

# A Comparative Study of Intravenous Patient-Controlled Analgesia Morphine and Tramadol in Patients Undergoing Major Operation

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## Summary

The success of major surgery depends partly on providing effective post-operative pain relief, which can be commonly achieved by morphine administration via patient-controlled analgesic (PCA) system. Alternatively, tramadol which is a weak opioid analgesic, can be used for post operative pain relief. The purpose of this study was to evaluate the effectiveness of intravenous PCA tramadol in comparison with PCA morphine in term of analgesic properties, sedation and side effects. A randomized, double-blinded study was conducted on 160 ASA I and II patients who underwent major operations. Eighty of them received a loading dose of intravenous morphine 0.1 mg/kg followed by PCA morphine bolus of 1 mg (1 mg/ml) as required, while the other 80 patients received a loading dose of 2.5 mg/kg of intravenous tramadol followed by PCA infusion of 10 mg (10 mg/ml) as required. Patients were monitored for pain, sedation and side effects as well as respiratory rate, nausea, vomiting, pruritus, blood pressure and pulse rate. Patients were evaluated 30 minutes, 4 hours, 24 hours and 48 hours post operation. There were no differences in the demographic data between the two groups ( $p > 0.05$ ). The overall mean pain score in tramadol group was  $0.70 \pm 0.60$  as compared to  $0.75 \pm 0.67$  for morphine group. The mean pain score for tramadol and morphine groups at 30 minutes, 4 hours, 24 hours and 48 hours post operation were  $1.32 \pm 0.79$ ,  $1.04 \pm 0.79$ ,  $0.35 \pm 0.48$ ,  $0.09 \pm 0.33$  and  $1.35 \pm 0.99$ ,  $1.14 \pm 0.81$ ,  $0.40 \pm 0.54$ ,  $0.10 \pm 0.34$  respectively. The overall mean sedation score in tramadol and morphine group was  $0.39 \pm 0.44$  as compared to  $0.35 \pm 0.43$  for morphine group. The mean sedation score for tramadol and morphine group at 30 minutes, 4 hours, 24 hours and 48 hours post operation were  $0.90 \pm 0.74$ ,  $0.56 \pm 0.59$ ,  $0.075 \pm 0.27$ ,  $0.025 \pm 0.16$  and  $0.84 \pm 0.70$ ,  $0.46 \pm 0.64$ ,  $0.08 \pm 0.27$ ,  $0.01 \pm 0.11$  respectively. There was no significant difference in the overall mean pain and sedation score between the two groups as well as for each duration assessed ( $p > 0.05$ ). There were also no significant differences between the two groups with regard to the blood pressure and heart rate. The incidence of nausea, vomiting and pruritus were the same in the two groups. This study indicates that PCA tramadol is as equally effective as PCA morphine for pain control following major surgery. The incidences of sedation, nausea or pruritus were the same in the two groups.

**Key Words:** Patient-controlled analgesic, Tramadol, Morphine

## Introduction

Postoperative recovery after major surgery depends on various factors, such as adequate pain relief, nausea or vomiting and mobilization. After surgery, some

patients experience pain of moderate intensity (20% – 40%), while another experience severe pain (50% – 70%). A reduction in the surgical stress responses (endocrine, metabolic and inflammatory) will lead to a

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reduced incidence of postoperative organ dysfunction and thereby to an improved outcome. The stress response has been termed "the integrated, adaptive lining web of neuroendocrine, immunologic, and intercellular biochemical signals evoked by tissue injury". The dominant neuroendocrine response to pain involved hypothalamic-pituitary adrenocortical and sympathoadrenal interactions<sup>1</sup>.

Immobilization or bed rest due to pain in peripheral sites can indirectly affect respiratory as well as hematologic function<sup>2</sup>. Moderate to severe acute pain, regardless of site, can affect nearly every organ function and adversely influence postoperative morbidity and mortality. Pain may also have other physical as well as psychological sequelae, including impaired respiratory function, long term pain depression, and post-traumatic stress reactions. Major operations are stressful psychological and physiological events, and patient may feel traumatized despite otherwise successful operations<sup>3</sup>.

