analogue Scale (VAS) of 0-10 with 0=no pain and 10=worst imaginable pain. Patients were assessed for pain with VAS at hourly interval for first 4 hours and then at 6^{th}, 8^{th}, 10^{th}, 12^{th} and 24^{th} hours. Rescue analgesia using injection Tramadol 1mg/kg was administered intravenously, anytime the VAS was found ≥ 3. Sedation was assessed by using Ramsey sedation score (RSS). Post-operative Aldrete score was also recorded. Frequency and total dose of Tramadol received and side effects such as nausea and vomiting were recorded over a period of 24 hours.

Vital signs viz; HR, NIPB, SpO_2, and ECG were also continuously monitored on hourly basis for 24 hours post-operatively.

The data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS (version 20.0) and Microsoft Excel were used to carry out the statistical analysis of data. Analysis of variance (ANOVA), Chi-square test or Fisher′s exact test, whichever appropriate were used for comparison of intergroup variables. p-value of<0.005 was considered as statistically significant.

III. Results

The demographic profile (Age, Sex, Weight, ASA status) and intra-operative & post-operative hemodynamic parameters (HR, NIBP, SpO_2, ECG) among two groups were more or less similar and were statistically insignificant

Table.1 Demographic Profile of patients in two groups.

Parameters	Group-1	Group-2	p-value	Remarks
Age(years)± Mean	41.43±5.11	42.53±9.32	0.497	Insignificant
Weight(kgs)± Mean	57.30±8.85	56.60±9.48	0.786	Insignificant
Sex(M:F)	8:22	9:21	0.796	Insignificant
ASA(1:2)	18:12	21:9	0.806	Insignificant

When the two groups were compared with regard to post-operative analgesia, as assessed by VAS scoring and requirement for rescue analgesia (tramadol) in terms of frequency and dosage at various time intervals, it was observed that 46.7% of patients in Group-1 and 40% of patients in Group-2 required no rescue analgesia. Also 33.3% of patients in Group-1 and 36.7% of patients in Group-2 received one bolus of tramadol. In Group-1, 16.7% and in Group-2, 13.3% of patients received two boluses, 3.3% and 10% of patients in Group-1 and Group-2 received three boluses of Tramadol in first 24 hours post-operative period. The data when compared among two groups was statistically insignificant with p-value of 0.602.

