

**Research Article**

**Oral Tapentadol as a premedication for the perioperative management of cardiac surgery**

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**Abstract**

**Background:** Tapentadol is a newly introduced analgesic drug from opioid group. Our goal is to study effect of oral tapentadol as premedication drug for intraoperative analgesia and studying its effect on hemodynamics during adult cardiac surgery .

**Material and Methods:** 50 Patients were randomly allocated into two Groups. Group T (N=25) received Oral Tapentadol 50 mg along with Tab. Diazepam 5 mg 1 hour before taking patient inside cardiac operation theatre. Group P (n=25) received placebo tablet with Tab. Diazepam 5 mg similarly. Patients were monitored for pain score experienced while inserting veinflow, the arterial pressure monitoring cannula and central venous catheter. Patients were monitored for intraoperative hemodynamic parameters such as SpO<sub>2</sub>, heart rate, arterial blood pressure, pulmonary artery pressure. All the patients were monitored for BIS for monitoring depth of anesthesia, urine output. They were also observed for overall requirement of anesthetic drugs and blood products requirement. Extubation time after shifting and rate of complications were observed as well.

**Observation & Results:** There was significant less pain score after line insertion in group T . In group T heart rate and arterial blood pressure was remaining stable throughout the surgery which was significant. Pulmonary artery pressure remains stable in comparison with placebo group .Side effects were less and quite acceptable in terms of severity. Depth of anaesthesia was better maintained in group T. It even reduces requirement of induction agents and maintenance agents as well. Post operative outcome was quite impressive in group T.

**Conclusion:** Oral tapentadol is very much helpful as premedication and as perioperative analgesic drug. Tapentadol helps for early extubation, reduces hospital length stay and provides better postoperative outcome.

**Keywords:** Tapentadol, cardiac surgery, perioperative analgesia, BIS data

**1. Introduction**

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP Pain Definition (1994, 2008))<sup>1</sup>.

Chest surgery via sternotomy is the most debilitating thing for the patients due to pain. During cardiac surgery incisional pain, putting indwelling thoracotomy tubes, sternal retraction, LIMA and SVG harvesting elicits strong pain response. Pain suffered by patients while inserting venous and arterial access line under local anesthesia before induction makes patient hemodynamically unstable for varying degree of times which required strong analgesic drugs to alleviate it.

In the thoracic region pain signals are relayed through myelinated A- $\delta$  and unmyelinated c-fibers in peripheral intercostals nerves. Sensory intercostals nerve fibers form a dorsal route that fuses with the spinal cord dorsal horn to enter the central nervous system. Spinal pain signals are transmitted to the brain after crossing from the dorsal horn to contralateral spinal cord structured such as spinothalamic tract. Distribution of nociceptive messages occurs to numerous locations in the brain resulting in cognitive, affective and autonomic responses to noxious stimuli.

In this era, application of “fast-track” principles to cardiothoracic surgery has become common and requires a rationale approach to intra-operative use of anesthetic drugs and post-operative analgesia<sup>2</sup>. This includes not only appropriate post operative analgesia delivery but also pre-operative education regarding pain reporting, procedures and devices to provide effective analgesia.

The effects of neglecting analgesic requirement may cause hemodynamic instability and psychological trauma. Activation of CNS-neuroendocrine reflexes due to pain causes catabolic state involving the release of numerous substances eg. Cortisol, vasopressin, renin and angiotensin leading to increase catecholamines, decrease vagal tone and increase oxygen consumption. "Spinal reflex response" to pain causes localized muscle spasm and activation of sympathetic nervous system.

Tapentadol is a novel centrally acting synthetic analgesic with opioids  $\mu$ -receptor agonist and norepinephrine reuptake inhibitor in a single molecule<sup>3,4,5</sup>. It is structurally and mechanistically similar to Tramadol .It displays a dual mode of action having mild opioid activity and possesses monoamine reuptake inhibitor activity<sup>6</sup>.

Stable hemodynamic parameters provide good surgical field, lesser requirements of Inotropes, less requirements of inhalational anesthetic agents, early extubation and better post operative outcome.

## 2. Material and Methods

After approval from the Institutional Ethical Committee and informed written consent, this prospective randomized study was carried out in our cardiac surgery unit. 50 adult patients of either sex scheduled for CABG were included in our study.

### 2.1 Inclusion criteria:

- Patients posted for off pump CABG
- Ejection fraction > 50%

### 2.2 Exclusion criteria:

- Patients who are not willing for central venous catheter and arterial catheter insertion under local anesthesia.
- Patients with history of bowel dysfunction prior to surgery.
- Opioid dependence
- History of renal or liver disorder
- History of Asthama
- History of CNS disorder
- Patient already taking MAO inhibitor or SSRIs.
- Patients with anxious personality.

