Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(1) (Part - II): 255-62
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6119.36

Role of Intravenous Paracetamol for Peri-Operative Pain Management in Head and Neck Cancer Surgeries

Jayshree M Thakkar[1], Anupama Tomer[2], Priti M Patel[3]

[1]Associate Professor, [2]Ex Resident, [3]Assistant Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India.

Abstract

Background: Inadequately controlled postoperative pain causes discomfort, increased use of medications, slower recovery, longer hospital stay and increased risk of pulmonary complications [5]. Postoperative analgesia with safer drugs and minimal side effects is the first choice. This study was undertaken to evaluate the role of Inj. Paracetamol vs. Inj. Tramadol in post-operative pain relief after head and neck cancer surgeries. *Material & Method:* After IRB approval and informed consent, this prospective, randomized study was conducted in 100 patients (ASA I & II) with age group of 18-60 years undergoing elective head and neck cancer surgery. Patients were divided into two groups. A) Group P: Inj. Paracetamol 15 mg/kg IV over 15 min, 30 min prior to the end of surgery and subsequent doses at 6 hours interval 24 hours. B) Group T: Inj. Tramadol 1 mg/kg diluted in 10 ml saline IV slowly over 10 min, 30 min prior to end of surgery and subsequent doses at 8 hours interval for 24 hours. *Results:* Postoperative VAS decreased at various time intervals in both groups. Time to 1st dose of rescue analgesia requirement was lower in Group T, with mean postoperative rescue analgesic free time interval of 6.23±1.72 hours as compared to Group P where it is 5.01±1.16 hours. Frequency of rescue analgesic requirement was lower in Group T, with mean of 1.20 (±0.41), in comparison to Group P 1.67 (±0.71). Postoperative nausea, vomiting is more in group Tas compared to group P. *Conclusion:* Intravenous paracetamol administration in peri-operative period provided adequate postoperative analgesia with fewer side effects in patients undergoing head and neck cancer surgery. Intraoperative IV paracetamol appears to be a reasonable choice for postoperative analgesia in this patient population.

Keywords: Pain; Paracetamol; Tramadol.

How to cite this article:

Jayshree M Thakkar, Anupama Tomer, Priti M Patel. Role of Intravenous Paracetamol for Peri-Operative Pain Management in Head and Neck Cancer Surgeries. Indian J Anesth Analg. 2019;6(1):255-262.

Introduction

The word "pain'' has been derived from the Latin word "poena'' for punishment [1]. The International Association for the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual damage or potential tissue damage or described in terms of such damage" [2]. The Joint Commission on Accreditation of Healthcare Organizations has coined the phrase "Pain: The 5th Vital Sign" to elevate awareness of pain treatment among health care professionals [3].

Pain, a common presenting feature of many disease processes, is usually associated with

Corresponding Author: Anupama Tomer, Ex Resident, Department of Anesthesia, Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad, Gujarat 380016, India.

E-mail: dr.anupama.tomer@gmail.com

Received on 20.11.2018, **Accepted on** 13.12.2018

actual or impending tissue damage. Acute pain in perioperative setting is defined as pain that is present in a surgical patient because of pre-existing disease, surgical procedure or a combination of these. It is an unpleasant and inevitable component of the postsurgical experience. It also exerts deleterious effects on systems like respiratory, cardiovascular, neuroendocrine, gastrointestinal and other systems of the body [4].

Inadequately controlled postoperative pain causes discomfort, increased use of medications, slower recovery, longer hospital stay and increased risk of pulmonary complications [5]. Postoperative analgesia with safer drugs and minimal side effects is the first choice.

NSAIDs, opioids and acetaminophens are used to alleviate postoperative pain. NSAIDs are associated with risk of bleeding and renal dysfunction while opioids are associated with potentially harmful effects like respiratory depression, post operative nausea and vomiting (PONV), sedation etc [6]. Acetaminophens are nowadays used for postoperative analgesia because of its well established safety and analgesic profile without significant drug interaction. Hepatic toxicity is rare but can occur with its overdose.

