Original Research Article

Comparative Evaluation of Preoperative Administration of Single Dose Intravenous Paracetamol or Intravenous Diclofenac for Management of Postoperative Pain in Laparoscopic Cholecystectomy

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Abstract

Background: Post-operative pain affects the patient's operative outcome, well being and satisfaction from medical care. Pain is one of the most common causes of delay discharge in patient undergoing surgery. Paracetamol and diclofenac are the two non-opioid drugs that are being used in postoperative care in combination with opioids or alonewhere uses of opioids are contraindicated. Thus, present study conducted to compare efficacy of pre operatively administered single dose iv paracetamol or iv diclofenac for treatment of postoperative pain in laparoscopic cholecystectomy. **Materials & Methods:** A prospective interventional randomized comparative study was conducted in the department of Anaesthesiology, Critical Care and Preoperative Medicine, Hindu Rao Hospital and North Delhi Municipal Corporation Medical College, Delhi after obtaining approval of the ethical committee of the institution and written informed consent from all patients. In this study 64 Patients were randomly divided into two groups: Group P (n=32) and Group D (n=32) denoting Paracetamol and Diclofenac respectively. Test drugs were administered 30 minutes prior to induction and postoperative pain was evaluated using Visual Analogue Scale (VAS) score at 30 min, 1 h, 2 h, 3 h, 4 h, 8 h, 12 h, and 24 h (T13, T14, T15, T16, T17, T18, T19 and T20 respectively). Postoperative consumption of injection tramadol (2 mg/kg) i.v. was measured which was given as a rescue analgesic, whenever the patient complained of pain or VAS >3 or both, at any time after surgery within the first 24 hrs with a minimum duration of 4 hours between each dose. **Results:** Visual analogue scale (VAS) score was significantly lower in group P (paracetamol) as compared to group D (diclofenac) in the post-operative period at 30 min (T13: p=0.040), 1 hour (T14: p= 0.025), 3 hour (T16: p=0.018), 4 hour (T17: p<0.001), 8 hour (T18: p=0.007) which was statistically significant (p value<0.05).Total dose of recue analgesic consumed was significantly higher in group D as compared to group P (P=0.006).Time at which first dose of rescue analgesic required was significantly higher in group D as compared to group P (p=0.05). First dose of recue analgesic was required in group P at 4th hour postoperatively as compared to diclofenac where first dose of recue analgesic was required at 1st hour. **Conclusion:** We concluded that preemptive administration of intravenous paracetamol 1g/100 ml in patients undergoing laparoscopic cholecystectomy surgeries has better hemodynamic stability and provides more effective and longer duration of postoperative analgesia with decreased pain scores during postoperative period.

Keywords: Preemptive Analgesia, Paracetamol, Diclofenac, Rescue analgesia, Pain

Introduction

Development of laparoscopic surgeries has brought a tremendous change in the field of general surgery in the last decade after its introduction by Dimitri Ott Georg Kelling and Hans Christian Jacobeus. Laparoscopic cholecystectomy was first performed by Phillipe Mouret of Lyon, France in 1987 and has received an rapid acceptance both by patients as well as surgeons[1].Laparoscopic surgeries are most popular in recent days because of lower post operative morbidity including faster recovery time, shorter hospital stay, less pain and in some cases fewer complications[2]. After laparoscopic surgery, postoperative pain is major concern that limit an otherwise speedy recovery. Individual variations in response to pain are influenced by the genetic makeup, cultural background and gender[3]. Pain after laparoscopic cholecystectomy is usually acute in character[4]. Although it is less intense than following open cholecystectomy[5]. and multifactorial [6]. In laparoscopic cholecystectomy, overall pain is a combination of three clinically different components: incisional pain (somatic pain), visceral pain (deep intra abdominal pain) and shoulder pain (presumably referred visceral pain). Acute postoperative pain is a complex physiological reaction results from the tissue damage and detrimental since it can increase the patient's discomfort and may get transformed into chronic pain due to sensitization of the peripheral and central pain pathways[7]. Tissue damage leads to alterations, or modulations, of both the peripheral and the central pain pathways. Post operative pain affects the patient's operative outcome, well being and satisfaction from medical care[8]. Pain is one of the most common causes of delay discharge in patient undergoing surgery. In untreated cases it could lead to chronic postoperative pain after surgery[9]. Successful postoperative analgesia prevents the majority of pain-related effects occurring in the patient, such as inadequate ventilation, increased workload in the cardiovascular system,

