

## A Randomized Double Blinded Study Comparing the Postoperative Analgesic Effects of Butorphanol, Parecoxib and Tramadol in Patients Undergoing Major Surgical Procedures

R. K. Ranjan, B.V. Sunil and Neeta Santha\*

Department of Anaesthesiology, Kasturba Medical College, Mangalore.  
Manipal Academy of Higher Education, India.

\*Corresponding author E-mail: drneetas@yahoo.com

<http://dx.doi.org/10.13005/bpj/1704>

(Received: 30 March 2019; accepted: 04 May 2019)

Post-operative pain is an acute pain which starts with the surgical trauma and usually ends with tissue healing. Our study was done to evaluate and compare the postoperative analgesic effect of Butorphanol, Parecoxib and Tramadol in patients undergoing major surgical procedures. Randomized double blinded study. Sixty patients of ASA I and II grades of the age group 20 to 50 years, undergoing major surgeries were included in the study. They were divided into three groups with 20 patients each. Group P-Parecoxib, Group B-Butorphanol group, and Group T –Tramadol group. Pain intensity score, pain relief score, sedation score, rescue analgesia and adverse events were noted. Hemodynamic parameters, respiratory rate and saturation were also recorded at regular intervals. The parameters observed were compared by ANOVA test. There was significant decrease in pain intensity scores from 10 minutes onwards which was observed in all the three groups but this decrease was more in Butorphanol group. In our study, higher sedation score was observed for Butorphanol group. Adverse effects like nausea, vomiting were more with tramadol group. Higher doses of rescue analgesia was required in Parecoxib group. Thus Butorphanol is a superior analgesic compared to tramadol and parecoxib, while side effects like nausea, vomiting was more in tramadol group.

**Keywords:** Analgesic, paracetamol, acute pain, sevoflurane, prodrug, respiratory rate, diclofenac, blood pressure.

---

The international association for the study of pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”<sup>1</sup>.

Postoperative pain is an acute pain which starts with the surgical trauma and usually ends with tissue healing. Incidence of postoperative pain varies individually, and is related to site and type of surgery, which is distressing, and can be associated with complications.

The use of analgesic drugs post operatively will enable patient to cough effectively. With the help of physiotherapy and breathing exercises, postoperative pulmonary complication could be reduced<sup>2</sup>.

The goal of postoperative pain management is to reduce or eliminate pain and discomfort with a minimum of side effects. Opioids have been mainstay of postoperative pain control for decades. Opioid analgesics exert their therapeutic effects by mimicking the action of

endogenous opioid peptides at opioid receptors mu, kappa, and delta receptors<sup>3</sup>.

However, opioid analgesics are associated with several limitations. Gastro intestinal side effects such as impairment of both motility and secretion as well as nausea and vomiting limit their extensive usage. Opioids also cause respiratory depression, sedation and have abuse potential<sup>4</sup>. Parecoxib is a water soluble pro drug of nonsteroidal anti-inflammatory drug (NSAID) Valdecoxib, a potent and selective inhibitor of the cyclooxygenase2 (cox2) isoenzyme. Analgesic and anti-inflammatory effects of Valdecoxib are related to inhibition of prostaglandin synthesis, via inhibition of the cyclooxygenase2 (cox2) isoenzyme. In spite of some adverse effects related to Valdecoxib like cutaneous reactions and thromboembolic events, they are useful adjuncts to opioids as a part of multimodal analgesia in managing non cardiac surgical patients<sup>5</sup>.

Butorphanol is a nitrogensubstituted 3, 14 dihydroxy morphinan. This synthetic congener of morphinan series is structurally similar to other drugs having the various degrees of narcotic agonist and antagonist properties at room temperature. Butorphanol tartrate has demonstrated safety and effectiveness in the treatment of moderate to severe post-operative pain<sup>6</sup>.

We have undertaken this study to evaluate and compare the postoperative analgesic effects of three drugs, Butorphanol, Parecoxib and Tramadol in patients undergoing major surgical procedures. There are not many literatures available comparing these three drugs in alleviation of postoperative pain.

## MATERIALS AND METHODS

After institutional ethics committee approval and taking informed written consent, this study was carried out on sixty patients of either sex of age group 20 to 50 years of ASA I and II grades, undergoing major surgeries.

Exclusion criteria included patients with severe pain preoperatively, pregnant and lactating women, patients who were already receiving other analgesics like NSAIDs, patients with cardiac diseases, patients with significant renal and hepatic disease, patients with severe or moderate haemodynamic disturbances, patients prone for

respiratory depression (ASA III & IV grades) and patients who are asthenic with deprived muscle mass.