Paracetamol is commonly used drug for the treatment of pain and fever. Intravenous paracetamol crosses blood brain barrier easily and its analgesic action starts within 15-20 min. Maximal analgesic activity occurs 1-2 hours after peak plasma levels and peak plasma concentration is achieved approximately 25 min after 1 gm of IV infusion of paracetamol. Adverse reactions occurring from the use of IV paracetamol are extremely rare (1/1000).

Tramadol is a centrally acting analgesic. It has effect on norepinephrine and 5- hydroxytryptamine neurotransmitters. It has weak opioid agonist properties. Onset of IV formulation is within 5 min, analgesic effect peaks within 15 min and last for 4-6 hours.

This study was undertaken to evaluate the effect of two different drugs Inj. Paracetamol vs. Inj. Tramadol in terms of post-operative pain relief, hemodynamic stability and side effects after head and neck cancer surgeries.

Material and Methods

After institutional review board approval and informed consent, the study was conducted in 100 patients belonging to both sexes in the age group of 18-60 years with ASA physical status I & II, undergoing elective head and neck cancer surgery. Patients excluded were those with known allergy or hypersensitivity to paracetamol or tramadol, patients with history of alcohol, coagulopathy, and impaired liver and renal function. Patients were assessed in the preoperative visit and routine general and systemic examination was done. Preoperative vital parameters were noted. Patients were kept nil by mouth after 10 PM on the previous night before operation.

Patients were divided into two groups: Group P (Paracetamol): Inj Paracetamol 15 mg/kg IV over 15 minutes and 30 minutes prior to the end of surgery and subsequent doses at 6 hours intervals for 24 hours. Group T (Tramadol): Inj Tramadol 1 mg/kg diluted in 10 ml saline IV slowly over 10 minutes and 30 minutes prior to the end of surgery and subsequent doses at 8 hours interval for 24 hours.

After taking patient on the OT table, IV line was established and monitoring in the form of ECG, HR, NIBP, SpO_2 and $EtCO_2$ was done. Patients were pre-oxygenated with 100% O_2 for 3 minutes and general anaesthesia was administered with Inj Glycopyrolate 0.04 mg/kg + Inj Fentanyl 2 µg/kg + Inj Thiopentone Sodium (2.5%) 5 mg/kg and intubation was facilitated using Inj Succinylcholine HCL 2 mg/kg IV. Patients were intubated with appropriate size portex cuffed endotracheal tube. Bilateral air entry was checked and tube was fixed. Anesthesia maintained with O_2, N_2O, Isoflurane with controlled ventilation using Inj Vecuronium bromide 0.08 mg/kg IV. Intraoperative HR, BP, SpO_2, ECG and $EtCO_2$ were monitored. All the study drugs namely Paracetamol and Tramadol were given as described above to two groups of 50 patients each. After completion of surgery, neuromuscular blockade was reversed with Inj Glycopyrrolate 0.08 mg/kg and Inj Neostigmine 0.05 mg/kg IV. Extubation was done after adequate oropharyngeal and endotracheal suctioning when they were fully conscious.

In the postoperative period vital parameters heart rate (HR), systolic & diastolic blood pressure (SBP) (DBP) and pain score (VAS) (0-10) were assessed and documented at 0 min, 3, 6, 9, 12, 16, 20 and 24 hours intervals.

If VAS > 4, rescue analgesic Inj. Tramadol 1 mg/kg IV was given. Need of rescue analgesia in 24 hours was assessed and documented.

Adverse effects like nausea, vomiting, respiratory depression, abdominal pain, allergic reactions, alteration in liver function tests within 24 hours of surgery were assessed and documented in both

the study drug groups. Ondansetron 4 mg IV was administered if patient experienced severe nausea and episode of vomiting.

Results

This study was a prospective, randomized one. The total number of 100 patients, who were posted for head and neck cancer surgeries, were enrolled in the study. The data was recorded in Excel panel and statistical analysis was done after completion of the study. Data was analyzed by standard statistical unpaired t-test using Graph pad software and for significant difference between the groups, p-value of < 0.05 was taken as a reference of significance.