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thromboembolic events with delayed mobilization, and increased stress response with neuroendocrine and sympathetic nervous system activation[10] and thus leads to early ambulation and discharge, reducing duration of hospital stay. Preemptive analgesia is a treatment that is initiated before and is operational during the surgical procedure in order to reduce the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this 'protective' effect on the nociceptive pathways, preemptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate post-operative pain may be reduced and the development of chronic pain may be prevented[7].Local anesthetics, opioids, non-steroid anti-inflammatory drugs (NSAIDs) and acetaminophen group drugs can be delivered either alone or in combination for preemptive analgesia [11]. Opioids has good analgesic properties in the treatment of acute, intense postoperative pain after major and minor surgery[12]. Prophylactic use of opioids in patients after laparoscopic cholecystectomy is best avoided for rapid recovery and to facilitate earlier discharge[13].Non opioid analgesics (Paracetamol, NSAIDS) are commonly used alone or in combination with opioids for relieving postoperative pain. Thus, prescribed method of reducing and minimizing side effects is concomitant administration of nonopioid analgesics[14].Paracetamol and diclofenac are the two non-opioid drugs that are being used in postoperative care where uses of opioids are contraindicated[15].Paracetamol mechanism of action is complex and includes the effects of both the central (COX, seretoninergic descending neuronal pathway, L-arginine/ NO pathway cannabinoid system) antinociception processes and "redox" mechanism and the peripheral (COX inhibition)[16].Diclofenac is a phenyl acetic acid derivative belonging to the carboxylic acid class of NSAIDS. It is an inhibitor of cycloxygenase enzyme, involved in the metabolism of arachidonic acid into various prostaglandins mediators of inflammation and pain[17].Non steroidalanti-inflammatory drugs (NSAIDS) block the nociceptive response to endogenous mediators of inflammation, with the effect being greatest in tissues that have been subjected to injury and trauma[18].Preemptive analgesic efficacy of paracetamol and diclofenac has been demonstrated in earlier studies[19-21].Previous studies have concluded that iv paracetamol gives better quality of analgesia than iv diclofenac in postoperative period but some studies concluded that in spite of that it is not suitable analgesic for moderate pain control in acute phase of surgery[20]. Some other studies concluded that NSAIDS like ketorolac provides better pain relief with less complication than single dose preemptive iv paracetamol alone[21].Thus present study conducted to compare efficacy of pre operatively administered single dose iv paracetamol or iv diclofenac for treatment of postoperative pain in laparoscopic cholecystectomy.

Materials& Methods

A prospective interventional randomizedcomparativestudywas conducted in the department of Anaesthesiology, Critical Care and Perioperative Medicine, Hindu Rao Hospital and North Delhi Municipal Corporation Medical College, Delhi after obtaining approval of the ethical committee of the institution and written informed consent from all patients. Patients were subjected to thorough pre-anaesthetic check-up comprising general physical examination, airway examination and routine investigations. Special relevant investigations were conducted as and when required.

Inclusion Criteria

- Adult patient aged between 18-60 years of either sex, scheduled to undergo elective laproscopic cholecystectomy under general anaesthesia.
- ASA Grade I and II patients.
- Mallampatti grade I and grade II
- Patient weighing 45 kg to 80 kg

Exclusion Criteria

- Psychiatric diseases
- Patients with a known history of allergy, sensitivity.
- Any coexisting condition like hypertension, diabetes, cardio-pulmonary, hepatic, renal, metabolic diseases.
- Patients with clotting disorder
- Laparoscopic cholecystectomy converted to open due to any reason.

Groups-Patients were randomly divided into two groups through a computer-generated sequence of random alphabets 'P' and 'D' denoting Paracetamol and Diclofenac respectively.

Group P (n=32) Paracetamol group: This group was received 100 ml of paracetamol preoperatively over 15 minutes, Paracetamol 1% (10 mg/ ml).

Group D (n=32) Diclofenac group: This group was received 75 mg of diclofenac diluted in 100 ml of 0.9% normal saline infused over 15 minutes (75 mg/ ml).

