



**ORIGINAL RESEARCH PAPER**

**Anaesthesiology**

**INTRAVENOUS PARACETAMOL FOR POST OPERATIVE ANALGESIA IN LAPAROSCOPIC CHOLECYSTECTOMY SURGERY**

**KEY WORDS:** Paracetamol, Diclofenac, laproscopic cholecystectomy, postoperative analgesia.

**Dr. Anisha Chokshi** MD Anaesthesia, Associate Professor, B.J. Medical College, Ahmedabad, Gujarat, India

**Dr. Hetal Sonavane\*** Senior Resident Doctor, B.J. Medical, College, Ahmedabad \*Corresponding Author

**Dr. Dinesh Babariya** 3<sup>rd</sup> yr Resident Doctor, B.J. Medical College, Ahmedabad

**Dr. Maulik Zalavadia** 3<sup>rd</sup> yr Resident Doctor, B.J. Medical College, Ahmedabad

**ABSTRACT**

**Aims of Study:** Find out the utility of IV Paracetamol for the purpose of post operative analgesia, To evaluate the efficacy and safety of IV Paracetamol for post operative analgesia, To compare the effectiveness of IV Paracetamol with the IV Diclofenac.

**Material and Method:** Study was conducted on 50 adult patients of either sex and ASA grade 1 and 2 undergoing laproscopic cholecystectomy, Patients were randomly divided into two groups; each group included 25 patients. **Group D**, patients received diclofenac 75 mg intravenous. **Group P**, patients received Paracetamol 1 gm intravenous. The drug was given 30 min before extubation intravenously. HR, BP, and pain scores were recorded immediately after surgery and at 30 min, 4, 8, 12 and 24 hr after surgery. Pain scores were evaluated using a 0–10 mm VAS (0 - no pain, to 10 - worst pain imaginable). Inj Diclofenac was used as rescue analgesia when VAS score>4.

**CONCLUSION:** IV paracetamol is safe and effective alternative for postoperative analgesia compared to IV diclofenac; which results in prolonged duration of analgesia and significant reduction in requirement of supplementary analgesic postoperatively without any significant side effect.

**INTRODUCTION**

The relief of pain has been one of the major reasons for the development of health care. Acute pain management as a specialty came into force in 1988 in Seattle when Brain Ready published his concept of acute pain services. Pain is recognized by the INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN (IASP), which defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"(IASP 1979). Pain has been introduced as the 5th vital sign by the Joint Commission on Health Care Organizations (JCAHO).

Inadequate postoperative pain relief is the most frequent complaint of surgical patients in postoperative settings. It is well documented that pain is often inadequately treated, can be deleterious and can lead to a number of complications in post operative period.

The technical skills & pharmacological knowledge required to treat the pain during surgery render the anesthesiologist as an ideal person to do so in the postoperative period. Any method of postoperative analgesia must meet basic criteria like it must be safe, effective and feasible.

Laparoscopic surgery is the most popular trend in recent days. It is a minimal invasive surgery with early ambulation and early discharge, which is the main advantage of this surgery. So, for that, adequate analgesia is of utmost importance.

Different modes of modality for pain relief used for the relief of postoperative like epidural, spinal, intravenous, intramuscular and transdermal. Intravenous route of analgesia is routinely used and widely accepted Paracetamol is COX-3 mediated central action and that's why it is not associated with the increased incidence of nausea, vomiting, respiratory depression and biliary spasm observed with opioids. The NSAIDs and cyclooxygenase (COX)-2 inhibitors are associated with deleterious gastrointestinal, hematologic, and renal effects. Lack of inhibition of COX-1 peripherally by paracetamol may explain its favorable safety effect. Perioperative administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) has been advocated to provide

"multimodal" or "balanced" analgesia that decreases opioid dose requirements and may reduce associated adverse events while reducing postsurgical pain intensity.

The purpose of this study was to determine the efficacy and safety of the paracetamol for the control of postoperative pain and to compare the effectiveness of paracetamol with Diclofenac in terms of analgesic requirement and level of pain relief.