Table 1 shows demographic details. Mean age (yr) and wt (kg) in both the groups are comparable and statistically not significant ($p > 0.05$). Mean surgical duration in both groups is statistically not significant ($p > 0.05$).

Table 2 shows heart rate changes in both groups at different intervals**.** Changes in heart rate between the two groups at different intervals were not significant and were statistically comparable in both the groups. Heart rate was on the higher side just after the recovery from anesthesia with a mean value of 87.34 (±4.03) in Group P and 86.68 (±3.28) in Group T and their P value is 0.3713 that is insignificant, but after 3 hours interval, there is mild decrease in the values for heart rate with highest value reaching in Group P is 78.88 (±2.45), and in Group T, it is 78.64 (±2.31), which are statistically insignificant.

Table 3 shows systolic blood pressure changes in both groups at different intervals. Changes in systolic blood pressure at different intervals between the two groups were not significant and were statistically comparable in both the groups. Highest mean value of SBP was 131.74 (±4.47) mm of Hg in Group P and 130.88 (±4.37) mm of Hg in Group T, are statistically insignificant on comparison with a p value > 0.05.

Table 4 shows diastolic blood pressure changes in both groups at different intervals. Changes in diastolic blood pressure at different intervals between the two groups were not significant and were statistically comparable in both the groups. There is no significant variation in both the groups at different intervals, with highest mean value of 86.26 (±2.55) mm of Hg in Group P and 85.66 (±1.72) mm of Hg in Group T, are statistically insignificant on comparison with a P value > 0.05.

Table 5 shows visual analogue score (VAS) at different intervals. VAS was significantly lower at certain time intervals in both the groups. First analgesic time was longer in the Tramadol group as compared to Paracetamol group. Mean VAS was statistically comparable in the immediate postoperative period with a p-value of 0.3953 which is insignificant. At an interval of 3 hours, the mean VAS is 3.10 (±0.51) in Group P and it is 2.94 (±0.24) in Group T and they are statistically significant (P=0.0458). But after 6 hours interval, the mean VAS decreased to 0.88 (±0.59) in Group P and it is increased to 3.84 (±1.47) in Group T, which is statistically significant (p<0.0001). This indicates that after administration of subsequent

Table 1: shows Demographic Data

Variables	Group P	Group T	p value	Significance
Age (Years)	48.40±12.18	48.04±10.70	0.8756	NS
Weight(kgs)	60.18±6.48	58.96±5.37	0.3079	NS
Sex (M/F)	39/11	40/10	-	-
ASA status(I/II)	24/6	25/5	-	-
Duration of surgery(mins)	210.83±41.83	219.33±47.32	0.7434	NS

Table 2: shows Heart rate changes (BPM) in both groups at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
00 min	87.34±4.03	86.68±3.28	0.3713
03 hrs	81.94±2.66	81.80±2.64	0.7922
06 hrs	78.88±2.45	78.64±2.31	0.6154
09 hrs	75.50±2.45	75.52±2.20	0.9658
12 hrs	73.84±1.87	73.90±1.64	0.8649
16 hrs	73.22±1.45	73.10±1.39	0.6736
20 hrs	72.74±1.06	72.60±1.07	0.5125
24 hrs	72.54±0.91	72.48±0.84	0.7326

dose of paracetamol in Group P patients, the mean VAS score decreased significantly, whereas it is on higher side in Group T patients in whom next dose was due at that time.

Table 6 shows rescue analgesic requirement in both the groups. Time to 1st dose of rescue analgesia requirement was lower in Group T in the 24 hours study period, with the mean postoperative rescue analgesic free time interval of 6.23±1.72 hours, as compared to Group P where it is 5.01±1.16 hours. This is found to be statistically significant with p-value of 0.0001.

Frequency of rescue analgesic requirement was lower in Group T in the 24 hours study period. Patients in Group T required 1 to 2 times of rescue analgesia with a mean of 1.20 (±0.41), in comparison to the Group P, where patients required 2 to 3 times of rescue analgesia with a mean of 1.67 (±0.71). However, this was also found to be statistically significant with p value of 0.001.