Methodology

After shifting the patient to preoperative room iv line was secured with 18G/20G cannula and the study drugs were administered in double blind manner approx 30 minutes prior to induction and after giving test drug ringer lactate was started.Anaesthesia was standardized in all patients. After preoxygenation for 3 minutes with 100% oyygen, patient was induced with intravenous propofol 1-2 mg/kg iv titrated to the loss of verbal response. Inj. vecuronium was administered at a dose of 0.1mg/kg, to produce neuromuscular block, the patient was mask ventilated for 3 minutes (min). The patient was intubated with an appropriate sized, cuffed,oro tracheal tube under direct vision laryngoscopy and the correct position of tube was verified by auscultation of the chest and by capnography. After securing airway patients were maintained on O_2 and N_2O (40:60 ratio), Sevoflurane (MAC- 1.3) and Vecuronium 0.05mg/kg intermittently. The incisional sites were infiltrated with 12 ml of 0.25% bupivacaine. At the end of surgery, ondansetron 0.01mg/kg i.v. was administered. The lung was ventilated at the rate of 12-16/min to maintain the end-tidal carbon dioxide partial pressure within normal limits. All patients received calculated fluid intraoperatively as per requirement. After the procedure patient was reversed with Inj. neostigmine 0.05 mg/kg and Inj. glycopyrrolate 0.01 mg/kg IV. The patient was extubated after proper oropharyngeal suctioning and after returning of airway reflex with adequate reversal of muscle power. In the event conversion to open surgery or other patient was excluded from the study group.Postoperative pain was evaluated using Visual Analogue Scale (VAS) score. Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score determined by measuring in millimetres from the left-hand end of the line to the point that the patient marks. In this study VAS score of 0 was considered as no pain, 1 as mild, 2-3 as moderate and more than 3 as severe pain.

Rescue Analgesic-Injection tramadol (2 mg/kg) i.v. was given as a rescue analgesic, whenever the patient complained of pain or VAS >3 or both, at any time after surgery within the first 24 hrs with a minimum duration of 4 hours between each dose. The total dose of rescue analgesic consumed postoperatively and time to first dose of rescue analgesia required were noted.

Statistical Analysis-Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Results

The mean age (yrs) in Group D (diclofenac) was found to be 37.34±10.94, in Group P (paracetamol) was 37.16±10.91 which were comparable with each other with a p value of 0.945 which was not significant. The mean weight(kg) in Group D (diclofenac) was found to be 54.97 ± 7.24, in Group P (paracetamol) was 55.59±8.14 which were comparable with each other with a p value of 0.747 which was

not significant (table 1). There was no statistically significant difference in the distribution of gender in between the two groups (table 2).Visual analogue scale (VAS) score was significantly lower in group P (paracetamol) as compared to group D (diclofenac) in the post-operative period at 30 min (T13: p=0.040), 1hour(T14: p=0.025), 3 hour(T16: p=0.018), 4 hour(T17: p<0.001), 8 hour(T18: p=0.007) which was statistically significant (p value<0.05) (Figure 1).Four out of 32 patients in group D (diclofenac) developed nausea and vomiting postoperatively. One out of 32 patients in group P (paracetamol) developed postoperative nausea and vomiting. This was not statistically significant with the p value of 0.355 (table 3).Total dose of recue analgesic consumed was significantly higher in group D as compared to group P (P=0.006).Time at which first dose of rescue analgesic required was significantly higher in group D as compared to group P (p=0.05). First dose of rescue analgesic was required in group P at 4th hour postoperatively as compared to diclofenac where first dose of recue analgesic was required at 1st hour (table 4). Comparison of duration of surgery between both the groups were comparable (p=0.764)(table 5).

