Comparison of Continuous Infusion of Intravenous Tramadol and Fentanyl on Postoperative Analgesia in Cardiac Surgery

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Abstract

Background: Adequate postoperative analgesia can help in decreasing patient discomfort and in reducing hospital stay after cardiac surgery. This study was designed to compare the effect of tramadol and fentanyl infusion on post operative pain relief after cardiac surgery.

Methods: Forty one patients undergoing open heart surgery were randomly assigned into two groups; Fentanyl group (21 patients) and Tramadol group (20 patients). Both groups received the same anaesthetic technique. Infusion of both drugs started directly after the end of cardiopulmonary bypass and continued for 48 hours after surgery. Fentanyl was given at a dose of 0.5-1 µg.kg⁻¹.h⁻¹ by continuous infusion for 48 hours, while Tramadol was infused at a dose of 0.1-0.2 mg.kg⁻¹.h⁻¹. In addition, both groups received 1 gm rectal paracetamol every six hours.

Patients were assessed for the analgesic efficacy by 11-point verbal rating scale (VRS), sedation by Ramsay sedation scale and patients’ satisfaction with analgesia using a 100-point verbal rating scale, with 1 = highly dissatisfied to 100 = highly satisfied [1] at the following time points; 6h, 12h, 24h, 36h and 48h after surgery.

Results: Both groups were matched as regard age, sex, bypass and ischemic times as well as to the type of surgery and duration of mechanical ventilation and hospital stay. No significant differences were observed between groups as regard the analgesic efficacy, sedation scale and satisfaction with analgesia using a 100-point verbal rating scale, with 1 = highly dissatisfied to 100 = highly satisfied [1] at the following time points; 6h, 12h, 24h, 36h and 48h after surgery.

Conclusion: It appears from this study that tramadol infusion offers a comparable analgesic efficacy to fentanyl after cardiac surgery.

Key Words: Cardiac surgery – Postoperative – Analgesia – Pain assessment – Drugs – Fentanyl – Tramadol.
Comparison of Continuous Infusion of Intravenous
mobilize effectively [7]. In addition, unrelieved postoperative pain can have a negative psychological effect and hinder postoperative recovery. As such, it is vital that the cardiac surgical patient receives optimal postoperative pain management.

Fentanyl, N-(1-phenethyl-4-piperidyl) propionanilide, is structurally related to meperidine. Continuous Intravenous Fentanyl Infusion has been used to provide postoperative analgesia after abdominal [8], peripheral orthopedic [9], and major spinal surgery [10]; thoracotomy [11], and cesarean section delivery [12].

Tramadol hydrochloride (tramadol) is a centrally acting analgesic that is structurally related to codeine and morphine. It was first synthesized in 1962 and has been available for pain treatment in Germany since 1977 [13].

Continuous intravenous infusion of tramadol 12 mg/h showed a trend towards better pain relief than with intermittent intravenous bolus doses of tramadol 50mg following abdominal surgery [14]. Two studies demonstrated that continuous infusion of tramadol, titrated to the patient’s requirements, provides adequate analgesia after cardiac surgery, comparable with the effects of alfentanil or morphine infusion [15,16].

To the best of our knowledge studies that comparing the analgesic efficacies of fentanyl versus tramadol after cardiac surgery are lacking.

Aim of the study:
This study was designed to compare the effect of tramadol and fentanyl infusion on post operative pain relief and patients’ satisfaction after cardiac surgery.

Patients and Methods
After approval of ethical committee and obtaining an informed consent from all patients, forty one adult patients undergoing cardiac surgery included in this study.

Adult patients undergoing valve replacement surgery, repair congenital heart defects (ASD, VSD) were included in the study.

Exclusion criteria:
- Children.
- Geriatric patients.
- Patients with renal impairment.
- Patients with hepatic impairment.
- Patients with neurological impairment.
- Patients with previous cardiac surgery.