50 Patients were randomly allocated into two Groups. Group T (N=25) received oral Tab. tapentadol 50 mg along with Tab. Diazepam 5 mg 1 hour before taking patient inside cardiac operation theatre. Group P (n=25) received placebo tablet with Tab. diazepam 5 mg similarly.

All the patients were subjected to venous and arterial line insertion under local anesthesia using Inj. Lignocaine 1% 2 ml for radial artery cannulation and 5-7 ml each for IJV and femoral arterial cannulation. After the procedure, pain score assessment was carried out on a scale of 1-10.

All the patients were induced with inj. glycopyrrolate 10 mcg/kg iv., inj. fentanyl 5-10 mcg/kg iv, Inj. midazolam 0.05-0.1 mg/kg iv and Inj. vecuronium 0.1-0.2 mg/kg iv. All the patients were maintained on O<sub>2</sub>, air and isoflurane 0-1%.

Inj. vecuronium 0.05 mg/kg repeated as per train of four (TOF) response. Inj. midazolam 0.02 mg/kg and Inj. fentanyl 2mcg/kg repeated whenever BIS scale crossed value of 60.

After intubation, all the patients were kept on ventilator with O<sub>2</sub>-Air 50-50% and tidal volume of 10 ml/kg, respiratory rate was set according to pCO<sub>2</sub> and EtCO<sub>2</sub> level. Inspiratory: Expiratory ration was set at 1:2.5 and in all the

patients' peak airway pressure was noted.

Patients were monitored for pain score experienced while inserting the lines on a scale of 1-10. Patients were also monitored for intraoperative hemodynamic parameters such as SpO<sub>2</sub>, heart rate, rhythm disturbance, arterial blood pressure, mean PA pressure. They were also observed for requirement of isoflurane and other analgesic drugs, fluid and blood products requirement and urine output in both the groups. Extubation time after shifting and post operative well being were also looked for. They were observed for any types of complications such as nausea, vomiting, dizziness, headache, somnolence etc.

Patients were given inj. Tramadol 1 mg/kg iv and inj. paracetamol 15 mg/kg iv. just before the shifting in both the groups as a post-operative analgesic agents.

### 2.3 Statistical Analysis

All data were analyzed statically using T- test and a value of P<0.05 was considered significant. The data were presented as Mean ± SD and percentage. For this statistical analysis we have used Graphpad Prism V.6.0 software.

### 3. Observation and Results

A total of 50 patients were recruited for the study. There were no significant differences between the two groups in demographic data and duration of surgery (Table 1). Pre-operative baseline hemodynamic parameters were comparable in both the groups (p >0.05).

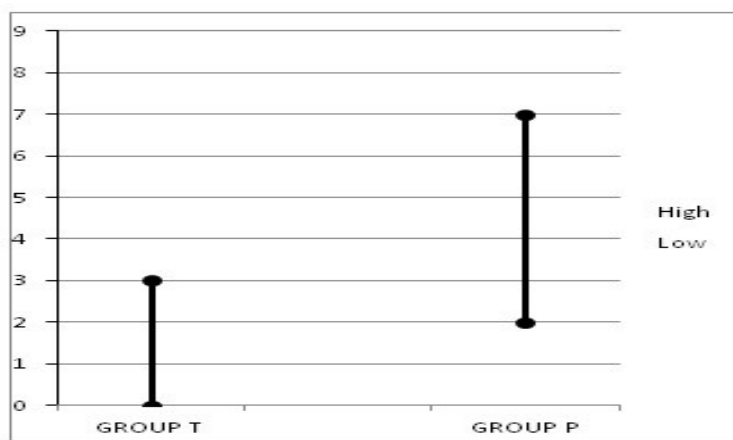
**Table 1: Demographic Profile**

Parameters	Group T n=25	Group P n=25	P Value	
Mean Age (years)	61.6 ± 11.9	62.06 ± 10.9	p>0.05	NS
Sex (m/f)	13/12	14/11		
Duration of surgery (min)	198.6 ± 27.2	192.4 ± 23.4	p>0.05	NS

NS – Non Significant; S- Significant

Out of all the patients included in group T, one patient showed anxious behavior while shifting the patient to operation theatre. To alleviate anxiety inj. midazolam 1 mg iv. was given and patient's anxiety was suppressed.