**AIMS AND OBJECTIVE**

- To evaluate the efficacy and safety of IV Paracetamol for post operative analgesia
- To compare the effectiveness of IV Paracetamol with the IV Diclofenac;
- The total duration of post operative analgesia
- Total requirement of supplementary analgesic
- Level of pain relief
- Side effects of IV Paracetamol

**History and review of literature**

Paracetamol was discovered in 1877. And since then it is most commonly and widely used medication for pain and fever.

**Hyllested et al. 2002** did a quantitative review of postoperative pain management comparing paracetamol 1gm with NSAID in a double blind randomized manner. They concluded that paracetamol is an alternative to NSAID, esp. because of low incidence of adverse effect and should be preferred choice in high risk patient. They also suggest to combine Paracetamol with NSAID for better outcome

**Cakan T et al** in 2008 evaluated the analgesic efficacy, opioid-sparing effect and effects on opioid-related adverse effects of intravenous (IV) paracetamol in combination with IV morphine after lumbar laminectomy and discectomy. It demonstrated a significant opioid-sparing effect, it did decrease visual analog scale scores at certain evaluation times.

**Winger et al. (2010)** reported the results of a randomized double-blind placebo-controlled clinical trial evaluating the analgesic efficacy of repeated doses of two dosing regimens of IV

paracetamol (1,000 mg every 6 hours or 650 mg every 4 hours for 24 hours) versus placebo in 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery (included hysterectomy, cholecystectomy, and hernia repair). Patients in both IV paracetamol-dosing groups experienced statistically significantly greater pain relief over 24 hours compared with placebo.

**Goel et al in 2013** Studied pre-emptive analgesia with iv paracetamol and iv diclofenac sodium in 60 patients undergoing various surgical procedures and concluded that preemptive iv paracetamol is long acting and provides better analgesia than diclofenac with less side effects.

**Debashish paul et al in 2015** studied paracetamol and diclofenac as post-operative analgesic in 68 patients divided in two different groups for postoperative analgesia after laparoscopic cholecystectomy. They found the significant outcome (p-values are 0.0005 at 0 hrs, 0.003 at 2 hrs, 0.001 at 6 hrs, 0.0005 at 12 hrs) in VAS pain score in between the two groups at different intervals and concluded that Administration of intravenous paracetamol in the intra-operative period 30 minutes prior to the completion of surgery followed by administration of 1g paracetamol every 8 hourly in the post-operative period gives better quality of analgesia

**Manjunath K.R et al in 2015** studied analgesic activity of intravenous Paracetamol as preemptive analgesic in patients who underwent laparoscopic surgeries in 70 patients. Group A-Paracetamol (1g/i.v), Group-B 100 ml of normal saline. Paracetamol and saline were administered to their respective groups 30 minutes before induction of anesthesia and concluded that intra-venous administration of paracetamol showed significant reduction in post-operative pain in patients underwent laparoscopic surgeries.

**MATERIAL AND METHOD**

We have done our study to evaluate the efficacy and safety of IV paracetamol for postoperative analgesia with the permission of ethical committee of hospital and after written informed consent of 50 adult patients of either sex and ASA grade I and II undergoing laparoscopic cholecystectomy and to note the total doses of supplementary analgesic and the level of pain relief postoperatively.

**Exclusion criteria-** Patients with ASA grade III and IV Cardiovascular, Hepatic and Renal dysfunction With severe hemodynamic instability like severe anemia, hypotension.

Patients with history of bleeding and coagulation disorders.