Anaesthetic technique:
All patients were premedicated with oral diazepam 10mg 60-90 min before their operations. After arrival to the anaesthetic room, 2-5mg intravenous midazolam were given to facilitate insertion of lines (arterial and central venous catheter) under local anaesthesia infiltration. Anaesthesia induced with thiopental sodium 4-6 mg.kg⁻¹ and fentanyl 5-10 µg.kg⁻¹. Pancuronium 0.1mg kg⁻¹ administered to facilitate tracheal intubation. Anaesthesia will be maintained with continuous infusion of fentanyl 1-2 µg.kg⁻¹.h⁻¹ and isoflurane in oxygen/air at a concentration of 0.5-1.0%.

All patients monitored during surgery with ECG, direct arterial blood pressure, pulse oximetry, capnography and urinary output. Surface and core temperature measured using skin and nasopharangeal probes. Cardiopulmonary bypass (CPB) will be established using a membrane oxygenator and a roller pump with an arterial line filter. Non-pulsatile perfusion used with a flow rate of 2.4 L.m⁻² body surface area. Intermittent, antegrade cold crystalloid cardioplegia administered to all patients.

Postoperative ventilation of the patient will be carried out using the protocol adopted in the postoperative cardiac intensive care unit. Patients mechanically ventilated using FIO2 of 0.6, tidal volume of 6-8 ml/Kg and respiratory frequency of 10-12 cycles/min.

After the end of surgery, forty one patients undergoing open heart surgery were randomly assigned into two groups; Fentanyl group (21 patients) and Tramadol group (20 patients).

Group "F"; received fentanyl for postoperative analgesia at dose of 0.5 µg.kg⁻¹.h⁻¹ by continuous infusion for 48 hours.

Group "T"; received tramadol for postoperative analgesia at dose of 0.1-0.2 mg.kg⁻¹.h⁻¹ by continuous infusion. Tramadol infusion started directly after separation of the patient from CPB for 48 hours. In addition, both groups received 1 gm rectal paracetamol every six hours.

Patients evaluated for their chest pain using an 11-point verbal rating scale (VRS), with 0= no
pain to 10= worst pain imaginable [17] at specific intervals:

- At six hours.
- At twelve hours.
- At twenty four hours.
- At thirty six hours.
- At forty eight hours.

Also, patient satisfaction with their pain management assessed at same intervals during the postoperative period using a 100-point verbal rating scale, with 1 = highly dissatisfied to 100= highly satisfied [17]. If any patient requires further analgesia a bolus dose of 25-50 g of fentanyl was given in the fentanyl group and 25-50 mg of tramadol in the tramadol group until verbal rating scale become less than 3. During the 48 hours postoperative pain score (VRS) not allowed to be more than 3.

Furthermore, patient sedation was assessed at the same time intervals using Ramsay Sedation Scale [18]:

- Level 1: Patient anxious, agitated, restless or all of three.
- Level 2: Patient cooperative, accepting ventilation, oriented and tranquil.
- Level 3: Patient asleep, brisk response to light glabellar tap or loud auditory stimulus.
- Level 4: Patient asleep, sluggish response to light glabellar tap or loud auditory stimulus but does respond to painful stimulus
- Level 5: Patient does not respond to painful stimulus.

Also, the following parameters were assessed:

- The total dose of fentanyl and tramadol will be estimated.
- The duration of mechanical ventilation.
- Respiratory rate, heart rate, blood pressure and blood gases were assessed at the same intervals.

### Results

No significant differences were observed between both groups regarding to patients’ characteristics (Table 1).

There were no statistical differences observed among the two groups regarding intraoperative and postoperative Patients’ variable namely, cross clamping time cardiopulmonary bypass time, duration of mechanical ventilation, ICU stay or hospital days.

Furthermore, there were no significant differences between both groups in mean heart rate, respiratory rate, arterial carbon dioxide tension and mean arterial pressure at any of the studied periods. Mean central venous pressure was significantly higher in tramadol group only at 12h after surgery (Table 3).

The analgesic efficacy as measured by VRS, sedation scale and satisfaction with the type of analgesia were comparable between both groups (Figs. 1,2,3).

However, 11 patients in tramadol group experienced nausea and vomiting versus 7 patients in fentanyl group (p=0.215 by Fisher’s exact test). Also, 13 patients requested boluses of tramadol as rescue analgesia 50 mg in tramadol group, while 8-patients required 50 g g fentanyl in fentanyl group, p=0.121 by Fisher’s exact test.