The cases were randomly divided into 3 groups based on computer generated randomization technique. The three groups were Group P-Parecoxib (ParecoxibIntas pharmaceuticals) containing twenty patients, Group B-Butorphanol group (Butrum Aristo pharmaceuticals) with twenty patients and Group T –Tramadol group (Tramazac ZydusCadila health care) with twenty patients. The drug syringes were prepared by an anaesthesiologists who was blinded to the drug (Randomized double-blind pattern). The drug doses were calculated according to body weight and were diluted in one hundred millilitres of 0.9% normal saline and given intravenously over ten minutes. These drugs were administered when he / she reported pain in the immediate postoperative period. Group P Inj Parecoxib 20 mg IV if wt< 50 kg 40 mg IV if wt> 50 kg Group B Inj. Butorphanol 0.04 mg per Kg. Group T Inj. Tramadol 2 mg per Kg. A thorough preanaesthetic evaluation was done. Prior to surgery patients were explained about the visual analogue scale, pain intensity scale and pain relief scale. Pulse rate, blood pressure, temperature and respiratory rate were recorded and all investigation reports were noted. Height and weight were also noted.

After shifting the patient to the operation theatre standard monitors were applied. All the patients were induced with a propofol followed by neuromuscular blockade with Rocuronium intravenously. After adequate relaxation, trachea was intubated under direct vision with appropriate size endotracheal tube. Anaesthesia was maintained with a mixture of N<sub>2</sub>O and O<sub>2</sub> and sevoflurane. Vitals like heart rate, blood pressure, saturation were recorded at regular intervals. At the end of surgery neuromuscular blockade was antagonized with a combination of Inj. neostigmine (0.05 mg/kg) and Inj atropine (0.02 mg/kg) and extubated after complete recovery.

The following parameters are recorded in a main observation of 24 hours postoperatively. 1- Level of consciousness: This was measured by means of sedation scoring scale in following pattern at 0, 10, 20, 30, 60, 120 min and 3, 6, 12 & 24 hours. Sedation Score- Patient fully awake  
1 Patient somnolent, responds to verbal commands

2 Patient somnolent, responds to tactile stimulation  
 3 Patients asleep, responds to painful stimulation  
 4. Postoperative pain intensity score- Postoperative intensity of pain was measured by Visual Analogue Score, recorded at 0, 10, 20, 30, 60, 120 min and 3, 6, 12, & 24 hrs. Pain Relief Score- Pain relief was noted at 0, 10, 20, 30, 60, 120 min and 3, 6, 12 and 24 hours and graded on a scale of 0 to 3. 0. No relief 1. Mild or some relief 2. Good relief 3. Excellent (or) total relief. Complications such as vomiting and nausea were noted. If the patient complained of pain, (i.e., after the analgesic effect of study drug was worn off) rescue analgesia was given in the form of diclofenac sodium as per the surgical unit's routine prescription. The parameters observed were compared statistically for any significant difference between the groups using ANOVA (one way analysis of variance and Two way analysis of variance Friedman's rank test wherever required).

**RESULTS**

The cases were studied under the following demographic data shown in the table 1. The patients in the three groups were comparable with respect to age, and weight (p>0.05).

Postoperative pain relief between all the three groups was measured by pain intensity score and pain relief score. These values are shown in tables 2 and 3 respectively.

In our study we found that there was a statistically significant difference in the pain relief obtained between the Butorphanol group compared with rest of the two groups. The initial or basal pain scores were statistically insignificant in all the three groups. The onset of analgesia was faster in Butorphanol group. There was significant decrease in pain intensity scores from 10 minutes onwards which was observed in all the three groups but this decrease was more in Butorphanol group.

**Table 1.** Demographic Data (Mean ± SD)

Group	Age (years)	Sex Ratio (M:F)	Weight (kg)
Group P	38.4 ± 9.77	11:9	58.44 ± 7.32
Group B	38.13 ± 12.10	11:9	54.14 ± 12.36
Group T	44.2 ± 7.90	10:10	57.32 ± 8.44

When Parecoxib group was compared with Butorphanol group, Butorphanol group showed better analgesia throughout 24 hours (P< 0.001) and when Butorphanol group was compared with Tramadol group patients who received Butorphanol showed better analgesia upto 2 hours (P<0.001) there after no significant change in pain score was observed between these two group (P> 0.05). The sedation scores in all the three groups are shown in the table 4.