The principal intention of pain control is to substantially reduce or possibly eliminate postoperative pain. Pain relief may be a powerful technique to modify surgical stress responses<sup>3</sup>. Prevention of postoperative sensitization has been attempted by various methods including oral medication, suppositories, intramuscular, intravenous or regional technique with varying outcome<sup>4</sup>. More recently, patient satisfaction with opioids has improved with the introduction of PCA system<sup>5</sup>. Morphine is the opioids analgesic most commonly used in PCA system.

Apart from morphine, tramadol has been used in a number of European countries for many years and has been approved by the Food and Drug Administration (FDA) in the United States<sup>1</sup>. Tramadol is a weak opioid analgesic, mainly act on  $\mu$  opioids receptor but also has additional analgesic action through the inhibition of neuronal re-uptake of neurotransmitter 5-hydroxytryptamine and noradrenaline as well as stimulation of 5-hydroxytryptamine release. Unlike conventional opioids, tramadol has not been associated with clinically significant respiratory depression<sup>6</sup>.

The purpose of this study was to evaluate whether an analgesic dose of tramadol using PCA system is similar to conventional opioids, morphine in terms of analgesic properties, sedation, and common side effects of opioids such as nausea, vomiting and pruritus. This study was also aimed at evaluating whether tramadol can serve as an alternative opioid analgesic in acute

pain service (APS) in post operative patients in our community.

## Materials and Methods

This is a randomized, double blinded, prospective study which was carried out from June 2002 until May 2003. A total number of 160 subjects were included in this study with equal number in tramadol and morphine group based on sample size calculation using PS software version 2.1.31. The sample size was calculated so that it fell within 95% confidence interval ( $\alpha=0.05$ ) with 80% power of study ( $\beta=0.8$ ). The formula for independent t test was utilized in the calculation. The ratio of subjects in the morphine and tramadol group was taken as 1 ( $m=1$ ). The detectable difference of 1 ( $\delta=1$ ) was used in order to detect the difference of 1 pain score (according to Modified Pain Score) between the morphine and tramadol group. The moderate effect was taken as two times detectable difference ( $\sigma = 2$ ).

$$\alpha = 0.05; \beta = 0.8; \delta = 1; \sigma = 2; m = 1$$

Therefore, to achieve 80% power with 0.05 alpha, and in order to detect the difference of 1 pain score (according to Modified Pain Score), 64 subjects were needed in each group. Taking into account 20% dropout rate, 80 subjects were included in each study making a total number of 160 subjects.

Inclusion criteria include age between 18 – 55 years, weight of more than 25 kg or less than 100 kg and classified as American Society of Anaesthesiologist Physical Status Grade I to II. Exclusion criteria include lactating, pregnancy, renal or liver impairment identified after routine preoperative screening of blood biochemistry.

After the approval by the Ethical Committee, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, patients who fulfilled the criteria were included in the study after obtaining an informed-consent. Closed-envelope techniques were used to allocate patient randomly to receive either morphine PCA system (M) or tramadol PCA system (T) for postoperative analgesia.

## Protocol

The anaesthetic regimens were standardized for all patients<sup>7</sup>. Premedication with 7.5 mg midazolam orally were given at night and two hours before surgery. Three to four mg/kg of thiopentone and 3  $\mu$ g/kg

fentanyl were given for induction of anaesthesia with non depolarizing muscle relaxant given once patient was under anaesthesia. Inhalational anaesthesia with O<sub>2</sub>/N<sub>2</sub>O and isoflurane were given, dosed to maintain a clinically adequate depth of anaesthesia. Patients were reversed with 1.0 mg atropine and 2.5 mg/kg neostigmine at the end of operation.

### **In Recovery Room**

#### **In Morphine PCA system group**

Loading dose of 0.1 mg/kg IV morphine<sup>8</sup> up to a maximum dose of 10 mg<sup>9</sup> was administered by slow intravenous injection before starting the PCA. Morphine solutions were diluted as 1 mg/ml. The devices were set to deliver 1.0 mg IV bolus dose of morphine with 10 minutes lockout time. No baseline infusion was given. Rescue intravenous bolus of 1.0 mg morphine was prepared as standby.