### Table (1): Mean (SD) of patient characteristics in fentanyl and tramadol groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group F</th>
<th>Group T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.1 (2.22)</td>
<td>27.1 (2.68)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11/10</td>
<td>12/8</td>
</tr>
<tr>
<td>Weight</td>
<td>57.79 (6.57)</td>
<td>53.2 (6.44)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>63.68 (16.6)</td>
<td>59.67 (10.16)</td>
</tr>
<tr>
<td>Type of the operation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve replacement (MVR)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Mitral valve replacement and tricuspid valve repair (MVR &amp; TVR)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Aortic valve replacement (AVR)</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>MVR and AVR</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular septal defect (VSD)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Atrial septal defect (ASD)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MVR, TVR and AVR</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

### Table (2): Mean (SD) of intraoperative and postoperative variables in group F and group T.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group F</th>
<th>Group T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross clamping time (min)</td>
<td>89.57 (37.5)</td>
<td>86.3 (31.82)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>117.9 (45.26)</td>
<td>110.7 (34.16)</td>
</tr>
<tr>
<td>Mechanical ventilation (min)</td>
<td>590 (211.23)</td>
<td>506.75 (134.01)</td>
</tr>
<tr>
<td>ICU days (days)</td>
<td>4.47 (0.74)</td>
<td>4.10 (0.79)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>7.52 (1.07)</td>
<td>7.15 (1.26)</td>
</tr>
</tbody>
</table>
### Table (3): Mean (SD) of arterial carbon dioxide (PaCO2), respiratory rate (RR), heart rate (HR), central venous pressure (CVP), and mean arterial pressure (MAP).

<table>
<thead>
<tr>
<th>Time</th>
<th>Fentanyl PaCO2 (mmHg)</th>
<th>Fentanyl RR (cycle/min)</th>
<th>Fentanyl HR (beats/min)</th>
<th>Fentanyl CVP (mmHg)</th>
<th>Fentanyl MAP (mmHg)</th>
<th>Tramadol PaCO2 (mmHg)</th>
<th>Tramadol RR (cycle/min)</th>
<th>Tramadol HR (beats/min)</th>
<th>Tramadol CVP (mmHg)</th>
<th>Tramadol MAP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hour</td>
<td>32.73 (6.6)</td>
<td>10.29 (1.1)</td>
<td>96.48 (15.37)</td>
<td>9.29 (2.81)</td>
<td>79.14 (8.98)</td>
<td>34.47 (5.41)</td>
<td>10.75 (1.77)</td>
<td>28.1 (7.35)</td>
<td>93.3 (14.86)</td>
<td>76.51 (3.34)</td>
</tr>
<tr>
<td>6 hour</td>
<td>35.41 (5.74)</td>
<td>26.14 (7.19)</td>
<td>96.48 (18.73)</td>
<td>10.24 (2.49)</td>
<td>80.19 (9.11)</td>
<td>35.91 (5.0)</td>
<td>28.1 (7.35)</td>
<td>93.3 (14.86)</td>
<td>76.51 (3.34)</td>
<td>83 (7.97)</td>
</tr>
<tr>
<td>12 hour</td>
<td>34.33 (4.47)</td>
<td>25.61 (6.65)</td>
<td>92.67 (17.62)</td>
<td>10.8 (3.11)</td>
<td>79.1 (9.95)</td>
<td>34.73 (4.55)</td>
<td>28.1 (7.35)</td>
<td>93.3 (14.86)</td>
<td>76.51 (3.34)</td>
<td>83 (7.97)</td>
</tr>
<tr>
<td>24 hour</td>
<td>33.56 (8.78)</td>
<td>24.1 (5.48)</td>
<td>94.1 (16.07)</td>
<td>12.86 (2.15)</td>
<td>83.23 (10.28)</td>
<td>34.77 (3.69)</td>
<td>28.1 (7.35)</td>
<td>93.3 (14.86)</td>
<td>76.51 (3.34)</td>
<td>83 (7.97)</td>
</tr>
<tr>
<td>36 hour</td>
<td>37.63 (6.12)</td>
<td>23.14 (6.22)</td>
<td>93.29 (12.94)</td>
<td>13.06 (2.33)</td>
<td>82.29 (9.43)</td>
<td>37.8 (4.88)</td>
<td>26.4 (5.68)</td>
<td>91.9 (12.46)</td>
<td>79.89 (1.24)</td>
<td>83 (7.92)</td>
</tr>
<tr>
<td>48 hour</td>
<td>37.42 (3.85)</td>
<td>25.41 (5.23)</td>
<td>94.47 (12.5)</td>
<td>13.99 (2.2)</td>
<td>80.76 (9.78)</td>
<td>37.06 (5.21)</td>
<td>28.63 (4.86)</td>
<td>95.37 (11.98)</td>
<td>79.89 (1.24)</td>
<td>83 (7.92)</td>
</tr>
</tbody>
</table>