Table1: Age (years) and Weight (kg) distribution between the two groups: Group D (diclofenac) and Group P (paracetamol)

		Group D(Diclofenac)	Group P(Paracetamol)	P value
Age (Yrs.)	Mean ±SD	37.34 ± 10.94	37.16 ± 10.91	0.945(NS)
Weight (kg)	Mean±SD	54.97 ± 7.24	55.59 ± 8.14	0.747(NS)

NS- Not significant (P<0.05 is significant)

Table 2: Sex Distribution Between The Two Groups

Sex	Group D(Diclofenac) Frequency(%)	Group P(Paracetamol) Frequency(%)	Total	P value
F	26(81.25%)	24(75.00%)	50(78.13%)	0.545(NS)
M	6(18.75%)	8(25%)	14(21.88%)	
Total	32 (100%)	32 (100%)	64 (100%)	

Table 3: Comparison of various adverse effects between the two groups

		Group D(Diclofenac)	Group P(Paracetamol)	Total	P value
Vomiting	No	28 (87.50%)	31 (96.88%)	59 (92.19%)	
	Yes	4 (12.50%)	1 (3.13%)	5 (7.81%)	
Total		32 (100.00%)	32 (100.00%)	64 (100.00%)	0.355

Table 4: Comparison of total dose of rescue analgesic consumed (mg) in both the groups:

Rescue analgesic	Group D(Diclofenac)	Group P (Paracetamol)	P value
Total dose of tramadol consumed (mg)	Mean±SD	Mean±SD	
	134.375 ± 54.53	93.75 ± 56.44	0.006
Time at which first dose of rescue analgesic required	2.94 ± 2.45	5.69 ± 5.41	0.05

S-Significant, NS- Not significant

Table 5: Comparison of duration of surgery between both the groups

Duration of surgery	GroupD(Diclofenac)	Group P (Paracetamol)	P value
Sample size	32	32	0.764
Mean ± SD	74.06 ± 12.6	73.12 ± 12.49	
Median	75	75	
Min-Max	60-90	60-90	
Inter quartile Range	60 - 90	60 - 90	