#### **In Tramadol PCA system group**

Loading dose of 2.5 mg/kg IV tramadol<sup>8</sup> up to a maximum dose of 100 mg<sup>9</sup> was administered by slow intravenous injection before starting the PCA. Tramadol solutions were diluted as 10 mg/ml. Tramadol is 1/10 equipotent of morphine<sup>10</sup>. The devices were set to deliver 10mg IV bolus dose of tramadol with 10 minutes lockout time. No baseline infusion was given. Rescue intravenous bolus of 10 mg tramadol was prepared as standby.

Patients were instructed properly on the use of standard PCA machine. They were monitored by using standard monitor in the recovery room for at least 30 minutes and supplemented with oxygen via face mask. Patients were evaluated at the end of 30 minutes before being discharged to the general ward. They were again evaluated in ward 4 hours, 24 hours and 48 hours post operatively. All patients who had nausea or vomiting were treated with iv metoclopramide 10 mg<sup>11</sup>.

### **Statistical analysis**

The data were analyzed by using computer software SPSS version 10.0. P value of < 0.05 was considered as statistically significant. Comparison of numerical data presented as mean  $\pm$  SD such as age, weight, height, demand and gain were analyzed by using independent t-test, while categorical data such as type of major operation, sex, ethnic groups, nausea, vomiting and pruritus were analyzed by using Pearson chi-square. All the categorical data were expressed as number and percentage (%). The pain score and sedation score were analyzed by using independent t-test and general linear model repeated measures. Results were presented as mean  $\pm$  SD.

## **Results**

### **Demographic Characteristics**

A total number of 160 patients undergoing major operation who fulfilled the criteria were included in this study after they consented. Thirty-five males (21.9%) and 125 females (78.1%) were involved in this study. Majority of the subjects were Malay which contributed to 94.4% of the total subjects as compared to 5.0% Chinese and 0.6% Indians. This is due to the higher percentage of Malay population in the study area (Kelantan) with 95.0% Malays<sup>12</sup>. There were no significant statistical differences in age, weight, height and type of operation between the two study group ( $p > 0.05$ ). Table I summarized and compared the patient characteristics in term of age, weight and height while Table II summarized the distribution of subjects according to type of operation in morphine and tramadol groups.

### **Side effects**

#### **Sedation score**

Figure 2 demonstrated mean sedation scores at 30 minutes, 4 hours, 24 hours and 48 hours post operation in morphine and tramadol groups. There were no significant statistical differences in the sedation scores at 30 minutes, 4 hours, 24 hours and 48 hours in both study groups ( $p > 0.05$ ).

#### **Nausea and vomiting**

There were 22 (27.5%) and 25 (31.2%) of patients having nausea and vomiting in morphine and tramadol groups respectively. There was no significant statistical difference between the two groups in term of side effects of nausea and vomiting ( $p > 0.05$ ).

#### **Pruritus**

In both groups, none of the patients complained of pruritus. There were also no flushing or urticaria noted at the site of venous cannula in any patient in both groups. None of the patients developed generalized flushing of the face, neck or upper chest while in the recovery room or in the general ward. No episode of bronchospasm noted in all patients in both groups.

#### **Demand and gain**

Demand is defined as the number of PCA device activation (by pressing the button). Gain is the number of demand that has been fulfilled which indicates the amount of drug that the patient received<sup>13</sup>. Table III below summarized the mean demand and gain by the postoperative patients in morphine and tramadol groups. There were no significant statistical differences between the two groups in term of demand and gain ( $p > 0.05$ ).

Table I: Patient characteristics

Parameters	Morphine Group (n = 80)	Tramadol Group (n = 80)	p Value
Age (years)	35.6 ± 10.8	36.7 ± 9.6	p = 0.119
Weight (kg)	58.0 ± 8.1	60.1 ± 8.3	
Height (cm)	158.1 ± 7.0	158.4 ± 7.9	

Table II: Distribution of subjects according to type of operation in morphine and tramadol groups

Type of Operation	Morphine Group (n = 80)	Tramadol Group (n = 80)	Total	p Value
General Surgery	28 (35.0%)	21 (26.3%)	49 (30.6%)	p > 0.05
Gynaecology	32 (40.0%)	45 (56.3%)	77 (48.1%)	p > 0.05
Orthopaedic	20 (25.0%)	14 (17.5%)	34 (21.3%)	p > .05