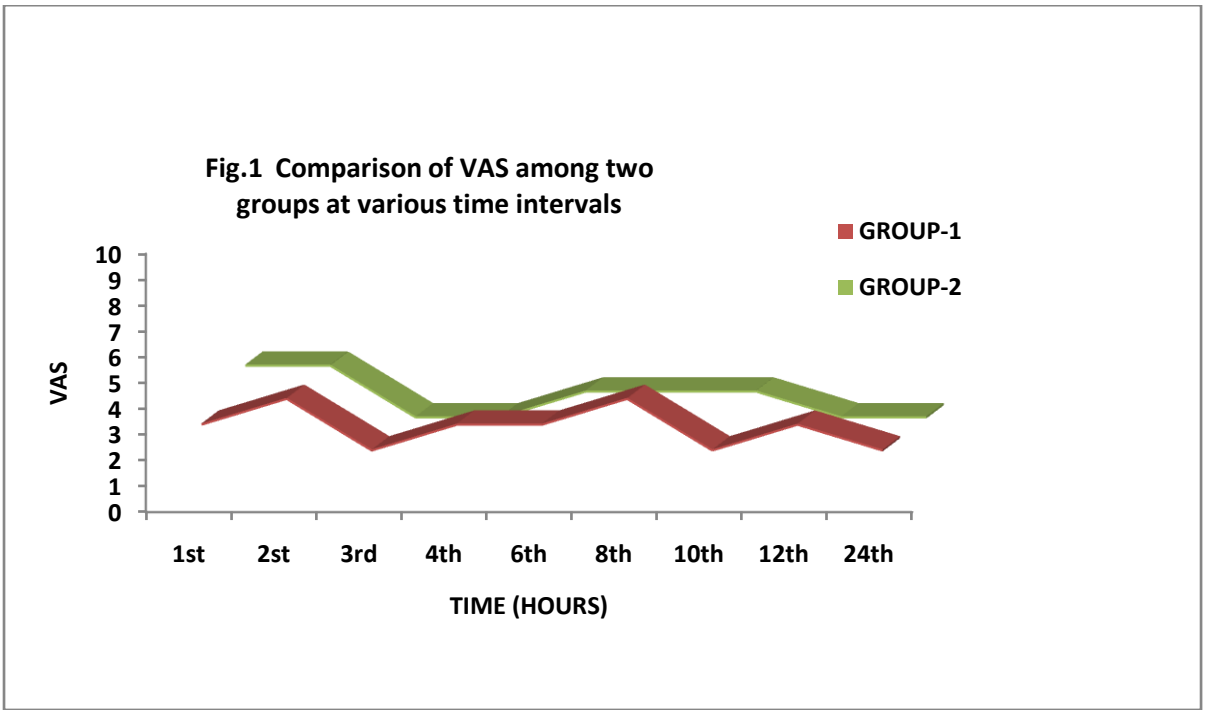


Fig.1 Comparison of VAS among two groups at various time intervals
GROUP-1
GROUP-2
VAS
10
9
8
7
6
5
4
3
2
1
0
1st
2st
3rd
4th
6th
8th
10th
12th
24th
TIME (HOURS)