In our study, statistically significant change in sedation score up to 6 hours was observed between Group B (Butorphanol) and Group P (Parecoxib) p< 0.001, with higher sedation for Butorphanol group. Sedation scores between Group B (Butorphanol) and Group T (Tramadol) were comparable and not statistically significant (p>0.05).

Post operatively, all patients were also monitored for oxygen saturation, heart rate, respiratory rate and blood pressure. There was no statistically significant difference between the three groups. The adverse effects in the 24 hours period post operatively namely nausea, vomiting, distension of abdomen and retention of urine were noted in all the three groups. These values were shown in table 5.

Incidence of nausea was 45% in tramadol group, 35% in Butorphanol group and 15% in Parecoxib group. Vomiting was seen in a few patients in all the groups but it is relatively more in Tramadol group. (45%) Incidence of epigastric pain was seen in 10% of the patients in Parecoxib group. Urinary retention was seen in 10% in Butorphanol group.

**Table 2.** Postoperative Pain Intensity in VAS (Mean ± SD)

Time	Group P	Group B	Group T
0 MIN	92.50 ± 7.57	88.89 ± 2.89	87.50 ± 4.82
10 MIN	47.50 ± 5.65	14.44 ± 3.75	21.67 ± 5.87
20 MIN	27.50 ± 6.75	10.56 ± 3.56	27.50 ± 1.78
30 MIN	36.67 ± 6.45	11.67 ± 1.09	23.33 ± 1.54
60 MIN	37.50 ± 4.75	16.67 ± 5.09	26.67 ± 4.64
120 MIN	54.17 ± 5.34	26.67 ± 3.98	45.00 ± 5.00
3HRS	53.5 ± 4.92	34.44 ± 4.65	35.83 ± 6.76
6HRS	66.50 ± 8.86	33.33 ± 8.67	39.17 ± 4.64
12HRS	52.50 ± 2.99	38.33 ± 4.27	40.83 ± 5.98
24HRS	46.5 ± 5.34	35.56 ± 3.87	30.00 ± 4.64

**Table 3.** Postoperative Pain Relief Score (Mean  $\pm$  SD)

Time	Group P	Group B	Group T
0 MIN	0	0	0
10 MIN	0.5 $\pm$ 0.02	1.8 $\pm$ 0.57	1.2 $\pm$ 0.52
20 MIN	0.75 $\pm$ 0.05	2.6 $\pm$ 0.71	1.75 $\pm$ 0.44
30 MIN	1.95 $\pm$ 0.21	2.7 $\pm$ 0.53	2.0 $\pm$ 0.39
60 MIN	2.3 $\pm$ 0.471	2.9 $\pm$ 0.32	2.2 $\pm$ 0.54
120 MIN	1.8 $\pm$ 0.58	2.6 $\pm$ 0.85	1.85 $\pm$ 0.42
3HRS	1.7 $\pm$ 0.56	2.5 $\pm$ 0.43	1.95 $\pm$ 0.32
6HRS	1.5 $\pm$ 0.51	2.35 $\pm$ 0.70	1.95 $\pm$ 0.32
12HRS	1.55 $\pm$ 0.41	2.1 $\pm$ 0.22	1.89 $\pm$ 0.32
24HRS	1.6 $\pm$ 0.31	2.0 $\pm$ 0.32	1.95 $\pm$ 0.20

**Table 4.** Postoperative Sedation Score (Mean  $\pm$  SD)

Time	Group P	Group B	Group T
0 MIN	1.15 $\pm$ 0.54	1.17 $\pm$ 0.98	1.25 $\pm$ 0.76
10 MIN	1.00 $\pm$ 0.56	3.00 $\pm$ 1.01	2.25 $\pm$ 0.89
20 MIN	1.00 $\pm$ 0.56	3.00 $\pm$ 1.01	2.25 $\pm$ 0.89
30 MIN	1.00 $\pm$ 0.57	3.00 $\pm$ 0.78	2.00 $\pm$ 0.79
60 MIN	1.00 $\pm$ 0.09	3.00 $\pm$ 0.64	1.67 $\pm$ 0.75
120 MIN	1.05 $\pm$ 0.05	2.89 $\pm$ 0.46	2.25 $\pm$ 0.99
3HRS	1.25 $\pm$ 0.87	2.72 $\pm$ 0.65	1.17 $\pm$ 0.97
6HRS	1.05 $\pm$ 0.08	2.67 $\pm$ 0.37	1.25 $\pm$ 0.08
12HRS	1.45 $\pm$ 0.57	1.44 $\pm$ 0.58	1.17 $\pm$ 0.69
24HRS	1.42 $\pm$ 0.26	1.11 $\pm$ 0.36	1.08 $\pm$ 0.06

The total rescue analgesic consumption is depicted in table 6. It shows that higher doses of rescue analgesia was required in Parecoxib group was significant decrease in pain intensity scores from 10 minutes onwards which was observed in all the three groups but this decrease was more in Butorphanol group.