Table III: Mean demand and gain in morphine and tramadol groups

	Morphine (n = 80)	Tramadol (n = 80)	p Value
Demand	41.30 ± 28.94	43.14 ± 31.80	0.703
Gain	30.01 ± 19.39	30.59 ± 9.93	0.854

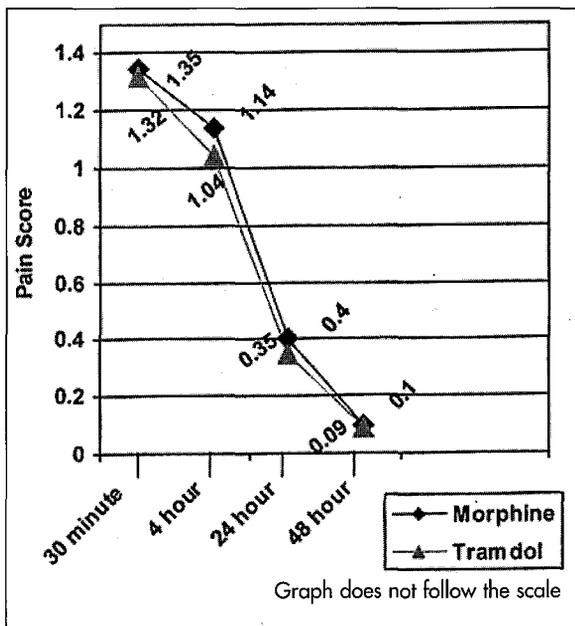


Fig 1: Mean post operative pain score at each assessment in morphine and tramadol groups

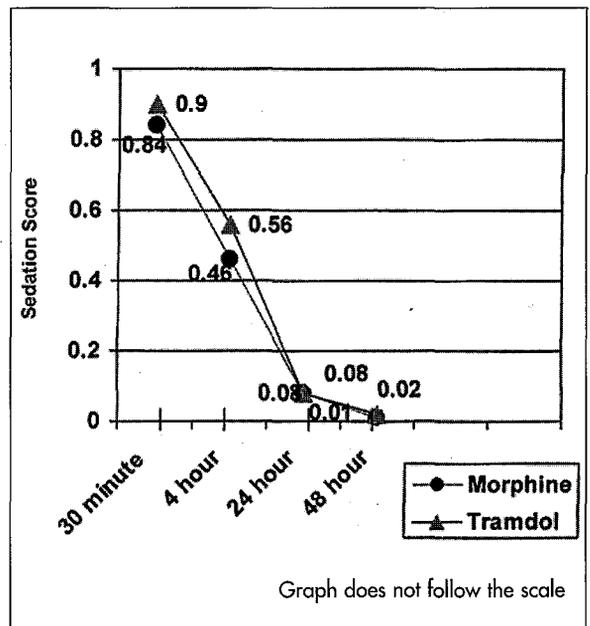


Fig 2: Mean post operative sedation score at each assessment in morphine and tramadol groups

## Discussion

This study was conducted for 48 hours since patients need 48 hours for complete control of pain postoperatively<sup>11, 14, 15</sup>. Since tramadol is quite a new drug in our acute pain service, it was chosen in comparison with morphine, a commonly used post operative analgesic. We chose PCA as means of drug administration because of patient safety and to avoid of bias from the health care personnel<sup>11</sup>.

Even though preliminary pilot study by Vickers, *et al.*, in 1992<sup>16</sup> reported that with lockout interval of ten minutes and an equivalent dose of 11:1 mg (tramadol:morphine) was ineffective in achieving satisfactory analgesia in many patients, the dose of tramadol used in this study (2.5mg/kg loading dose and 1 mg bolus dose) which is ten times the dose of morphine is comparable to the other studies. In clinical practice, Nagaoka, *et al.*, 2002<sup>17</sup> reported that the dose ranges for IV tramadol administration in pain control are approximately 1-3mg/kg, while Pang, *et al.*, in 2003<sup>18</sup> reported that tramadol 2.5mg/kg appeared to be the optimal intra-operative loading dose to provide effective postoperative analgesia with minimal sedation before patient-controlled analgesia.

