A COMPARATIVE STUDY OF INTRAVENOUS PATIENT- CONTROLLED ANALGESIA MORPHINE AND TRAMADOL IN PATIENTS UNDERGOING MAJOR OPERATION

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The success of major surgery depends partly on providing effective post-operative pain relief, which can be achieved by morphine administration via patient-controlled analgesic (PCA) system. Tramadol is a weak opioid analgesic, which act mainly on μ-opioids receptor. 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.In this study, a randomized, double-blinded study was conducted on 160 ASA I and II patients who underwent major operations. Pain was scored according to Modified Pain Score while sedation was scored according to Ramsay Sedation Score. There was no significant difference in the overall mean pain score between the two groups as well as for each duration assessed ($p>0.05$). There was also no significant difference in the overall mean sedation score between the two groups as well as for each duration assessed ($p>0.05$). The conclusion 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 also were the same in the two groups.

Key words : *patient-controlled analgesia, morphine, tramadol*

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 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 (Miller, 1999).

Immobilization or bed rest due to pain in peripheral sites can indirectly affect respiratory as well as hematologic function (Morgan & Mikhail, 1996). 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 fell traumatized despite otherwise successful operations (Kehlet, *et al.*, 2001).

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 (Kehlet, *et al.*, 2001). Prevention of postoperative sensitization has been attempted by various methods including oral medication, suppositories, intramuscular, intravenous or regional technique with varying outcome (Wilder-Smith, *et al.*,1999). More recently, patient satisfaction with opioids has improved with the introduction of PCA system (Chen, *et al.*, 2001). Morphine is the opioids analgesic most commonly used in PCA system.

Apart from morphine, tramadol has been use in a number of European countries for many years and has been approved by the Food and Drug Administration (FDA) in the united states (Miller, 1996). Tramadol is a weak opioid analgesic, mainly act on μ 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 (Mark, *et al.*, 2002).

The purpose of this study was to evaluate whether an analgesic dose of tramadol using PCA system 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.

Material and methods

This is a randomized, double blinded, prospective study. 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. 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.

Study protocol

The anaesthetic regimens were standardized for all patients. Premedication with 7.5 mg midazolam orally were given at night and 2 hours before surgery. Three to four mg/kg of thiopentone and 3 μg/kg fentanyl were given for induction of anaesthesia with non depolarizing muscle relaxant given once patient under anaesthesia. Inhalational anaesthesia with O_2/N_20 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 0.1 mg/kg of IV morphine were administered by slow intravenous injection before starting 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 given. Rescue intravenous bolus of 1.0 mg morphine prepared as standby.

In Tramadol PCA system group

Loading dose/bolus of 2.5 mg/kg of IV tramadol were administered by slow intravenous injection before starting PCA. Tramadol solutions were diluted as 10 mg/ml. Tramadol is 1/10 equipotent of morphine (Houmes, *et al.*, 1992). The devices were set to deliver 10mg IV bolus dose of tramadol with 10 minutes lockout time. No baseline infusion given. Rescue intravenous bolus of 10 mg tramadol prepared as standby.

Patients were instructed 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 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 and those who had pruritus were treated with iv chlorpheniramine (Piriton) 10 mg (Pang, *et al.*, 1999a).

Data and 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 ± 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 ± 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 (Department of Statistic, 2000). There were no significant statistical differences between the two study groups according to gender and ethnic groups ($p>0.05$). Table 1 summarized and compared the patient characteristics in term of age, weight and height while table 2 summarized the distribution of subjects according to type of operation in morphine and tramadol groups. There were no significant differences ($p > 0.05$) in the mean age, weight, height and type of operation between the two study groups.

Table 1: Patient characteristics

Parameters	Morphine Group (n = 80)	Tramadol Group (n = 80)	p Value
Age (years)	35.6 ± 10.8	36.7 ± 9.6	0.504
Weight (kg)	58.0 ± 8.1	60.1 ± 8.3	0.107
Height (cm)	158.1 ± 7.0	158.4 ± 7.9	0.816