Opioid abuse Allergy All these patients underwent a preanaesthetic checkup the day before surgery and all the routine and specific investigations were noted. The patients were electively kept NBM (Nil by Mouth) for 6 hrs before surgery. Informed consent was taken from each patient. Patients were randomly divided into two groups; each group included 25 patients

**Group D,** patients received Diclofenac 75 mg intravenous **Group P,** patients received Paracetamol 1 gm intravenous

After arrival in operating room, standard monitors like ECG (Electrocardiogram), pulse oximeter and NIBP (Non Invasive Blood Pressure) were applied. The patient was given premedication of Injection Glycopyrolate (4 µg/kg), Injection Ondansetron (150 µg/kg) and Injection Fentanyl (2 µg/kg) intravenously. Then patient was pre-oxygenated through a face mask for 5 min. The induction was done with Injection Thiopentone Sodium (2.5%) 5-7 mg/kg and Injection Succinylscoline 2mg/kg intravenously. The patient was intubated with a suitable size portex cuffed endotracheal tube. Throughout the procedure controlled ventilation was maintained with 50% O<sub>2</sub>, 50% N<sub>2</sub>O (Nitrous Oxide) and sevoflurane and muscle relaxant Injection Vecuronium Intravenously.

Heart Rate, Blood Pressure and Oxygen Saturation were recorded during surgery. Ventilation was adjusted to maintain ETCO<sub>2</sub> <40 mm Hg and intra abdominal pressure was maintained between 12-14 mm of Hg. 30 min before end of the laparoscopic procedure these patients were randomly allocated to

**Group D,** patients received Diclofenac 75 mg intravenous **Group P,** patients received Paracetamol 1 gm intravenous

After completion of surgery, residual neuromuscular block was reversed with Inj. Neostigmine 0.05 mg/kg and Inj. Glycopyrrolate 8 µg/kg. The patients were then extubated after thorough oral and ET suction.

After surgery, patients were transferred to the postoperative ward. HR, BP, and pain scores were recorded immediately after surgery and at 30 min, 4, 8, 12 and 24 hr after surgery.

Pain scores were evaluated using a 0–10 mm VAS (0 - no pain, to 10 - worst pain imaginable). Inj Diclofenac was used as rescue analgesia when VAS score>4.

**STATISTICAL METHODS**

All raw data were entered into an excel spread sheet and analyzed by SPSS 16.0 and GRAPHPAD software. Categorical variables (eg. demographic parameters like sex, ASA physical status) were analyzed using PEARSON'S Chi square test.

Normally distributed numerical variables such as VAS score, consumption of post-operative systemic analgesics, and antiemetics between two groups were analyzed using unpaired t-test. Data was expressed as mean values ± standard deviation (SD). P value <0.05 was interpreted as clinically significant and P value >0.05 considered as non-significant

**TABLE 1: DEMOGRAPHIC DATA: AGE, WEIGHT, SEX DISTRIBUTION AND DURATION OF SURGERY**

GROUP	AGE (MEAN± SD)	SEX M:F	DURATION OF SURGERY(Min)
GROUP P (n=25)	40.64 ± 11.21	5:20	114 ± 8.42
GROUP D(n=25)	38.24 ± 8.41	6:19	115.2 ± 9.73

As per the table the mean age and sex distribution in all groups are nearly same without any significant differences.

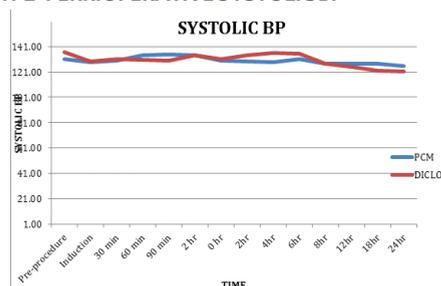
No significant difference seen in duration of surgery, as duration of surgery is almost same in both groups.

**GRAPH-1 PERIOPERATIVE HEART RATE**



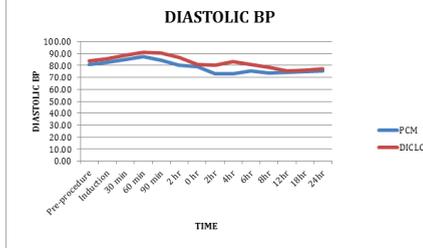
Above table & graph shows that there was no significant difference in both the groups.