### DISCUSSION

The relief of postoperative pain is a subject which has been receiving an increasing amount of attention in the past few years. Despite recent advances in the understanding of postoperative pain and wide spread recognition of the problem, clinical surveys indicate that routine treatment of postoperative pain remains unsatisfactory (with

nearly 80% of patients reporting moderate to extreme pain following surgery).

The current options for postoperative pain management include opiates, NSAIDS, epidural analgesia and local blocks. Opioids have been mainstay of postoperative pain control for decades. NSAIDS are used routinely for postoperative pain treatment.

In our study the onset of analgesia was found to be faster in Butorphanol group. There was significant decrease in pain scores from 10 minutes onwards and this significant decrease in pain scores in Butorphanol group lasted for 120 minutes and the slightly increased afterwards. This observation is consistent with previous study done on patients undergoing labour analgesia, who received 1mg Butorphanol intramuscularly during active phase of

**Table 5.** Adverse Effects

Group	Nausea	Vomiting	Epigastric pain	Abdominal distention	Urinary retention
Group P	3 (15%)	3 (15%)	2 (10%)	0	0
Group B	7 (35%)	5 (25%)	0	1 (5%)	2 (10%)
Group T	9 (45%)	9 (45%)	0	0	1 (5%)

**Table 6.** Rescue Analgesic Drug Consumption (Mean)

Group	Diclofenac sodium (mg)
Group P	225
Group B	150
Group T	150

labour analgesia. The analgesic effect was observed within 15 minutes<sup>7</sup>.

In our study the onset of analgesia in Parecoxib group was slightly delayed. Pain scores significantly decreased from 20 minutes onwards. In a randomized study comparing Parecoxib 40 mg intravenously and morphine 0.1 mg/kg, it was found that there was no statistically significant

difference in pain scores between the two groups. It was concluded in the study that the complications associated with opioid use can be avoided in Parecoxib use<sup>8</sup>.

The analgesic efficacy of Butorphanol tartrate injection in postoperative pain was investigated in several double blind active control studies.

Torokoli *et al* and Vogel sand etal conducted several double blind studies to evaluate the analgesic efficacy of Butorphanol tartrate and they reported that doses of 2 mg Butorphanol, 10 mg morphine, 40 mg pentazocine and 80 mg meperidine were found to have approximately equivalent analgesic effect<sup>9,10</sup>.

In our study we found that Butorphanol was superior to Tramadol and Parecoxib in producing pain relief. These findings were similar to another study conducted on patients undergoing dental extraction. It was found that Butorphanol was superior to tramadol in alleviating post procedure pain which was similar to our findings<sup>11</sup>. Similar findings were found in previous studies done on postoperative pain relief measures after abdominal surgeries<sup>12</sup>.

The slow onset of analgesic action of Parecoxib can be disadvantage when treating patients with acute pain. This initial delay in onset of analgesia probably reflects the mode of analgesic action of Parecoxib, the inhibition of prostaglandin production peripherally. It would also explain the more frequent requests for medication in parecoxib group compared with tramadol and Butorphanol.

In our study we found that parecoxib was the least potent of all the study drugs and the total rescue analgesic consumption was also highest with parecoxib. But these findings were contradictory to the study findings conducted by Zang etal where analgesic effect of Parecoxib was found to be superior to tramadol after uvulo palatopharyngeoplasty<sup>13</sup>. Incidence of drowsiness was found to be highest Butorphanol group. This group of patients was drowsy but easily arousable. In contrast to findings of the Butorphanol and Tramadol group, patients who received parecoxib were awake and complained of insomnia. This observation is consistent with previous study done by Lutful Aziz *et al*<sup>14</sup>. Regarding respiratory parameters there was no significant change in oxygen saturation and respiratory rate in all the