*p < 0.05 by using independent samples t test for comparison between groups.

### Discussion

Pain after cardiac surgery is multifactorial including sternotomy, thoracotomy, leg vein harvesting, pericardiotomy, intraoperative tissue retraction and dissection, multiple intravascular cannulations, and/or chest tube insertion/removal.

Most of pain occurs during the first and second days postoperatively in patients undergoing sternotomy for cardiac surgery [19].

In this study we have compared between two methods of analgesia after cardiac surgery in adults undergoing open heart surgery (valve replacement surgery and repair of congenital heart defects) with respect to their analgesic efficiency, sedation effect, ventilatory effect and their impact on an overall patient satisfaction score.
We found that both methods offer a comparable postoperative analgesia after cardiac surgery. There were no differences between them as regard to analgesic efficiency, sedation effect, ventilatory effect and their impact on the overall patient satisfaction scores.

The analgesic efficacy was similar in both groups. This can be explained by:

Fentanyl is a semisynthetic agonist opioid with strong affinity for the mu opioid receptor site. The mu opioid receptors are found in the periphery (following inflammation), at pre and postsynaptic sites in the spinal cord dorsal horn and in the brain stem, thalamus and cortex, which constitutes the ascending pain transmission system. In addition, opioid receptors are found in the midbrain periaqueductal grey, the nucleus raphe magnus, and rostral ventral medulla where they comprise a descending inhibitory system that modulates spinal cord pain transmission [20].

Also fentanyl causes inhibition of Gama Amino Butyric Acid (GABA) transmission in a local circuit (e.g., in the brain stem, where GABA acts to inhibit a pain-inhibitory neuron). This disinhibitory action has the net effect of exciting a descending inhibitory circuit [21].

Tramadol has a modest affinity for the mu opioid receptor. A second, non-opioid, mechanism is suggested by:

(i) Lack of naloxone reversibility.
(ii) Lack of significant naloxone-induced withdrawal.
(iii) Production of mydriasis (rather than miosis).
(iv) Attenuation of its antinociceptive or analgesic effect by non-opioid (i.e. serotonin or adrenergic) antagonists [22].

Several studies have compared tramadol versus different opioid drugs after cardiac surgery.

**Analgesic efficacy:**

We have found no significant difference between the two groups as regard analgesia. Verbal rating scale (VRS) values were similar for all groups but it is slightly increased after extubation. This may be explained by increasing cough and mobilization during and after extubation.

The analgesic effects of fentanyl, morphine and remifentanil by intravenous patient controlled analgesia technique were similar in patients’ undergoing off-pump coronary artery bypass surgery (CABG) [23].

Barilaro et al. [24] performed a prospective randomized study including 60 patients underwent cardiac surgery. Patients’ were randomly allocated into four groups, treated with a different postoperative analgesic therapy: A) tramadol in continuous infusion; B) ketorolac in continuous infusion; C) tramadol, in repeated boluses; D) morphine, in repeated boluses. They found that only tramadol, in continuous i.v. infusion, achieved the required analgesic effect. The previous two studies support the infusion of fentanyl and tramadol for postoperative analgesia after cardiac surgery.