**GRAPH-2 PERIOPERATIVE SYSTOLIC BP**



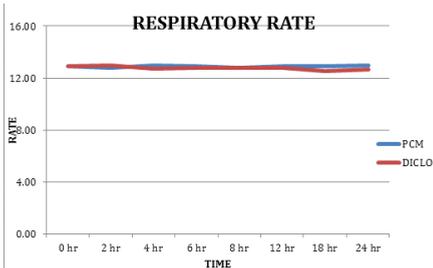
Above table & graph shows that there was no significant difference in diastolic blood pressure in both groups. P value was not significant except at 4hr post operative period where group D have higher systolic BP compared to Group P (p=0.008)

**GRAPH-3 PERIOPERATIVE DIASTOLIC BP**



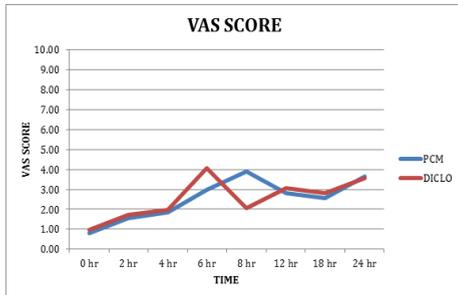
Above table & graph shows that there was no significant difference in diastolic blood pressure in both groups. P value was not significant except at 4hr post operative period where group D have higher diastolic BP compared to Group P (p=0.007)

**GRAPH -4 POST OPERATIVE RESPIRATORY RATE**



Above table & graph shows there was no significant difference in mean respiratory rate per minute in both groups. P value was not significant.

**GRAPH 5 VAS POST-OPERATIVE PERIOD**

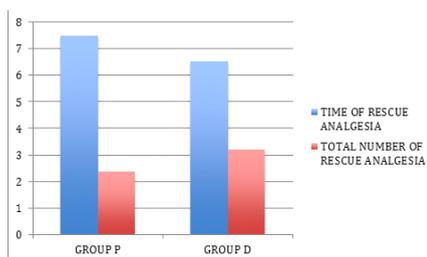


From above findings we can conclude that VAS score in group D is higher at 6hrs (4.08±0.57 compared to 2.96±0.57 compared to 2.04±0.57 in group P) with p value <0.05

**TABLE 2 – RESCUE ANALGESIA REQUIENMENT**

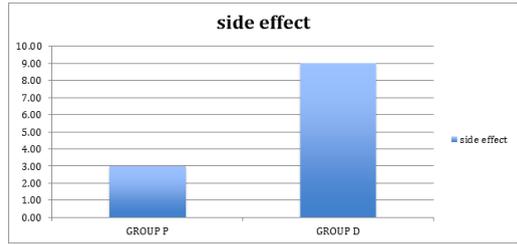
	GROUP P	GROUP D	p value
TIME OF RESCUE NALGESIA	7.50.61	6.520.49	0.0001
NO OF RESCUE ANALGESIA	2.360.48	3.20.4	0.0001

**GRAPH 6 - RESCUE ANALGESIA REQUIENMENT**



Above chart and table shows that there is no significant difference between time of rescue analgesia and number of rescue analgesia in both the groups (p>0.05)

**GRAPH 7 POST-OPERATIVE COMPLICATIONS**



From above table we noted that ,incidence of nausea and vomiting occurred in 3 patients of Group P and in 9 patients of Group D. significant difference between both groups noted, as p value was 0.0237.

**DISCUSSION**

Effective pain control is essential for optimum care of the patients in the postoperative period. Real art of medicine lies in the treatment of pain. Different routes for postoperative pain relief are like epidural, spinal, oral, intravenous, intramuscular and transdermal etc. From which best technique remains still debatable. Intravenous route is the simple and most commonly used technique in perioperative period.

Different drugs have been used for postoperative pain relief like opioid, NSAID, paracetamol, local infiltration. Though opioid gives adequate analgesia, it has significant side effects of nausea, vomiting, and respiratory depression. So opioids should be given cautiously. NSAID gives adequate analgesia as well but it is associated with side effect like vomiting, indigestion, stomach bloating, burning, cloudy urine. Comparatively, paracetamol is devoid of most of the side effects.

