

COMPARISON OF THE ANALGESIC PROFILE AND SIDE EFFECTS OF TRAMADOL VS PETHIDINE, FOLLOWING UROLOGICAL SURGERY

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ABSTRACT

The optimization of pain management following surgery with minimal side effects, is one the major goals of surgical and medical teams. In this randomized double blind study, sixty ASA (American Society of Anesthesiologist) class I or II patients, undergoing urological surgery, were assessed to receive either pethidine or tramadol using a standard method for general anesthesia. Pain intensity was assessed by verbal rating, through a 4-step scaling system. Results of this investigation have revealed that the mean total drug administered in tramadol group were 244.53 ± 56.95 mg and in pethidine group 176.78 ± 42.99 mg respectively. There were no significant differences in analgesic effect, observed in either group during early hours following surgery, but after 8,12 and 16 hours significant differences were observed. Analgesic properties of tramadol were almost comparable with pethidine nevertheless; pethidine was superior in some extent. No significant differences in patient's PaO₂ were found, but PaCO₂ at 1 and 4 hours after surgery had a greater retention in pethidine group. ($P < 0.001$). There was a significant reduction in respiratory rate in pethidine group at 4,8,12 and 16 hours following surgery, compared with tramadol group ($P < 0.001$). Incidence of dizziness was greater in patients who received pethidine ($P < 0.001$), and sweating was higher in tramadol group ($P < 0.01$). Also there was a greater need for metoclopramide to overcome nausea in tramadol group ($P < 0.05$). Results of this study may suggest that tramadol could be considered as a safe and effective analgesic, following urological surgery as compared with pethidine.

Keywords: Tramadol, Pethidine, Pain management, Urological surgery

INTRODUCTION

Pain is a significant cause of morbidity after all urological surgery especially in the cases that large incisions are performed. Surgery inevitably results in tissue trauma and release of potent mediators of inflammation and pain (1). One survey showed that 77% of adults believe that postoperative pain is to be expected, and almost 60% consider it as the reason for the primary fear before surgery (2). Surgical morbidity associated with poor postoperative pain control is also increasingly recognized. Adverse cardiovascular effects including hypertension, tachycardia and increased cardiac work may result from unrelieved pain. Pain may also lead to shallow breathing and cough suppression, which increases the risk of the retained pulmonary secretions and

chest infection (3).

Tramadol is a drug with mixed opioid and non-opioid activities (4,5). The non-opioid component is mediated through inhibition of the reuptake of norepinephrine and serotonin, and possibly displacement of stored 5HT from nerve endings in spinal and supraspinal pathways (6-9). Tramadol has been tested in patients with cancer and postoperative pain and the results of these investigations indicate that its action is comparable to that of opioids such as pentazocine, codeine and buprenorphine with minimal respiratory depression (10-13). In a pharmacoeconomic assessment, tramadol achieved a 19% saving compared with morphine (14).

The objective of this study was to evaluate the analgesic properties, respiratory effects and

adverse drug reaction induced by tramadol in post-urological surgery. Since pethidine is being used in this center as routine analgesic following urological operations, it was used as a reference drug.

Methods

Patients

Sixty patients with large flank incisions post urological surgery were enrolled in this study. The inclusion criteria were: age more than 18, pain after surgery, alertness, stability, ASA (American Society of Anesthesiology) I or II, using standard anesthesia protocol (Midazolam, Fentanyl, Atracurium, Thiopental, Halothane, N₂O) and receiving the first dose during the first hour after termination of surgery. The exclusion criteria were: pregnancy and lactation, history of drug or substance abuse, allergy to opioids or any other contraindication for the use of opioids, end stage renal disease, history of seizure or any abnormal laboratory tests that could interfere with our results.

Study design

This randomized, double blind clinical study took place in the department of urology at Sina hospital affiliated with Tehran University of Medical Sciences. Based on the recommendations of the ethic committee of the university, all patients were informed about the medical interventions and provided written informed consent prior to study commencement, but they did not know which analgesic was administered for their pain management. The pharmacy department of the hospital provided pethidine and tramadol injections in syringes and assigned a code for each syringe. Patients were randomly assigned in either treatment groups with an assigned code. The numbers of patients in each group were thirty. All codes were unlocked at the end of the study period. The patients received either an intravenous 100-mg bolus dose of tramadol over a 5-minutes period initially, followed by 50-mg repeated doses at patient request, or an IV 50-mg bolus dose of pethidine followed by 25-mg repeated doses in the same manner. Volumes of both injections were adjusted by addition of normal saline. In the case of intolerable nausea, 10 mg metoclopramide were administered intravenously.

Assessments

Pain intensity was assessed by verbal rating system through a 4-step scaling method according to a timetable in which 0 meant no pain and 3

meant severe pain even without movement. The patient's vital signs including heart rate, respiratory rate and blood pressure were recorded at the baseline and 5-minutes after first administration and then at 4,8,12 and 16 hours after termination of surgery.

Arterial blood gas (ABG) samples were obtained three times for each patient at times of 0 and 15-minute after the first dose and 15-minute after the second dose through an arterial line. During the period of the study, any probable subjective or objective adverse drug reactions, which could have been caused by either drug, were recorded.

Statistical analysis

Statistical analyses were performed using two samples Student's *t*-test and *Chi-square* test. *P* values less than 0.05 were considered statistically significant. The Statistical Package for Social Sciences (SPSS 10) was used for data analysis.