Table 3: Shows SBP changes (mm of Hg) in both groups at different intervals

Time	Group P(Mean±Sd)	Group T(Mean±Sd)	p Value
0 min	131.74±4.47	130.88±4.37	0.3331
3 hrs	128.02±4.11	127.58±3.96	0.5869
6 hrs	125.78±3.09	125.04±2.43	0.1862
9 hrs	123.52±2.13	123.14±1.78	0.3354
12 hrs	121.95±1.93	121.52±1.62	0.2305
16 hrs	120.54±1.82	119.86±1.68	0.0551
20 hrs	119.42±1.57	118.94±1.38	0.1076
24 hrs	117.98±1.67	117.52±1.53	0.1542

Table 4: Shows DBP changes (mm of Hg) in both groups at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
00 min	86.26±2.55	85.66±1.72	0.1709
03 hrs	82.80±2.29	82.36±1.85	0.2932
06 hrs	82.14±2.14	81.68±1.73	0.2401
09 hrs	81.62±1.88	80.96±1.71	0.0693
12 hrs	80.70±1.53	80.02±2.06	0.0639
16 hrs	79.68±1.43	78.98±2.08	0.0527
20 hrs	78.84±1.31	78.48±2.05	0.2980
24 hrs	76.72±1.75	76.10±2.00	0.1022

Table 5: shows Visual Analogue Score (VAS) at different intervals

Time	Group P (Mean±Sd)	Group T (Mean±Sd)	p Value
0 min	2.12±0.39	2.06±0.31	0.3953
3 hrs	3.10±0.51	2.94±0.24	0.0458
6 hrs	0.88±0.59	3.84±1.47	<0.0001
9 hrs	3.04±0.28	2.06±0.31	<0.0001
12 hrs	1.98±0.44	3.62±0.98	<0.0001
16 hrs	3.08±0.74	1.76±0.46	<0.0001
20 hrs	2.12±0.38	2.10±0.51	0.8243
24 hrs	0.88±0.59	0.76±0.48	0.2678

Table 6: shows Rescue analgesic requirement

Rescue analgesia	Group P	Group T	p Value
Time to 1st dose of rescue analgesia (hrs)	5.01±1.16	6.23±1.72	0.0001
Total no of doses of rescue analgesic in 24 hrs	1.67±0.71	1.20±0.41	0.001

Table 7: shows Side Effects

Side Effects	Group P	Group T
Sedation	nil	3
Abdominal pain	nil	nil
LFT complications	nil	nil
Nausea & vomiting	5	16
Respiratory depression	nil	nil
Allergic reaction	nil	nil

Table 7 shows side effects in both the groups. Group P recorded less number of patients (10%) with nausea and vomiting (PONV) as compared to Group T which recorded significantly higher number of patients (32%) in the immediate post-operative period. Also, sedation was seen in 3 patients (6%) in Group T. No alterations were seen in the liver function tests of the patients receiving paracetamol.

Discussion

Pain is a subjective and multidimensional experience that is often inadequately managed in clinical practice. It is a multifaceted and highly personal experience, as McCaffery described "pain is whatever the experiencing person says it is and exists whatever he/she says it does" [7]. It causes significant distress to patients and has adverse effects on the endocrine and immune system function, which can affect wound healing and cardiopulmonary and thromboembolic diseases. Post-operative pain is one of the most frequently reported post-operative symptoms. The post-operative period was defined as the period between arrivals of the patient in recovery to 7 days after surgery, with day 1 being 24 hours after surgery. The incidence of moderate to severe pain with cardiac, abdominal or orthopedic inpatient procedures has been reported to be as high as 25% to 76% [8].

Management of post-operative pain in the initial 24 hours is critical. Inadequate pain management leads to delayed mobilization and longer duration of stay in the hospital. Post-operative pain is an unpleasant sensory, emotional and mental experience which is precipitated as a result of surgery and is often associated with autonomic, endocrine, metabolic, physiological and behavioral response.

With this background, we designed the study to compare the post-operative analgesic effects of intravenous paracetamol and intravenous tramadol in head and neck cancer surgery patients. Analgesic effects were assessed with Visual Analogue Scale (VAS Score) in both the groups.