Pain after laparoscopic surgery has three different components: incisional pain (somatic pain), visceral pain (deep intra-abdominal pain) and shoulder pain (referred to visceral pain). Inadequately treated pain can result in various complications like atelectasis/ pneumonia/ hypoxemia, deep vein thrombosis, delayed recovery of bowel function, myocardial ischemia and infarction, urinary retention and residual psychological trauma. That is why pain relief in perioperative period is very important.

So with aim to provide postoperative pain and study efficacy of intravenous paracetamol in laparoscopic cholecystectomy, we studied 50 patients of ASA 1/ 2, and divide them into two equal group. Group P was given 1 gm IV Paracetamol and Group D given 75 mg IV diclofenac 30 mins before extubation and perioperative vitals , RR and post operative VAS score and side effect noted and Rescue analgesic (Inj. Diclofenac 2mg/kg IV) was given to patients if they complained of pain or if VAS score was greater than 4 postoperatively for 24 hours.

**Perioperative vitals**

**Goel et al.** in their comparative study for preemptive analgesia with iv paracetamol and iv Diclofenac sodium in patients undergoing various surgical procedures, found that heart rate was almost equal to base line value in both the groups. Similarly in our study heart rate were comparable in both the group.

**Debanshish Paul et al.** compared paracetamol and diclofenac as postoperative analgesic in two different groups in 68 patients. They assessed SBP, DBP and MAP in both the groups and observed that there is no significant variation in both the groups in different intervals except the mean values for DBP at 12hr of post-operative period where it was found that DBP is higher in the diclofenac group Similarly SBP and DBP both comparable in both the groups except at 4hr where group D has higher SBP (133.76±10.34 compared to 128.56±7.86 in group P) and DBP (83.48±7.53 compared to 72.84±12.49 in group P) with p value 0.007 and 0.008 respectively. The predominant action of diclofenac is to inhibit the enzyme cyclooxygenase (COX), which mediates the conversion of arachidonic acid to prostaglandins and thromboxane. The significant increase in BP in diclofenac group might be explained by this effect of diclofenac.

### Respiratory Rate

Postoperative rapid shallow breathing is a feature of inadequate pain relief. In our study, there was no significant difference found in respiratory rate between both the groups. So, it's suggestive that both the drugs have not any deleterious effect on

### Postoperative analgesia

**Wininger et al.** reported the results of a randomized double-blind placebo-controlled clinical trial evaluating the analgesic efficacy of repeated doses of two dosing regimens of IV paracetamol (1,000 mg every 6 hours or 650 mg every 4 hours for 24 hours) versus placebo in 244 patients with moderate to severe postoperative pain after abdominal laparoscopic surgery. Patients in both IV paracetamol-dosing groups experienced statistically significantly greater pain relief over 24 hours compared with placebo (1000 mg q6h,  $p < 0.007$ ; 650 mg q4h,  $p < 0.019$ ). Similar study was done by **Debashish Paul et al.** who compared paracetamol and diclofenac as post operative analgesic in two different groups in 68 patients found significant high VAS Score in the paracetamol group in the initial 2 hrs post-operatively where as from 6 hr interval onwards; mean pain score was higher in the diclofenac group. Though the VAS score was higher in the paracetamol group in the initial hours, it was within the values for mild pain.

In our study we found significant difference in VAS score postoperatively at 6 hrs and 8 hrs ( $p$  value 0.001). In Group D, VAS score was high ( $4.08 \pm 0.57$  compared to  $2.96 \pm 0.45$  in Group P) at 6 hrs suggest need for rescue analgesia. Similarly in Group P VAS score was high ( $3.92 \pm 0.57$  compared to  $2.04 \pm 0.57$  in group D) suggest need for rescue analgesia. However, subsequent VAS score were comparable in both the groups due to supplant analgesia.

So, we concluded that IV paracetamol does not decrease VAS score as compared to NSAID as a sole agent. It has similar efficacy as compared to diclofenac as far as postoperative analgesia concerned.