RESULTS

The two study groups were comparable in terms of age, sex, weight and BMI (Body Mass Index)(Table 1). On an average basis, patients received either 2.51+0.59 mg/kg of pethidine, or 3.53+1.04 mg/kg of tramadol during the 16 hours study period.

There were no significant differences of analgesic control, in either group during early hours, following surgery. However after 8,12 and 16-hours remarkable differences were noted. None of the patients in pethidine group assessed their pain intensity as grade 3, but 16.7% and 20% of patients in tramadol group approached the pain intensity level of 3 at 12 and 16 hours, respectively ($p < 0.05$)(figure 1). There were no differences in either treatment groups as far as satisfactory level of pain control throughout the study.

Although there were no significant differences in heart rate and blood pressure between the two treatment groups, but at 4,8,12 and 16 hours post operation, there was a remarkable reduction in respiratory rate in pethidine group ($P < 0.001$). There were no significant differences in PaO₂, but significant differences were observed in PaCO₂ at 1, 4 hours after surgery showing greater PaCO₂ retention in pethidine group ($P < 0.001$).

Incidence of drowsiness was greater in pethidine group ($P < 0.001$) and sweating was more in tramadol group ($P < 0.01$). Also there was a greater need for metoclopramide to overcome nausea in tramadol group ($P < 0.05$)(table 2).

It might be important from the clinical point of view that fasciculation were observed in two patients who received tramadol, although it is statistically insignificant.

Table 1. Comparison of characteristics of patients between pethidine and tramadol groups

	Pethidine	Tramadol	p value
Sex (M:F ratio)	1:0.4	1:0.3	0.79
Age (year) mean±SD	45.46±18.10	44.63±19.97	0.86
Weight (kg) mean±SD	70.42±7.86	70.80±10.89	0.88
Body Mass Index (kg/m ²)	23.74±2.78	24.77±3.29	0.20

DISCUSSION

In this study, the tramadol/pethidine ratio of 1:0.7 was used. There were not any differences in patient's satisfaction of analgesia, although significant differences were observed in pain intensity during the study. It was observed that in very intense pain pethidine is superior for induction of analgesia, which might be due to the potent μ -agonist activity of pethidine.

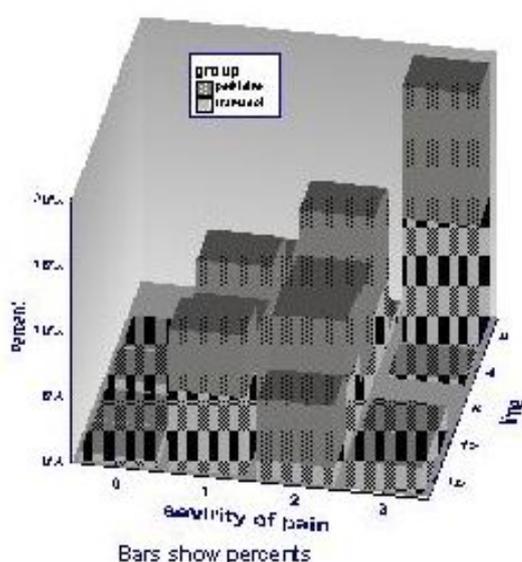


Fig. 1: Severity of pain in two groups in different times. Severity of pain score: 0=no pain, 1=mild pain on movement, no pain on rest, 2=mild pain on rest, intolerable on movement 3=intolerable pain

With regard to respiratory profile, there were clear differences between tramadol and pethidine. In this study pethidine caused higher decreases in respiratory rate in comparison with tramadol, which is consistent with results of previous reports (12,15-18). Although there was a reduction in respiratory rate in pethidine group, PaO₂ did not change significantly which might be due to an increase in tidal volume, which allows PaO₂ to approach normal level (15). However a significant elevation of PaCO₂ in pethidine group were observed in comparison with tramadol.

Table 2. Comparison of mean metoclopramide (mg), which was administered to control emesis.

Pethidine (mean±SD)	Tramadol (mean±SD)	Statistically Significance
11.42±5.75	16.50±8.92	P< 0.05

No significant changes in blood pressure were observed in either group and also there were no significant differences between the two treatment groups. This is consistent with result of other investigation (15-17). In this study no significant differences in heart rate between the two treatment groups were observed, but a very slight, non-significant rise in heart rate were observed after administration of tramadol. It might be due to inhibitory effect of tramadol on norepinephrine reuptake in neuronal pathways. Nevertheless according to one report after tramadol administration in healthy volunteers (15) any elevation in plasma level of norepinephrine could be determined.

Nausea was more evident after administration of tramadol, and the dose of methoclopramide to overcome nausea in two groups showed that a significant larger dose was required in tramadol group, which was congruent with the findings by others reports (12,15,19). Surprisingly, few studies have shown fewer incidences of nausea and vomiting after tramadol administration (20). It seems that the rate of drug administration may reduce the occurrence of this emetogenic effect. Drowsiness was reported to be significantly higher in pethidine group and sweating was more common in tramadol group. There were no clear previous reports on the incidence of fasciculation after tramadol administration, but in this study; there were found two cases of bothering fasciculation.

In conclusion, this study demonstrated that tramadol is a safe and useful drug in pain management following urological surgery, but it seems that a larger trial is required to evaluate the real incidence of some side effects like fasciculation, nausea and drowsiness after tramadol administration.

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