three groups. There was no statistically significant alterations seen in pulse rate and blood pressure in the patients of all groups of our study these findings were similar to the studies conducted by Lutful Aziz etal and Scharffer *et al*<sup>14, 15</sup>. The incidence of nausea was the highest in Tramadol group followed by Butorphanol and Parecoxib groups. Our findings are similar to that of studies conducted by Lutful Aziz *et al*<sup>14</sup>. The incidence of vomiting was the highest in Tramadol group followed by Butorphanol and Parecoxib groups. This observation were well supported by Hubbard R etal who reported that parecoxib is generally well tolerated when compared with ketorolac and other NSAIDS even by elderly patients<sup>16</sup>. As mentioned in previous studies, care is to be taken during the administration of injection butorphanol because of the risk of respiratory depression. However, we did not experience any episode of respiratory difficulty in any of our study

## CONCLUSION

From this study we conclude that postoperative pain relief obtained was maximum with Butorphanol followed by Tramadol and Parecoxib. Duration of pain relief was maximum with Butorphanol followed by Tramadol and Parecoxib. Adverse effects like nausea, vomiting were found more in tramadol group. Thus Butorphanol is a superior analgesic compared to tramadol and parecoxib with minimal side effects.

## REFERENCES

1. Gorczyca R, Filip R, Walczak E. Psychological aspects of pain. *Ann Agric Environ Med*; **1**:231 (2013).
2. Ana D, Humberto S. Postoperative Pulmonary Complications: An Epidemiological, Risk Factors and Prevention *Review J Anesth Clin Res*, **7**:1 (2016).
3. Ream A, Michael R. Molecular Mechanisms of Opioid Receptor Dependent Signaling and Behavior. *Anesthesiology*; **115**(6): 1363–1381 (2011).
4. Benyamin R, Trescot A, Datta S. Opioid complications and side effects. *Pain Physician*; **11**:10520 (2008).
5. Nussmeier N, Whelton A, Brown M, Joshi G. Safety and efficacy of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib after

- noncardiac surgery. *Anesthesiology*.; **104**(3):518-26 (2006).
6. Commiskey S, Fan L, Ho I. Butorphanol: effects of a prototypical agonist-antagonist analgesic on kappa-opioid receptors. *J Pharmacol Sci.*; **98**(2): 10916 (2005).
  7. Ajay H, Rachana A. Butorphanol in labour analgesia: A prospective cohort study Turkish-German Gynecol Assoc; **14**: 2214 (2013).
  8. Kamarul A, Nik H, Rahman N, Intravenous parecoxib sodium as an analgesic alternative to morphine in acute trauma pain in the emergency department. *Int J Emerg Med.*; **7**: 2 (2014).
  9. Tarokoli, Corsen G. Butorphanol and morphine a double blinded comparison of their parenteral analgesic activity. *Anesthesia Analgesia.*; **55**: 394401 (1976).
  10. Vogel W, Burchardi H. The effect of tramadol, a new analgesic on respiration and cardiovascular function. *Drug research*; **28**: 183186 (1978).
  11. Syed S, Anees, Manjunath R, Kalappa M. Analgesic Efficacy of Tramadol and Butorphanol in Mandibular Third Molar Surgery: A Comparative Study. *The Journal of Contemporary Dental Practice.*; **13**(3): 364370 (2012).
  12. Pallavi A, Fauzia R, Amit A. Comparison of Butorphanol Tartrate and Tramadol Hydrochloride for Postoperative Pain Relief Following Abdominal Surgery: A Prospective, Randomized, Double-Blind Study *International Journal of Scientific Study.*; **3**: 9 (2015).
  13. Zhang L, Shao D, Liang Z, Wang D. Comparison of the effects of different analgesic methods after UPPP. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.*; **29**(11):9913 (2015).
  14. Lutfi A, et al. A comparative study of tramadol, diclofenac and ketorolac infusion in management of postoperative pain. *Journal of Anesthesiology and Pharmacology.* **19**;2:187192 (2003).
  15. Schaffer *et al.* Tramadol; pain relief by an opioid without depression of respiration. *Anesthesia.*; **47**: 2916 (1992).
  16. Hubbard R, et al. The COX 2 specific inhibitor parecoxib sodium is effective in treating postoperative pain in total hip arthroplasty patients. *Anesthesiology*; **95**:807 (2001).
  17. Dnyaneshwar R, Tirpude G. Comparative study between injection parecoxib and butorphanol for postoperative analgesia in laparotomy patients. *International Journal of Research in Medical Sciences.*; **5**(3):773 777 (2017).