### Rescue analgesia

**Manjunath KR et al.** studied analgesic activity of intravenous Paracetamol (group A) and IV Diclofenac (group B) as preemptive analgesic in patients who underwent laparoscopic surgeries, which concluded that intra venous administration of paracetamol showed significant reduction in postoperative pain. They found that number of rescue analgesics in control group during the postoperative period was found to be significantly higher ( $p < 0.05$ ) than that in groups A.

Similarly in our study we found that time of rescue analgesia is prolonged in group P patient ( $7.5 \pm 0.61$ ) compared to group D patient ( $6.52 \pm 0.49$ ). And total number of rescue analgesia is more in group D ( $3.2 \pm 0.4$ ) patient compared to group P ( $2.36 \pm 0.48$ ) patient. Which suggests prolong duration of analgesia with 1 gm IV paracetamol.

This result was comparable with the result of **Debashish Paul et al.** who found that patients who were administered paracetamol had shown better outcome with less requirement of rescue analgesia compared with diclofenac Paracetamol rapidly crosses the blood brain barrier, reaches a high concentration in the cerebrospinal fluid and has an anti-nociceptive effect mediated by CNS. This central effect has been regarded primarily as an indirect and reciprocal influence through cyclooxygenase enzyme inhibition and probably through serotonergic system as well. Besides this central effect, it is accepted that paracetamol has a peripheral anti-inflammatory effect although this effect is limited.

### Side effect

**Debashish Paul et al.** have found that patients in the diclofenac group had more incidences of complications like nausea and vomiting. They also have found that in paracetamol group, there is not a single case of post-operative complication whereas in diclofenac group, total number of patients requiring management for post-operative complications is 13.33%.

Similarly we concluded that the patients of Group P have lesser amount of nausea and vomiting (3 patients) compared to Diclofenac (9 patient). This can be explained by, group P patient receives less doses of rescue analgesia in form of diclofenac, which causes nausea and vomiting. Paracetamol does not inhibit COX-1 peripherally, which can explain its favorable safety effect compared to diclofenac.

So we can conclude that paracetamol is better choice as far as side effect is concerned compared to diclofenac. However, both Diclofenac and Paracetamol spare the side effects of opioids like respiratory depression, constipation and urinary retention.

### SUMMARY

In this randomized control study we evaluate the efficacy and safety of IV paracetamol for control of postoperative pain by comparing with IV Diclofenac in patients undergoing laparoscopic cholecystectomy. Our study comprises of 50 patients of comparable age, weight and sex of ASA physical status I and II. They were randomly divided into 2 groups.

**GROUP P:** 1 gm IV Paracetamol

**GROUP D:** 75 mg IV Diclofenac

All kinds of biological parameters like age, sex and weight were comparable among two groups. Postoperative Visual Analogue Scale score, Supplementary Analgesic Requirement and side effects evaluate the efficacy and safety of IV paracetamol.

- Perioperative vitals were comparable in both groups.
- In both the groups, VAS score was comparable with significant difference in  $p$  value at 6hrs in Group D (VAS score was high  $4.08 \pm 0.57$  compared to  $2.96 \pm 0.45$  in Group P) and at 8 hrs Group P (VAS score was high  $3.92 \pm 0.57$  compared to  $2.04 \pm 0.57$  in group D) suggest need for rescue analgesia.
- Time of rescue analgesia is prolonged in group P patients ( $7.5 \pm 0.61$ ) compared to group D patients ( $6.52 \pm 0.49$ ). And total number of rescue analgesia is more in group D ( $3.2 \pm 0.4$ ) patients compared to group P ( $2.36 \pm 0.48$ ) patients.
- Patients receiving 1gm IV paracetamol have lesser amount of nausea and vomiting (experienced in 3 patients) compared to Diclofenac (experienced in 9 patients). None patient have experienced respiratory depression

### CONCLUSION

We conclude from our study that IV paracetamol is safe and effective alternative for postoperative analgesia compared to IV diclofenac; which results in prolonged duration of analgesia and significant reduction in requirement of supplementary analgesic postoperatively without any significant side effect. IV paracetamol is one of the safe and effective modality for postoperative pain relief.