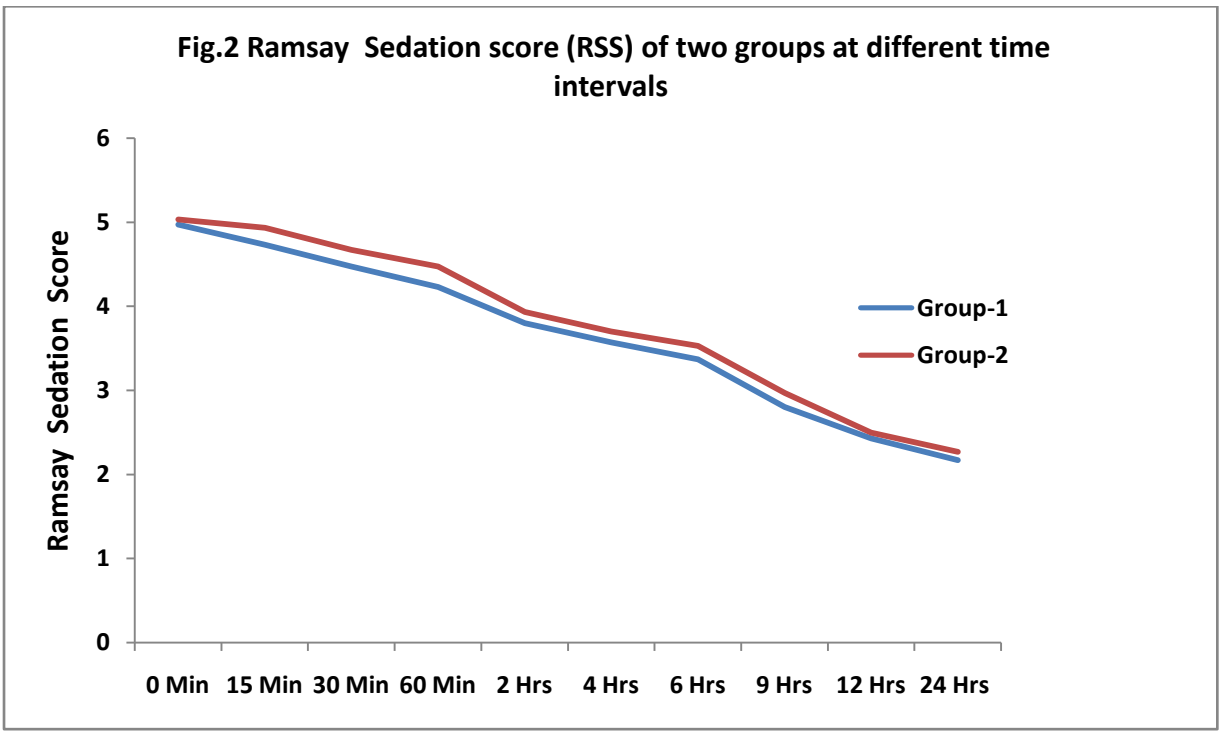
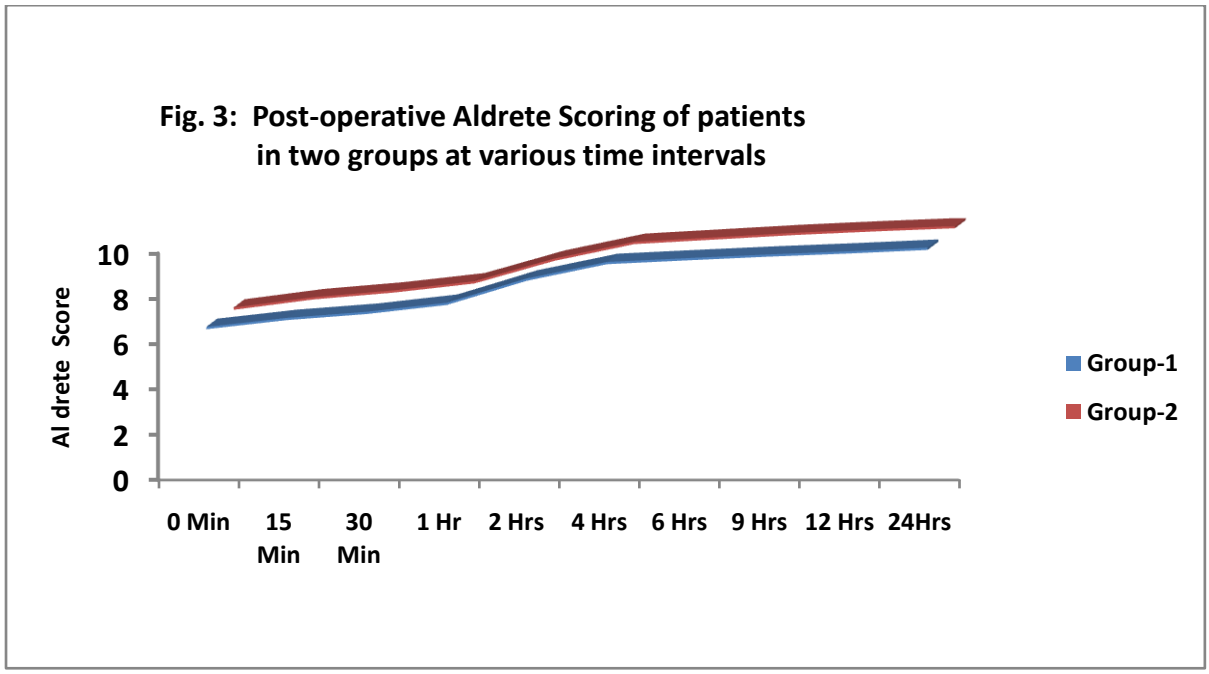