This study demonstrated that, with the same PCA set up as morphine, tramadol provided effective analgesia similar to that of morphine. Since our subjects are Asian people, this finding is expected since the occurrence of CYP2D6\*10 allele was reported to be common in Asian people<sup>19</sup>. This CYP2D6\*10 allele is associated with the sparteine oxygenase enzyme which is required for formation of (+)-O-desmethyl tramadol that is responsible for the weak  $\mu$ -opioid agonist effects of tramadol. This enzyme is deficient in up to 7% of Caucasian individuals, leading to the reduced formation of (+)-O-desmethyl Tramadol and reduced analgesic effect in these 'poor metabolizers'.

Since pharmacokinetic and pharmacodynamic showing that tramadol are equipotent to morphine (ratio 1:10) (Houmes, *et al.*, 1992) in term of analgesic properties and other side effect such as nausea, vomiting, pruritus, demand and gain, we would expect that intravenous PCA tramadol can be used as an alternative analgesic in acute pain service. Postoperative analgesia with fewer side effects is not only important for patient but is also important for the management team. The drawback of intravenous opioid PCA was its association with high incidence of nausea and vomiting.

In the study done by Murphy *et al.* 1997<sup>16</sup> showing that despite its conventional opioid structure and qualitatively similar pharmacological profile, tramadol has less effect on gastric motility. Tramadol is known to have weak opioid effects through  $\mu$ -receptor and a non-opioid mode through blocking the re-uptake of serotonin and norepinephrine in the central nervous system. Even though Tramadol has weak opioids effect, it does not possess the euphoric and addictive effect.

In a study by Houmes, *et al.*, 1992<sup>7</sup> on efficacy and safety of postoperative analgesia, tramadol was found to have less respiratory depression than morphine. This safety feature makes tramadol a very suitable analgesic to be used in acute pain service in ward after major postoperative where intensive nursing monitoring is not a routine. Tramadol has also shown to induce an improvement in postoperative immunosuppression and, therefore, may be preferred for the treatment of postoperative pain.

Sedation was not common in our study. There were no statistical differences in the sedation score at 30 minutes, 4 hours, 24 hours and 48 hours in both study groups. This finding is rather different from a study by Pang, *et al.*, in 1999<sup>8</sup> that reported more sedative effect in morphine group. Murphy *et al.* in 1997<sup>20</sup> reported that despite its conventional opioid structure and qualitatively similar pharmacological profile, tramadol has less effect on gastric motility. In our study, tramadol has the same nausea and vomiting effects as morphine. Nausea has been reported with rapid intravenous injection of tramadol but this can be reduced by slow intravenous injection over 1-2 minute especially during loading dose. Murphy *et al.*, 1997<sup>20</sup> noted in his study that if loading doses was given by intravenous infusion over 10 minutes, nausea was not a clinical problem. Adding metoclopramide to tramadol PCA will further decrease nausea or vomiting<sup>18</sup>.

No patients in both group developed pruritus during this study. There were no cutaneous manifestations due to histamine release such as mild flushing or urticaria over the hand at the site or branulla. There were also no generalized flushing of face, neck or upper chest in recovery room or in the general ward during this study and no episode of bronchospasm in all patients. This is not surprising because other study has also shown that the incidence of pruritus in morphine is more in case of central blockade rather than intravenously<sup>8</sup>.

In this study, we also monitored the demand and gain by assessing the number of PCA device activation by the patient. This is to indicate patient satisfaction and effectiveness of our post-operative pain control. In the present study, the demand and gain in both groups were the same which indicate that both drugs have the same outcome in term of acute pain service. This finding pointed out that in comparison with morphine, tramadol can be used as an alternative to morphine for intravenous PCA in postoperative patients with the same satisfaction in term of demand and gain. Tramadol is also a good alternative in patients who have history of allergy to opioid.

Nevertheless, pain is an individual experience. Pain management including the cessation of patient-controlled analgesia should be individualized<sup>5</sup>. Perhaps further patient education at the time of cessation of patient-controlled analgesia may improve patient acceptance and satisfaction. Follow up by Acute Pain Service team after cessation of patient-controlled analgesia may benefit in some patients.

### Conclusion

Patient-controlled analgesia tramadol is as equally effective as PCA morphine in controlling post operative pain.

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