1. Ramkumar V, Prasad KN. Management of postoperative pain. *Indian J Anaesth.* 2006; 50(5): 345-354.
2. Smith CHW, Hill L, Dyer RA. Post-operative sensitization and Pain after cesarean delivery and effect of single intramuscular doses of tramadol and diclofenac alone and in combination. *Anesth Analg.* 2003; 97: 526-33.
3. Haas DA: An update on analgesics for the management of acute postoperative dental pain. *J Can Dent Assoc* 2002; 68:476-82
4. Bonnefont J, Courade JP, Allaoui A, Eschaliier A: Mechanism of the antino- ciceptive effect of paracetamol. *Drugs* 2003; 63(suppl 2):1-4
5. Kehlet H, Dahl JB: The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. *Anesth Analg* 1993; 77:1048-56
6. Jahr, J.S., Lee, V.K. Intravenous acetaminophen. *Anesthesiology Clinics.* 2010;28:619-645
7. MI Tawalbeh, "comparative study of diclofenac and paracetamol for treatment of pain after Adenotonsillectomy", *Saudi Medical Journal*, 2001, 22:121-23.
8. M. Hyllested, S. Jones, J.L. Penderson, H. Kehlet; comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review; *British Journal of Anaesthesia* 88(2): 199-204 (2002)
9. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER (2005) Administration of 1 gram intravenous paracetamol injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 102(4):822-831
10. cakan t, inan nurten et al. intravenous paracetamol improves the quality of postoperative analgesia but doesn't decrease narcotic requirement. *journal of neurosurgical anesthesiology* July 2008 vol 20(3):169-173
11. Steven J. Wininger, Howard Miller, Harold S. Minkowitz, Mike A. Royal, Robert Y. Ang, James B. Breitmeyer, Neil K. Singla A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Repeat-Dose Study of Two Intravenous Acetaminophen Dosing Regimens for the Treatment of Pain After Abdominal Laparoscopic Surgery; *Dec 2010; Volume 32, Issue 14, Pages 2348-2369*
12. Durak P, Yağar S, Uzuner A, Kılıç M, Dilber E, Özgök A.; Postoperative pain therapy

- after laparoscopic cholecystectomy: paracetamol versus diclofenac; 2010 Jul; 22(3):117-20
12. S Samal, E John, L Chandrasekar, S Nithianandam, S K Jena. A Comparative Study of Intravenous Diclofenac and Combination of Intravenous Paracetamol with Intravenous Diclofenac for the Postoperative Pain Management. *The Internet Journal of Anesthesiology*. 2013 Volume 32 Number 2
  13. Goel Pratyush et al. Pre emptive analgesia with iv paracetamol and iv diclofenac sodium in patients undergoing various surgical procedures: a comparative study *Int J Biol Med Res*. 2013; 4(3): 3294-3300.
  14. Rastogi B, Singh VP, Gupta K, Jain M, Singh M, Singh I. Postoperative analgesia after laparoscopic cholecystectomy by preemptive use of intravenous paracetamol or ketorolac: A comparative study. *Indian J Pain* 2016;30:29-33.
  15. Debashish Paul et al / *International Journal of Biomedical Research* 2015; 6(07): 482-487
  16. Manjunath K.R, Lohith B, Ramesh Kumar N, Ravishankar V Pre-emptive Analgesic Effects of intravenous Paracetamol in Laparoscopic Surgeries *Int J Med Health Sci*. Jan 2015, Vol-4; Issue-1
  17. Alexander JI. Pain after laparoscopy. *Br J Anaesth*. 1997; 79:369–78.
  18. Piletta P et al. Central analgesic effect of acetaminophen but not of Aspirin; *Clinical Pharmacology Therapy*, 1991
  19. Pickering G et al, Analgesic effect of acetaminophen in humans. First evidence of central serotonergic mechanism; *Clinical Pharmacology Therapy*, 2006; 79; 371-8.
  20. C.C. Apfel et al. *International journal of pain*, PAIN 154 (2013) 677–689