S-Significant, NS-Not significant

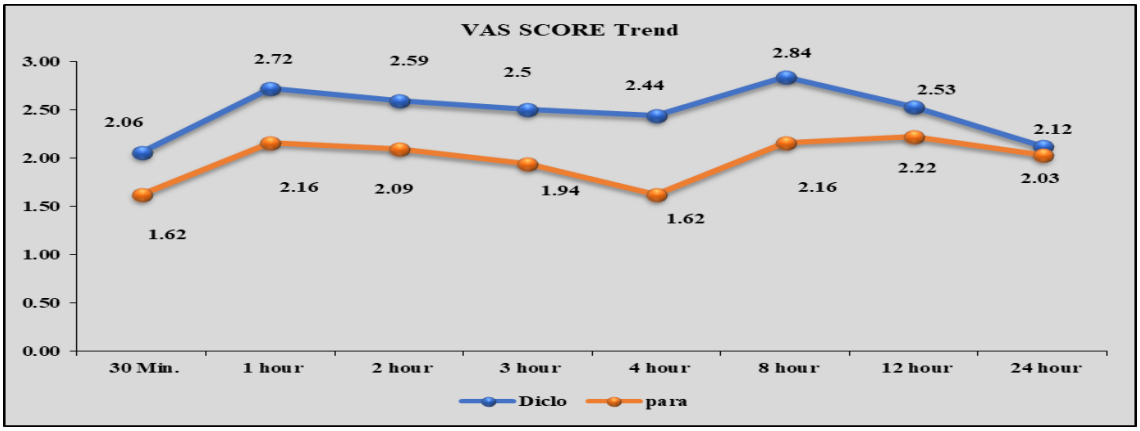

Fig 1: Intergroup comparison of VAS score changes between the two groups

Discussion

One of the major benefits of laparoscopic technique compared with standard open surgery is the reduction of post operative pain[22]. Although pain after laparoscopic cholecystectomy is less intense than open cholecystectomy, some patients still experience considerable discomfort. Laparoscopic pain is complex and consists of parietal pain (abdominal wall), visceral pain and shoulder pain. Shoulder pain secondary to diaphragmatic irritation as a result of CO2, pneumo peritoneum is a frequent postoperative observation after laparoscopy [23]. Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain (e.g., post laparoscopic cholecystectomy syndrome)[24]. Although pain is a subjective sensation varying from person to person depending upon psychosomatic personality, age and nature of operation. Inadequate pain management leads to various complications like atelectasis/ pneumonitis/hypoxemia, deep vein thrombosis, pulmonary embolism delayed recovery of bowel function, myocardial ischemia and infarction, urinary retention and residual psychological trauma thereby leading to `delayed immobilization and longer duration of hospital stay[25].The complex nature of pain after laparoscopic cholecystectomy suggests that effective analgesic treatment should be multimodal[26]. The most effective means to decrease pain significantly is a combination of pre-emptive analgesia and multimodal pain management. Multimodal therapy allows for lower dosages of any one medication to be used in combination, which reduces the risk of a significant side effect arising from administration of a single analgesic drug[27].Preemptive analgesia has been defined as an antinociceptive treatment starting before surgery that prevents establishment of altered central processing of afferent input from injuries. The nociceptive input is blocked, well into the postoperative period, and cover the period of tissue injury associated with post operative inflammation. Therefore, the concept of preemptive analgesia may have a role in reducing not only acute postoperative pain but also the chronic pain[21]. Preemptive analgesia gives rise to a subsiding pain pattern, a decrease in analgesic requirements, and a decline in morbidity, promoting wellness and shortening the length of hospital stays.

Hossam Ibrahim et al(2014)[28] did a study to compare between preemptive and preventive analgesic efficacy of i.v. paracetamol and concluded that preemptive paracetamol was more effective than preventive paracetamol.Kokhno VN et al(2009)also studied impact of preemptive analgesia using ketorolac and paracetamol on postoperative pain syndrome in laparoscopic surgery and observed that preemptive analgesia could reduce the degree of postoperative pain syndrome and paracetamol produced a more powerful antistress defense[29]

Rastogi B et al[21] compared the preemptive analgesic efficacy of intravenous paracetamol versus ketorolac after laparoscopic cholecystectomy and concluded that preemptive use of ketorolac provides better analgesia in comparison to paracetamol without any significant side effect.Effective analgesic therapy is an important component of post operative follow up. Opioids are the most preferable analgesic agents during early post operative period after laparoscopy. However, opioids could cause some serious adverse effects such as over sedation, depression of respiration and gastrointestinal motility, nausea and vomiting[13]To continue to improve the patient experience with laparoscopy and to minimize the opioid analgesia required after surgery some additive and synergic drugs such as local infiltration through incisional trocar sites, non steroids anti-inflammatory drugs (NSAID), paracetamol are used in pain management after laparoscopic surgery[30]