**Figure 1: Preoperative mean pain score while central and arterial line insertion.**

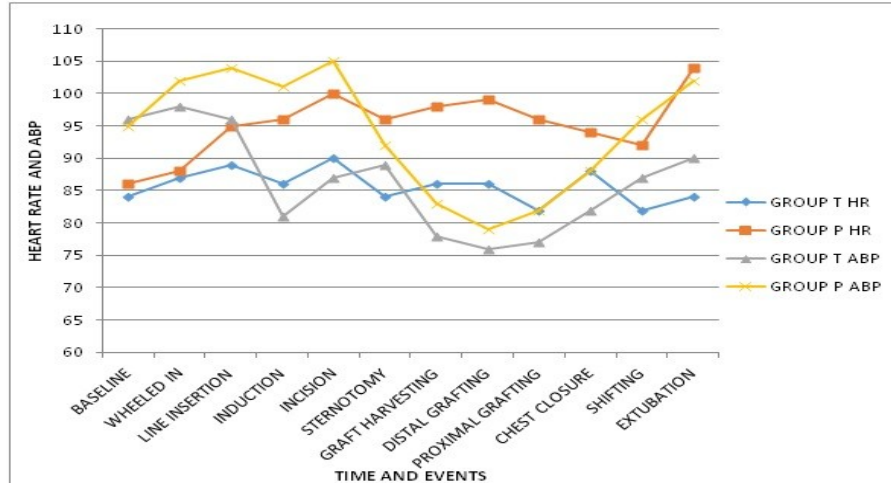


Above Figure 1 indicates significant less mean pain score in Tapentadol group just after line insertion.

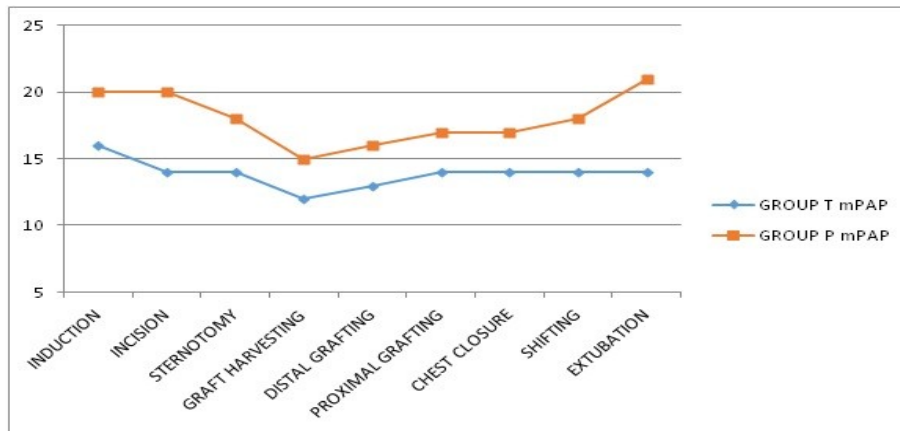
After completion of the cardiac surgery, in post operative ward each patient was asked about his/her experience while undergoing procedure under local anesthesia before induction. 96% of the group T patients said to have smooth procedure under local anesthesia while in group P, 64% of the patients complained of pain even while injecting local anesthesia and 32% of patients suggested to have other alternative techniques should be adopted.

Requirement of fentanyl was markedly lower in induction which is around 4-5 mcg/kg in group T while around 7-8 mcg/kg in group P. In maintenance, we have given incremental doses of fentanyl and Midazolam when BIS crossed 60. In group T, BIS crossed 60 after avg. 70 minutes while in group P it was avg. 55 minutes which was significant as well.

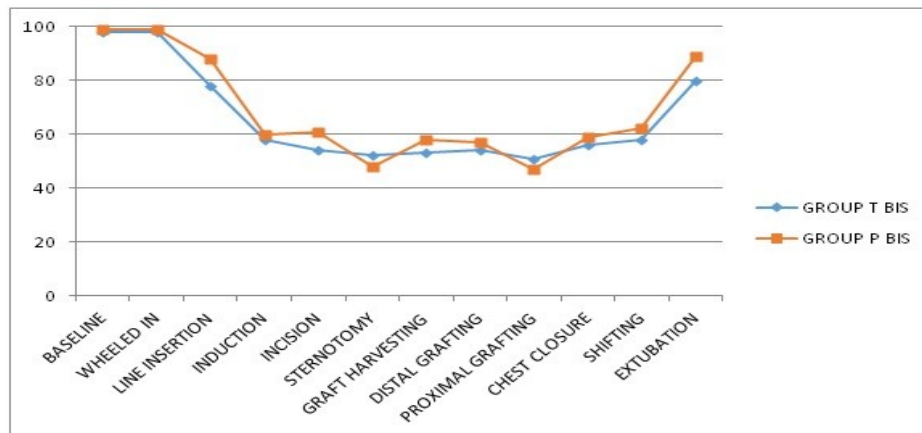
**Figure 2: Change in Heart rate and mean Arterial Blood pressure**



**Figure 3: Change in mean PA pressure**



**Figure 4: Change in Bispectral Index (BIS) Data**



In our study fluctuation in BIS value in group P was associated with hemodynamic variation, need of changing concentration of Isoflurane frequently and need of giving inj. fentanyl and inj. Midazolam to bring BIS value below 60.