In our study, we have found that there was no significant variation between the groups when comparing the demographic variables like age, sex, weight, ASA status and the duration of surgeries. Premedication and anaesthetic technique was kept constant in order to avoid variations in our observations.

While comparing the heart rate, we found that there was no statistically significant variation in both the groups. Heart rate was on the higher side just after the recovery from anaesthesia with a mean value of 87.34 (±4.03) in Group P and 86.68 (±3.28) in Group T and their P-value is 0.3713 that is insignificant, but after 3 hours interval, there is mild decrease in the values for heart rate with highest value reaching in Group P is 78.88 (±2.45), and in Group T, it is 78.64 (±2.31), which are statistically insignificant. So, we can correlate the initial increase in heart rate is due to anxiety and not due to pain. Mean changes in heart rate at different intervals are insignificant.

Mohammed Shahid et al. [9] (2015), in their comparative study of intravenous paracetamol and intravenous tramadol for postoperative analgesia in laparotomies found that nothing statistically significant was observed in terms of hemodynamics including VAS scores between either group. They said that IV paracetamol is a safer alternative to tramadol with lesser PONV in the postoperative period which results into the lesser duration of hospitalization and hence earlier discharge.

Pratyush Goel et al. [5] in their comparative study for pre-emptive analgesia with IV paracetamol and IV diclofenac sodium in patients undergoing various surgical procedures found the comparison of heart rate between paracetamol and diclofenac group was significant. Heart Rate was almost equal to base line value in Diclofenac group patients and it was increased in paracetamol group patients. Mean values of SBP and DBP showed increase in Paracetamol group however it was not significant.

While comparing SBP, we found that changes in SBP in both the groups at different intervals, with highest mean value of 131.74 (±4.47) in Group P and 130.88 (±4.37) in Group T, are statistically insignificant on comparison with a p value > 0.05.

While comparing the DBP, in both the groups, we have observed that there is no significant variation in both the groups at different intervals, with highest mean value of 86.26 (±2.55) in Group P and 85.66 (±1.72) in Group T, are statistically insignificant on comparison with a p value > 0.05.

Arici et al. [10] studied the pre-emptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy and found a decrease in mean values of heart rate, SBP, DBP intra-operatively after paracetamol administration. They also found decrease consumption of morphine post-operatively.

In this study, the mean VAS was statistically comparable in the immediate postoperative period with a p-value of 0.3953 which is insignificant. At 3 hours, the mean VAS is 3.10 (±0.51) in Group P and it is 2.94 (±0.24) in Group T and they are statistically significant (P=0.0458). But after 6 hours interval, the mean VAS is decreased to 0.88 (±0.59) in Group P and it is increased to 3.84 (±1.47) in Group T, which is statistically significant (p<0.0001). This indicates that after administration of subsequent dose of paracetamol in Group P patients, the mean VAS decreased significantly, whereas it is on higher side in Group T patients in whom next dose was due at that time.

Nikoda et al. [11] in his study of IV infusion of paracetamol in a single dose of 1g (4 g/day) for postoperative analgesia reported a reduction in the intensity and duration of pain and that the IV formulation of paracetamol should be used as multimodal therapy for mild to moderate postoperative pain management.

At 9 hours, the mean VAS is 3.04 (±0.28) in Group P and it is 2.06 (±0.31) in Group T, which is statistically significant (p<0.0001). And at 12 hours, the mean VAS is 1.98 (±0.44) in Group P and it is 3.62 (±0.44) in Group T, which is statistically significant (p < 0.0001). Again at 16 hours, the mean VAS is 3.08 (±0.74) in Group P and it is 1.76 (±0.46) in Group T. There is higher VAS score in Group P as compared to Group T, which is statistically significant (p < 0.0001). This indicates that after administration of subsequent doses of either paracetamol or tramadol, the pain relief is adequate, which is seen in decline in respective mean VAS score in both the groups.