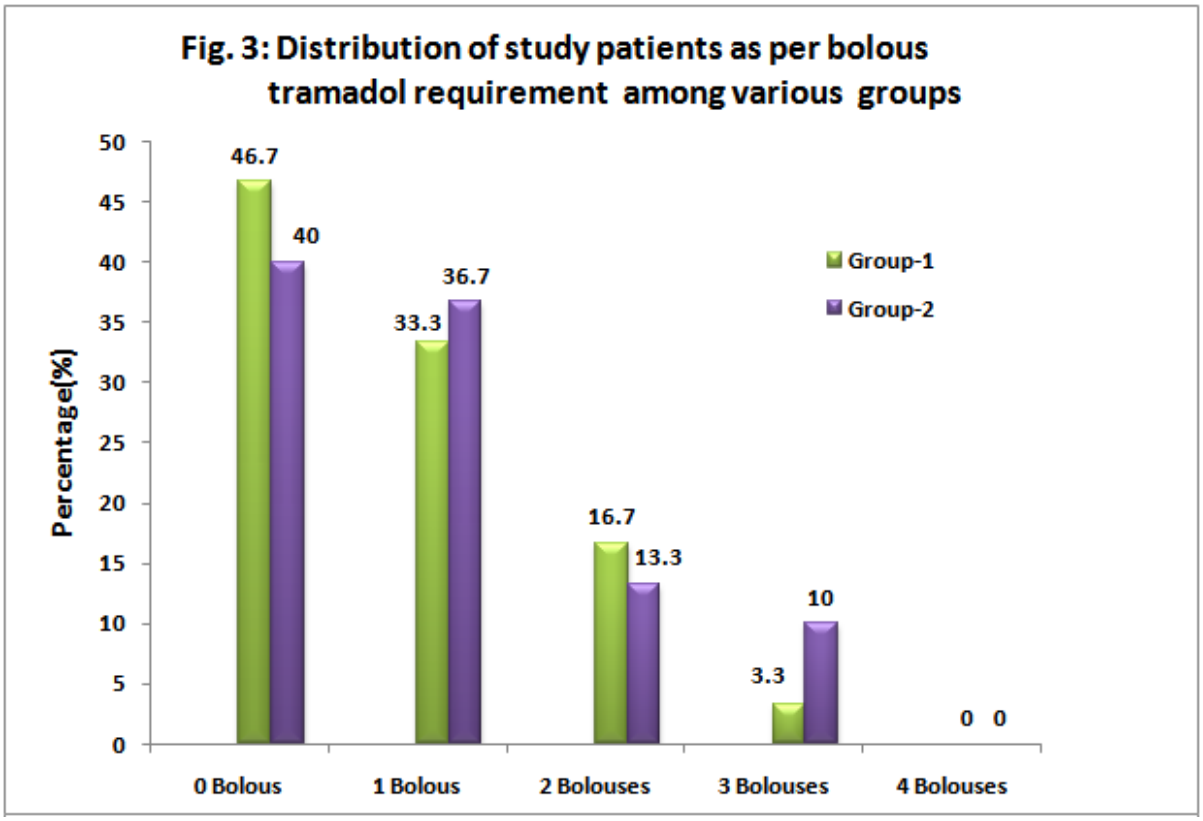
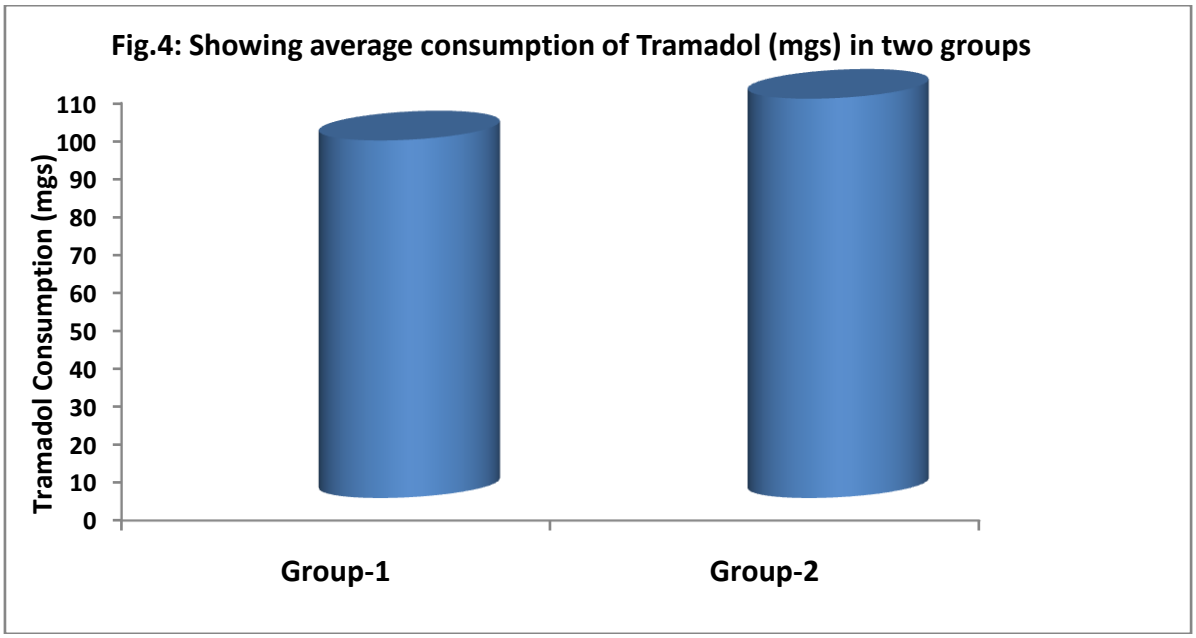