**Table 3: Perioperative and Postoperative Outcome**

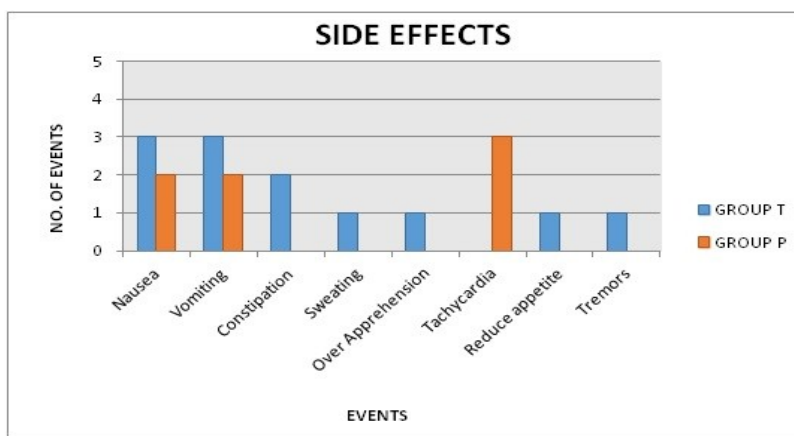
	Group T	Group P	P Value
Extubation Time (min)	90.9 ± 6.4	108.3 ± 7.9	P > 0.05
Length of ICU stay (hours)	82.6 ± 7.2	96.9 ± 6.9	P < 0.05
Intraoperative recall	0	1 (4%)	
Average Isoflurane concentration (%)	0.2-0.6%	0.8-1.2%	

We have observed no change in SpO<sub>2</sub> in both the groups. (P>0.05). In group T, 12% of patients had shown various kind of rhythm disturbance including AF, VPCs, SVT and nodal rhythm. In group P, 36% of patients showed above mentioned types of arrhythmia. Out of which 20% required various form of pharmacological treatment.

Comparison of peak airway pressure was not significant in both the groups but still it was lower In group T then group P.

Fluid requirement was higher in group P (avg. 2 liters) compare to group T (avg. 1.7 liters). Pack cell volume was transfused in 16% of group T and 32% of group P patients. There was no statistically significant change in urine output in both the group.

**Figure 5: Side Effects and Complications**



We have reported 8% of patients having nausea out of which 4% had vomiting which required anti-emetic treatment. One patient in Group T had headache that was moderate and relieved after medication. Apart from these we have not observed any major side effects. (Figure 4)

Tracheal extubation time after shifting was significantly less in group T and length of ICU stay was also less in the same group.

#### 4. Discussion

Tapentadol (chemical name: c<sub>14</sub>H<sub>23</sub>NO, molecular mass: 221.339 gm/mol) is a novel centrally acting synthetic analgesic with  $\mu$ -opioid receptor agonist and norepinephrine reuptake inhibition in a single molecule<sup>5,6</sup>. It has half life of appx. 4-6 hours so frequent administration is required<sup>7</sup>. It is 14 times more efficacious than Tramadol and two times less to morphine<sup>8,9</sup>. Tapentadol immediate release tablets have been approved by the FDA in 2008 for the relief of moderate to severe acute pain in adults and in 2011, for chronic pain in an extended release form<sup>10</sup>.

In all 4 phase 3 studies of Tapentadol for acute pain, improvements in pain intensity were observed with Tapentadol treatment (50 mg every 4 to 6 hours). The analgesic effects of Tapentadol are independent of metabolic activation, and

Tapentadol has no active metabolites.<sup>11,12</sup>

Role of Tapentadol in perioperative settings in maintaining hemodynamics has not yet studied previously. We have conducted a randomized prospective study to check effectiveness of Tapentadol as a premedication and a part for multimodal analgesia for perioperative management of cardiac surgery patients.

In our study, we have excluded patients who were already taking MAO inhibitors or SSRIs as Tapentadol acts by inhibition of norepinephrine reuptake and thus potentiate the effects of above mentioned drugs. Tapentadol causes over apprehension so we have excluded the patients with anxious personality.