After 20 hours in post-operative period, the mean VAS is 2.12 (±0.38) in Group P and it is 2.10 (±0.51) in Group T, which is statistically insignificant (p=0.8243). And at 24 hours, the mean VAS is 0.88 (±0.59) in Group P and it is 0.76 (±0.48) in Group T, which is also statistically insignificant (p=0.2678).

Sinatra RS et al. [12] in his study found that intravenous acetaminophen was consistently superior to placebo for pain relief and for pain intensity changes from 15 min to 6 h after the first dose and throughout the 24-h evaluation period after repeated dose administration. Jeong-Yeon Hong et al. [6] showed that VAS scores were significantly lower in the paracetamol group at 1, 3, 6 and 24 hours after surgery and significantly fewer patients in the paracetamol group received rescue analgesic than the placebo group.

Aghamir et al. [13] compared propacetamol and tramadol after urologic open surgeries and found propacetamol useful, but inadequate in cases of severe pain, whereas Uysal et al. [14] compared either of the drugs in post-adenotonsillectomy pediatric patients and found iv paracetamol to be superior in terms of early recovery, but associated with similar analgesic properties. Turhan Togrul et al. [15] studied the comparison of intravenous Paracetamol and Tramadol for postoperative analgesia in patients with septo-rhinoplasty and concluded that iv paracetamol administration provided adequate analgesia as opioids especially at early post-operative period for mild to moderate pain therapy in peri-operative period. Howard S. Smith et al. [16] studied the analgesic effects of intravenous paracetamol and NSAIDs and concluded that iv paracetamol represents a safe and effective first-line analgesic agent for the treatment of acute mild-to-moderate pain in the perioperative setting.

Sinatra et al. [12] found that IV paracetamol has rapid onset of analgesia in orthopaedic surgeries and IV paracetamol 1 g administered in patients with moderate to severe pain offered quick and effective analgesia. They found IV paracetamol significantly reduced morphine consumption over the 24 hours period and safe in terms of clinical and laboratory examinations. Cade et al. [17] and Hein et al. [18] in their study did not found postoperative analgesic or opioid sparing effects with paracetamol after minor and major surgery and this might be due to the single injection of paracetamol which would not be expected to provide pain relief even after minor surgery hence in our surgery we used repeated injections of paracetamol to get the desired effect.

We observed that the time to 1st dose of rescue analgesia requirement was lower in Group T in the 24 hours study period, with the mean postoperative rescue analgesic free time interval of 6.23±1.72 hours, as compared to Group P where it is 5.01±1.16 hours. This is found to be statistically significant with P value of 0.0001. Party's et al. [5] in his study found mean duration of analgesia in

paracetamol group to be 4.27 hours and slightly higher 4.86 hours in Tramadol group.

Also, the frequency of rescue analgesic requirement was lower in Group T in the 24 hours study period. The patients in Group T required 1 to 2 times of rescue analgesia with a mean of 1.20 (±0.41), in comparison to the Group P, where patients required 2 to 3 times of rescue analgesia with a mean of 1.67 (±0.71).This was also found to be statistically significant with P-value of 0.001.

In our study, 5 patients complained for PONV in Group P and 16 patients in Group T. Also, 3 patients complained of sedation in Group T. No cases of urinary retention were observed in either group.

Kela et al. [19] compared the efficacy of either drug in the postoperative period in cardiothoracic surgery and found 10.0% of the subjects in paracetamol group and 13.3% of the subjects in tramadol group suffered nausea and vomiting which were comparable and difference was insignificant. Caken T et al. [20], Mohammad Shahid et al. [9], Pratyush Goel [5] et al. and Jeong-Yeon Hong et al. [6] in their study found decreased incidence of nausea and vomiting with the use of IV paracetamol which is similar to our study.

It becomes evident from this study that the paracetamol can be a good alternative to tramadol and thus can avoid the complications associated with non-steroidal anti-inflammatory drugs and opioids.

Potential limitation of the study are that IV paracetamol in head and neck cancer offers central analgesic effects but the anti-inflammatory effects, which is enhances analgesia in the early post-operative period is not possible. So moderate to severe pain and bony pain may not be addressed adequately with paracetamol. Though it is having less incidence of PONV than tramadol, patients with borderline liver dysfunction patients may be at high risk as only repeated administration of paracetamol is effective.