Both the groups were comparable with respect to age, sex, weight. All patients in the study were of ASA class I with no significant comorbidities and were comparable in both the groups. Duration of surgery in both the groups were comparable (p=0.764). Hemodynamic parameters: Baseline hemodynamic parameters were comparable in both the groups (P>0.05) Mean changes in VAS score were significantly higher in group D as compared to group P post operatively at 30 min (p=0.040), 1hour (p=0.025), 3 hour (p=0.018), 4 hour (p=0.0001), 8 hour (p=0.007) which were statistically significant.However, at 2 hour (p=0.053), 12h (p=0.259) and 24h(0.737) the VAS score was comparable in the two groups. Salihoglu Z et al[31] in 2009 did a study to assess preemptive analgesic efficacy of intravenous paracetamol 1g/100ml administered after intubation before the start of surgery in patients undergoing laparoscopic cholecystectomy and 100ml 0.9% NaCl was infused iv in control group in 15 min. Verbal and visual pain score were significantly lower in paracetamol group than control group (P<0.05). They concluded that paracetamol has effective analgesic properties and hastens the recovery.Settecase C et al[32] in 2002 did a study to determine preemptive analgesic efficacy of diclofenac in the first 24 hours after elective laparoscopic cholecystectomy (ELC). Diclofenac 1 mg/Kg intramuscularly was administered 60 minutes before surgery and infused saline solution after extubation and found no significant differences in pain intensity (p=0.96) or need for rescue analgesia. They concluded that preemptive analgesia with diclofenac does not decrease pain intensity or the need for rescue analgesia in the first 24 hours after ELC. In our study we found mean VAS score was significantly higher in diclofenac group as compared to paracetamol group at different intervals.Bandey et al[33] in 2016 also found in their study that at 30 min and 1.5h, mean VAS score in paracetamol group (3.10±0.61 and 2.53±0.63 respectively) was significantly lower as compared to that in tramadol group (3.47±0.51 and 3.03±0.93 respectively). They concluded that paracetamol is better for post operative pain and recommended that intravenous infusion of paracetamol can safely and effectively be given for postoperative pain relief in patients undergoing laparoscopic cholecystectomy.Swaika S et al (2013)[34] did comparison between iv paracetamol and dexmedetomidine and they observed that visual analog scale scores were significantly lower in the Group P(paracetamol) compared with Group D (dexmedetomidine) at 8th, 16th, and 24th h (P < 0.001) and concluded that paracetamol peri-operatively provides adequate analgesia with the less sedation whereas dexmedetomidine provides analgesia and co-operative sedation.Ankaamin et al[35] in 2016 did comparison between iv paracetamol and iv diclofenac and they found lower mean score in paracetamol group which was statistically significant postoperatively at 0h, 1h, 4h, 6h (p=0.005, p=0.003, p=0.001, p=0.005 respectively) and concluded prolonged analgesia with low pain scores and lesser requirement for rescue analgesia compared to diclofenac with less complications.Goel P et al (20130[36] found mean pain score was higher in diclofenac group as compared to paracetamol group and they concluded that preemptive paracetamol is long acting and provides better analgesia than diclofenac with lesser side effects.Arici S et al (2009)[37] found in their study that VAS score was significantly higher in group III(control) compared to group II(preventive) and in group II as compared to group I(preemptive). They concluded that preemptive iv paracetamol provided good quality of analgesia.Hossam Ibrahim et al[28] in 2014 also found preemptive group had higher pain scores in immediate postoperative period and after 6h (P<0.001) but preventive group had higher pain scores at 4 and 8 h postoperatively (P<0.01). They concluded that preventive paracetamol had longer duration of analgesia and longer time for first analgesia required with less opioid related complications.In our study total dose of recue analgesic consumed postoperatively was significantly lower in group P (134.375 ± 54.53) as compared to group D (93.75±56.54) (p=0.006). Time at which first dose of rescue analgesic required was significantly higher in group P (5.69±5.41) as compared togroup D (2.94±2.45) (p=0.05) and it was observed that paracetamol had longer duration of analgesia than paracetamol. Salihoglu Z et al[31] in 2009 did a study and observed time at which first dose of rescue analgesic required in paracetamol group was higher 15±3min as compared to control group 5±3min. Total administered dose of rescue analgesic in

paracetamol group was lower 2.3±3mg as compared to control group 6.1±5mg. They concluded that paracetamol has effective analgesic properties.

Arici et al in 2009 did study to assess efficacy of iv paracetamol as preemptive and preventive and found that total dose of rescue analgesic consumed was lower with pre-emptive group (25.93±5.69) as compared to preventive (35.73±5.24) and control group (62.93±8.67)[37] They concluded that preemptive iv paracetamol reduced rescue analgesic consumption and side effects thereby shortens the length of hospital stay.

In our study 4 patients in group D (diclofenac), 1 patient in group P (paracetamol) developed postoperative nausea and vomiting. This was not statistically significant with the p value of 0.355.

Arici et al (2009) found that in preemptive group 5 patients, preventive group 6 patients and in control group 19 patients developed nausea vomiting. They concluded that preemptive iv paracetamol had minimal postoperative side effects[37]

Kumkumgupta et al (2012) compared between iv paracetamol(1g) and parecoxib(40mg) and found that only 2 patients had nausea in paracetamol group as compared to 4 patients in parecoxib group and concluded that both study drugs were well tolerated with less side effects postoperatively[38]

Hossam Ibrahim et al (2014) found that postoperative nausea vomiting seen in 4 patients with pre-emptively administered paracetamol as compared to 6 patients in preventive group and concluded that low incidences of side effects with preemptive paracetamol[28]

Debashish Paul et al2015 found that postoperative nausea vomiting seen in 4 patients in the diclofenac group none of the patients in paracetamol group had any complications and they concluded that there was no significant difference in both the groups with respect to side effects[39]

Conclusion

We concluded that preemptive administration of intravenous paracetamol1g/100ml in patients undergoing laparoscopic cholecystectomy surgeries has betterhemodynamic stability and provides more effective and longer duration ofpostoperative analgesia with decreased pain scores during postoperative period.

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