Role of premedication in coronary artery bypass graft surgery is to minimize myocardial oxygen demand by reducing the heart rate and systemic arterial pressure and to improve myocardial blood flow. We have used diazepam as a premedication agent in both the groups to provide sedation with amnesia for cardiac surgery patients. We have not registered any event such as respiratory depression or hypotension in both the groups with above mention dosages.

At least 8 hours of fasting is required for any type of surgery. Now several anesthesia societies recommend two hours pre-operative fast for clear fluids. We have oral premedication 1 hour before the shifting and same duration was taken for insertion of arterial and central venous line and urinary catheter. So after around two hours of preoperative fast patient was induced.<sup>13</sup> We have observed significantly less pain score after line insertion that is mainly because it is very strong analgesic similar to oxycodone with better tolerability as compared to placebo. Islam *et al*<sup>14</sup> demonstrated that hemodynamic and stress response following arterial and central venous access under local anesthesia with premedication is no different than under general anesthesia in open heart surgery patient. We found similar results in our study as well.

The onset of action of fentanyl is almost immediate when the drug is given intravenously; however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes.<sup>15</sup> Because of this reason we have used Tapentadol as a premedication as analgesic effect has already been established so during intubation hemodynamics was maintained in group T while patients had hemodynamic instability in group P.

In group T, requirement of fentanyl during induction was significantly reduced as compared to placebo group because moderate to severe analgesic effects of tapentadol. Requirement of fentanyl and midazolam as an induction agent was almost half compare to other group but it was proven that Tapentadol has no effect on non-depolarizing muscle relaxants so requirement of vecuronium remained same in both the groups<sup>7</sup>.

Previous study suggests that tapentadol is associated with mild tachycardia in less number of patients. But in our study we have not observed any such unwanted hemodynamic effect which may be due to drug profile itself or effect of benzodiazepine or fentanyl on the heart rate. Pain is associated with intense sympathetic activity which leads to increase heart rate and blood pressure but as tapentadol is very much effective in moderate to severe pain it also reduces sympathetic activity and heart rate & mean arterial pressure remain stable.

Increase mean arterial pressure and tachycardia causes elevated pulmonary artery occlusion pressure which ultimately reflects increase in PA pressure and increase in fluid requirement in group T also associated with increase in PA pressure. There was a clear correlation between pulmonary vascular resistance and pain perceive during surgery.<sup>16</sup>

Intraoperative SpO<sub>2</sub> remains same in both the groups. In early postoperative period before extubation, when patients were kept on ventilator (CPAP mode with FIO<sub>2</sub> 50%) SpO<sub>2</sub> in group T was 99% due to improved vital capacity while in group P it fluctuated from 96-98%.

Tapentadol provides better analgesia intraoperative so adequate depth of anesthesia (BIS value 40-60) was maintained and thus we have not observed any greater fluctuation in BIS data of group T while in group P it was quite fluctuating. Thus it is quite helpful to maintain hemodynamics in perioperative settings as well. Earlier study done by G. Barr *et al* mentioned that during clinically adequate anesthesia with Midazolam and fentanyl BIS varies considerably.<sup>17</sup>

Ranta *et al*<sup>18</sup> mentioned that incidence of awareness and intraoperative recall is 4% in patients undergoing cardiac surgery. We have found 4% of patients had intraoperative awareness while none of them in group T though we could not correlate it with BIS data.

There is no direct correlation between requirement of Isoflurane and Tapentadol but as hemodynamics were stable

in group T requirement of Isoflurane was quite low which ultimately leads to early extubation as well.

Tapentadol and Oxycodone both have similar effect in terms on analgesia but Tapentadol has better gastric tolerability.<sup>19</sup> In all Phase 3 trials the most commonly reported treatment emergent adverse events were typical of drugs with  $\mu$ -opioid agonist activity, and those were nausea, vomiting, dizziness, constipation, headache and somnolence.<sup>20-23</sup> These are considered the most undesirable side effects associated with opioids leads to its discontinuation<sup>24</sup>.

Nausea and vomiting were the most commonly reported side effects in our study. Over apprehensive behavior is the commonest side effect of Tapentadol, to prevent that we have added Tab. Diazepam 5 mg. Though the number of side effects is much higher than what we had encountered but as our study group comprises of 25 subjects we did not register much side effects. The reason may also be good drug profile<sup>25</sup>.

Oral Tapentadol provides sustain analgesia and definitely improves post operative outcome as well.<sup>26</sup>

## 5. Conclusion

Oral Tapentadol as a premedication is very helpful in terms of preoperative and perioperative analgesia as well as reducing requirements of Induction and inhalational agents and thus provides early extubation, shorten ICU stay and better post operative patient outcome.

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