Fig.2 Ramsay Sedation score (RSS) of two groups at different time intervals
Ramsay Sedation Score
6
5
4
3
2
1
0
Group-1
Group-2
0 Min
15 Min
30 Min
60 Min
2 Hrs
4 Hrs
6 Hrs
9 Hrs
12 Hrs
24 Hrs



The mean dose of Tramadol as rescue analgesia, consumed in Group-1 was 94.2 mgs and 105.2 mgs in Group-2. So overall, the rescue analgesic requirement was more or less same and when compared among two groups, was statistically insignificant.





IV. Discussion

The nature of pain varies depending on the surgical technique. Following laparotomy, patients complain more of parietal pain (e.g. abdominal pain) whereas after laparoscopic cholecystectomy, patients also report visceral pain. In addition to post-operative pain of various types, the most frequent complaints are headache, nausea and vomiting etc. Post-operative nausea and vomiting (PONV) is one of the main complaints after laparoscopy (40-70% of patients) and one of the important factors determining the delay in discharge from a day care facility.[13]

Diclofenac sodium is a traditional NSAID that possesses anti-inflammatory, analgesic and antipyretic properties. [14] It is among the most widely prescribed NSAIDs worldwide. [15]

Pre-emptive analgesia gives rise to a subsiding pain pattern, a decreased analgesic requirement, and a decline in morbidity, promoting wellbeing and shortening the length of hospital stay.[16-19]

The present study was undertaken with the aim of evaluating the effectiveness of transdermal Diclofenac and compare it with intramuscular route, as assessed by VAS scoring and consumption of rescue analgesia in post-operative period in patients undergoing elective laparoscopic cholecystectomies in our institution.

In our study, there was no significant difference among two groups as far as demographic profile (age, sex, weight, ASA status) and baseline hemodynamic parameters (HR, NIBP, SpO_2, ECG) were concerned. Similar results were observed by *Sedef Gulcin Ural et al (2014)* [20] in their study regarding demographic profiles and hemodynamic parameters.

In our study, post-operative sedation score (Ramsay Sedation Score) and post-operative Aldrete scoring among two groups were statistically insignificant, which was in consensus with *Sedef Gulcin Ural et al (2014).*

As regards to post-operative analgesia**,** as assessed by VAS scoring and requirement for rescue analgesia, when VAS scoring was compared between two groups at various time intervals, there was statistically insignificant difference among two groups with p-value of 0.532. When compared, the frequency of bolus administration in two groups, 46.7%(14) in Group-1 and 40%(12) in Group-2 required no rescue analgesia. 53.3% of patients in Group-1 and 60% of patients in Group-2 required rescue analgesia, which was statistically insignificant among two groups with p-value of 0.602. When considered the total dose of rescue analgesia, Group-1 received mean tramadol dose of 94.2 mgs, while as patients in Group-2 received mean tramadol dose of 105.2 mgs. Comparison of tramadol consumption between two groups was statistically insignificant with p-value of 0.597. Our study results were in consensus with the results of *Krishna & Natraj (2012)*[21] and *Pragiti Arora Trivedi (2015)*[22] where they compared efficacy of single dose of Diclofenac transdermal patch with Diclofenac injection (IM) as a pre-emptive post-operative analgesia.

In our study, the side effects like PONV, had occurred in 10%(3) patients in Group-1, while in Group-2, 6.7%(2) patients developed PONV. However, the results were statistically in significant with p-value of 0.455.

After analyzing the results, it can be concluded that in patients undergoing elective laparoscopic cholecystectomy, intramuscular Diclofenac provides almost same analgesia as transdermal patch of Diclofenac. However, transdermal patch of Diclofenac, being non-invasive, seems to be a promising analgesic modality for the management of mild to moderate pain given the evidence of its established analgesic efficacy and lower incidence of systemic adverse effects. When applied six hours prior to surgery Diclofenac patch effectively reduced the post-operative pain.

V. Conclusion

For patients undergoing laparoscopic surgeries having mild to moderate pain, NSAIDs, especially Diclofenac is the most widely prescribed analgesic in post-operative period. Transdermal patch of Diclofenac provides as effective analgesic as intramuscular injection of Diclofenac, bur being non-invasive, transdermal patch of Diclofenac seems to be a promising alternative analgesic modality for the management of mild to moderate pain given the evidence of its established analgesic efficacy and lower incidence of systemic adverse effects. When applied six hours before surgery, Diclofenac transdermal patch effectively reduced the post-operative pain, hence reducing the requirement of post-operative opioids.

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