Conclusion

Intravenous paracetamol administration in peri-operative period provided adequate postoperative analgesia in patients undergoing head and neck cancer surgery. In contrast to opioids, paracetamol does not produce sedation, respiratory depression or constipation, nor is it associated with a risk of substance abuse or misuse. Based on these findings, intraoperative IV paracetamol appears to be a reasonable choice for postoperative analgesia in this patient population.

References

1. Lai DC. History of pain relief. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002.p.3-5.
2. Suchdev PK. Pathophysiology of Pain. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd edition. Philadelphia: Lippincott Williams and Wilkins; 2002.p.6-12.
3. Asdourian CP. Acute pain management. In: Warfield CA, Fausett HJ. Manual of Pain Management: 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2002.p.215-22.
4. James D, Justins D. Acute postoperative pain. In Thomas H, Knight PR, eds. Wylie's Textbook of Anesthesia, 7th Ed. 2003.pp.1213-34.
5. Pratyush Goel 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.
6. Jeong-Yeon Hong, Won Oak Kim, WoongYoun Chung, Joo Sun Yun, and HaeKeumKil. Paracetamol Reduces Postoperative Pain and Rescue Analgesic Demand After Robot-Assisted Endoscopic Thyroidectomy by the Trans axillary Approach. World J Surg. 2010;34:521-26.
7. McCaffery M: pain: clinical manual for nursing practice, 2nd edition. Mosby, St. Louis, 1989: page 7.
8. Svensson, Sjostorm B. influences of expectations and actual pain experiences on satisfaction with postoperative pain management. Eur J Pain. 2001; 5:125-33.
9. Shahid M, Manjula BP, Sunil BV. A comparative study of intravenous paracetamol and intravenous tramadol for postoperative analgesia in laparotomies. Anesth Essays Res. 2015;9:314-9.
10. Semih Arici et al. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. AGRI. 2009;21(2):54-61.
11. Nikoda VV, Makarova VV, Maiachkin RB, Bondarenko AV. Clinical aspects of analgesia with intravenous paracetamol in the early postoperative period. Anesteziol Reanimatol. 2006;6:54-8.
12. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER. Efficacy and safety of single and repeated administration of 1 gram intravenous paracetamol injection for pain management after major orthopedic surgery. Anesthesiology. 2005;102(4):822–31.
13. Aghamir SK, Mojtahedzadeh M, Alizadeh F, Alizadeh F, Khalili H, Najafi A, et al. Propacetamol Vs. tramadol for post-operative pain management after urologic surgery. Internet J Pharmacol. 2005;4:2.
14. Uysal HY, Takmaz SA, Yaman F, Baltaci B, Basar H. The efficacy of intravenous paracetamol

versus tramadol for postoperative analgesia after adenotonsillectomy in children. J ClinAnesth. 2011; 23:53-7.

15. Turhan Togrul et al. Comparison of intravenous Paracetamol and Tramadol for postoperative analgesia in patients with septo-rhinoplasty. Journal of Anesthesia. 2011;19(4):213–16.
16. Howard S. Smith. Perioperative Intravenous Acetaminophen and NSAIDs. Pain Medicine 2011; 12:961–81.
17. Cade L, Ashley J. Prophylactic paracetamol for analgesia after vaginal termination of pregnancy. Anaesth Intensive Care. 1993;21:93–96.
18. Hein A, Jakobsson J, Ryberg G. Paracetamol 1 g given rectally at the end of minor gynecological surgery is not efficacious in reducing postoperative pain. Acta Anaesthesiol Scand 1999;43:248–51.
19. Kela M, Umbarkar S, Sarkar M, Garasia M. Comparative study of efficacy of IV paracetamol Vs IV tramadol for postoperative pain relief after cardiac surgery. Bombay Hosp J. 2011;53:582-6.
20. Cakan T, Inan Nurten et al. Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirement. Journal of neurosurgical anesthiology. 2008 July;20(3):169-173.