Values are expressed as mean ± SD

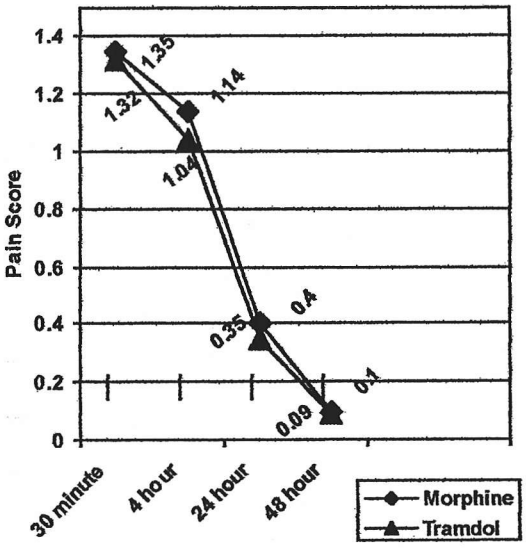
Table 2: Distribution of subjects according to type of operation in morphine and tramadol groups

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%)	0.119
Gynaecology	32 (40.0%)	45 (56.3%)	77 (48.1%)	0.119
Orthopaedic	20 (25.0%)	14 (17.5%)	34 (21.3%)	0.119

Values are expressed as mean ± SD

Pain score

Figure 1 demonstrated mean pain 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 pain scores at 30 minutes, 4 hours, 24 hours and 48 hours in both study groups ($p>0.05$).



Graph does not follow the scale

Figure 1: Mean post operative pain score at each assessment 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 ($p>0.05$).

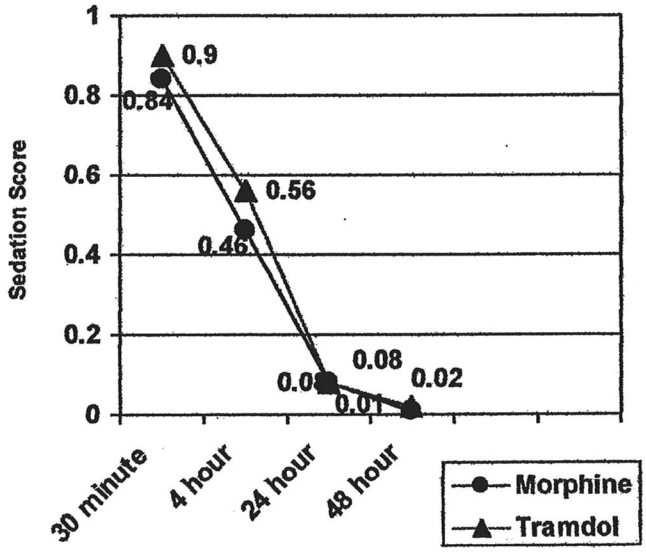


Figure 2: Mean post operative sedation score at each assessment in morphine and tramadol groups Graph does not follow the scale

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 (Sechzer, 1971). Table 6.8 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 3: 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 ± 19.93	0.854

Values are expressed as mean ± SD .

Discussion

This study was conducted for 48 hours since patients need 48 hours for complete control of pain postoperatively. 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 avoidance of bias from the health care personnel (Pang, *et al.*, 1999).

Eventhough preliminary pilot study by Vickers, *et al.*, in 1992 reported that with lockout interval of 10 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 10 times the dose of morphine is comparable to the other studies. In clinical practice, Nagaoka, *et. al*, 2002 reported that the dose ranges for IV tramadol administration in pain control are approximately 1-3mg/kg, while Pang, *et al.*, in 2003 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 (Gan, *et al.*, 2002). 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 μ-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) 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 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 μ-receptor and a non-opioid mode through blocking the re-uptake of serotonin and norepinephrine in the central nervous system. Since Tramadol has weak opioids effect, so it does not posses the euphoric and addictive effect.

In a study by Houmes, *et al.*, 1992 on efficacy and safety of postoperative analgesia, tramadol was found to have less respiratory depression than with 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 immuno-suppression and, therefore, may be preferred for the treatment of postoperative pain.

Sedation

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 that reported more sedative effect in morphine group.

Murphy *et al.* in 1997 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 noted in his study that if loading doses was given by intravenous infusion over 10 minutes, nausea was not a clinical problem. Adding metoclopropamide to tramadol PCA will further decrease nausea or vomiting (Pang, *et. al*, 2003).

No patients in both group developed pruritus during this study. There were no cutaneous manifestation due to histamine release 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 (Pang, *et. al.*, 1999).

In this study, we also monitored the demand and gain by the number of patient using PCA machine. 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 demand and gain. Tramadol is also a good alternative in patient having history of allergy to opioid.

Nevertheless, pain is an individual experience. Pain management including the cessation of patient-controlled analgesia should be individualized (Chen, *et al.*, 2001). 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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