Tramadol infusion after cardiac surgery offers similar analgesic effects when compared with to morphine and to alfentanil infusions after cardiac surgery [15,16,25]. Similarly, in this study tramadol offers a similar analgesic effect to fentanyl when used by continues infusion after cardiac surgery.

Also, after thoracotomy, intravenous tramadol in the form of a bolus followed by continuous infusion was as effective as epidural morphine, and the use of tramadol avoids the necessity of placing a thoracic epidural catheter [26]. In addition, Erolçay et al. [27] compared tramadol versus morphine using PCA device throughout a 24 h period and also concluded that postoperative analgesia provided by tramadol was similar to that of morphine at rest and during deep inspiration after thoracotomy. Similarly, Aygun et al. [28] also compared the effect of intravenous tramadol, intravenous. Fentanyl, epidural tramadol, and an epidural ropivacaine+fentanyl in combination with PCA after lower abdominal surgery in 80 patients (20 patients in each group). They suggested that adequate pain relief was achieved with all regimens.

Furthermore, it is clear from the previous reports that intravenous. Tramadol offered adequate analgesia after thoracotomy, and this analgesia was similar to different opioids and even comparable to thoracic epidural analgesia.

**Rescue analgesia:**

More patients in tramadol group requiring bolus of analgesia after extubation (13 patients) than in fentanyl group (8 patients). This can be explained by the very low dose of tramadol infusion 0.1-0.2 mg.kg⁻¹.h⁻¹ without a background dose. However, [15] Manji et al. compared between tramadol infusion and alfentanil infusion in coronary artery bypass graft surgery patients and they reported that the rescue analgesia was more in alfentanil group (7 patients) than in tramadol group (3 patients).
Comparison of Continuous Infusion of Intravenous Fentanyl and Tramadol: A Randomized Controlled Trial

As regard sedation:

Sedation scores values were similar in both groups in our study. This can be explained by the low dose of infusion of both drugs. No significant difference was observed as regard to sedation scores between fentanyl, morphine and remifentanil using intravenous patient controlled analgesia technique in patients underwent CABG surgery [23]. Also, tramadol offers a comparable sedation score to morphine when both drugs were used in combination with droperidol [25] and even less sedation scores when both drugs were compared separately [27].

As regard side effects:

Nausea and vomiting were more in tramadol group (11 patients) than fentanyl group (7 patients).

Cossmann et al. [29] reported that nausea and vomiting were the most common adverse effects after i.v. administration of tramadol as tramadol inhibits the neuronal reuptake of 5-hydroxytryptamine [30].

Gurbet et al. studied fentanyl against morphine and remifentanil using PCA technique and found that nausea and vomiting were higher in the morphine group and less in fentanyl group [23]. Also, it has been reported after thoracotomy that more nausea and vomiting with morphine (7 patients) than with tramadol (5 patients) in [27] Erolçay et al. study. This can be explained by morphine causing more nausea and vomiting than tramadol and fentanyl.

Aygun et al. compared i.v. tramadol, i.v. fentanyl, epidural tramadol, and an epidural ropivacaine-fentanyl in combination patient-controlled analgesia (PCA) after lower abdominal surgery. They reported nausea and vomiting more with i.v. tramadol (11 patients) and less with i.v. fentanyl (8 patients) [28]. However, Cagney et al. [30] found no difference between i.v. tramadol and i.v. fentanyl as regard nausea and vomiting in ambulatory knee surgery. This can be explained by Aygun et al. i.v. tramadol and fentanyl were administered by PCA for 24 hours but Cagney et al. [30] gave single dose of i.v. tramadol and fentanyl at the induction of anaesthesia.

As regard satisfaction:

Satisfaction scores were nearly the same in both groups in our study. Similarly, Ng et al. [31] compared fentanyl PCA versus tramadol PCA in 30 patients undergoing lower abdominal surgery. They reported no difference between them as regard satisfaction. However, tramadol PCA offers a less satisfaction score than morphine [25] PCA.

Conclusion:

It appeared from this study that iv fentanyl versus iv tramadol analgesia after cardiac surgery with CPB offer a comparable pain relief with minimal side effects.

References