TRAMADOL VERSUS FENTANYL INFUSION DURING ANAESTHESIA; HAEMODYNAMIC EFFECTS, POSTOPERATIVE ANALGESIA AND OUTCOME

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ABSTRACT

This prospective randomized study compared I.V. infusion of tramadol "T" with fentanyl "F" for analgesia and postoperative outcome in 30 patients undergoing major abdominal surgery. A balanced general anaesthetic technique was given to both groups. In "T" group (n=15), tramadol (1mg.kg-1) was given firstly then infusion started as follow: 1st hr: 1mg.kg-1.hr-1, 2nd hr.: 0.75 mg.kg-^{1}.hr^{-1} and 0.5 mg.kg-^{1}.hr^{-1} for the following hours. In "F" group (n=15), Fentanyl (1.5 µg/kg^{-1}) was given firstly then infusion was given in the following regimen: 1st hr: 1µg.kg^{-1}.hr^{-1}, 2nd hr.: 0.75 µ.kg-$^{-1}$hr^{-1} and 0.5 µg.kg^{-1},.hr^{-1} for the following hours. Infusion stopped at time of closure in both groups. No significant haemodynamic differences were detected between both groups. The early postoperative gasometric readings were within acceptable values in both groups. Mean VPS ranged from 0.47 ± 0.9 to 1.2 ± 0.4 and from 0.73 ± 0.3 to 1.33 ± 0.5 in "T" and "F" groups respectively in the first 6 hours postoperatively. VPS showed no significant differences between both groups. It increased significantly as related to basal value after 5 and 4 hours in "T" and "F" groups respectively. We concluded that tramadol given by I.V. infusion appears to be a promising analgesic with respiratory and haemodynamic stability.

INTRODUCTION

In the last few years, many serious attempts have been tried to manage postoperative pain. Opioids and non-steroidal anti-inflammatory drugs have been the corner-stone of pain management. Respiratory depression represents the most dreadful side

effects of opioid analgesia(1). In the last 2 decades, new drugs have been applied in clinical practice for management of postoperative pain.

Tramadol hydrochloride is a centrally acting synthetic analgesic. Its effect is mediated via: week opioid μ agonist action and non-opioid action i.e. enhancement of monoaminergic descending inhibitory spinal transmission(2). It has been studied extensively for management of postoperative pain by either I.V. bolus dose(3) or by infusion(4). The drug was compared with pethidine(5) and fentanyl(6) for analgesic potency and respiratory depressant effects. Tramadol proved to be different from other opioids in its side effects profile, with little cardiovascular and respiratory depression, as well as low dependency potential(7,8,9).

More evaluation of the optimal dosage and best route of administration of tramadol is needed. This study was designed to test the hypothesis that analgesic effect of tramadol-given by intravenous iniusion intraoperatively-can continue on the post-operative period without haemodynamic or respiratory complications. This effect was compared with that of a popular, short acting opioid agonist analgesic i.e. fentanyl.

PATIENTS AND METHODS

This prospective randomized, single center study was conducted on thirty patients (ASA I & II) of either sex, scheduled for major elective abdominal surgery in Gastroenterology Center, Mansoura University. The age of patients ranged from 20 to 60 years. Patients having pain syndrome or receiving regular analgesics before the operation were excluded from the study. The protocol was approved by the Research Ethical Committee of Mansoura University.

Preoperative assessment included medical history, clinical examination, chest X-ray, ECG and complete laboratory investigations. Premedication was done by 5 mg diazepam orally on the night before operation and the same dose was repeated on the morning of surgery. On arrival to the theatre, basal readings of HR, MBP and blood gasometry were recorded.

According to the type of analgesic given, patients were randomized into 2 groups: group 1 (n=15) received

Tramadol "T" and group 2 (n=15) received fentanyl "F". The randomization list was computer generated. In "T" group, atropine was given (0.005 mg.kg-1), then anaesthesia was induced by midazolam (0.1 $mg.kg^{-1}$), tramadol (1$mg.kg^{-1}$) and thiopentone (5 $mg.kg^{-1}$). Suxamethonium (1 $mg.kg^{-1}$) was given for facilitation of endotracheal intubation. Tramadol infusion was started at time of induction and the rate was adjusted as follows: first hour: 1 $mg.kg^{-1}.hr^{-1}$., second hour: 0.75 $mg.kg^{-1}.\ hr.^{-1}$ and the following hours: 0.5 $mg.kg.^{-1}hr^{-1}$; then infusion stopped at time of peritoneal closure. Maintenance of anaesthesia was done by N_2O : O2 (FIO_2= 0.4), halothane (0.2-0. 8%) and atracurium (0.5 mg.kg-1 initially, followed by incremental doses of 0.1 $mg.kg^{-1}$). Reversal of neuromuscular blockade was done by prostigmine (0.04 mg.kg-1) and atropine (0.02 $mg.kg^{-1}$).

In the fentanyl group "F", the same anaesthetic technique was followed except that fentanyl bolus (1.5 µg.kg-1) was given at time of induction, then fentanyl infusion was given in the following regimen: 1st hour: 1 $\mu g.kg^{-1}.hr^{-1}$, 2nd hour : 0.75 $Mg.kg^{-1}$.hr-1 and the following hours: 0.5 $\mu g.kg.^{-1}.hr^{-1}$

Patients were monitored by 5 leads ECG, non-invasive arterial blood pressure, pulse oximetry and capnography. The haemodynamic data (HR and MBP) were recorded 15, 30, 60, 120 min. after induction, at recovery and 30, 60, 120 min afte recovery. Blood gasometric data (PaO_2, SaO_2, pH, $PaCO_2$, $HCO\overline{3}$) were recorded preoperatively, one hour after induction and one hour postoperatively (on room air).

Postoperative pain was assessed using verbal pain score "VPS"(10) every 1 hour till 6 hours postoperatively as follow: "O" = No pain at rest or movement, "1" = No pain at rest, slight pain on movement; "2" = Intermittent pain at rest, moderate pain on movement; "3" = continuous pain at rest, severe pain on movement. This assessment was done by an independent observer who was blinded to the type of analgesic used. Any postoperative complications e.g. nausea, itching and respiratory depression were recorded. Additional doses of the same analgesic (Tramadol 0.5 $\mu g.kg^{-1}$ or fentanyl 0.5 $\mu g.kg^{-1}$) were given if VPS reached 2 in the postoperative period.

STATISTICAL ANALYSIS

Analysis of variance (ANOVA two ways test) was used for the parameteric values and Tukey (HSD) was used for comparison of means. A non-parameteric Kolomgrov-Simirnov test and Wilcoxon matched pairs test was used for VPS values. The level of significance was considered when P-value <0.05.

RESULTS

The demographic and clinical data (table 1) demonstrated no significant changes between the two groups. The preoperative haemodynamic values were within accepted levels. Comparing both groups, haemodynamic variables did not show significant differences during intra-and postoperative periods. Fentanyl group "F" showed significant decrease in HR and MBP 30, 60 min. and 30,60, 120 min. respectively after start of fentanyl infusion when compared with the basal values (Table 2).

Blood gasometric values showed no significant changes between both groups (Table 3). Intraoperatively, PaO_2 in both groups were significantly higher than basal readings with the increased FIO_2. $PaCO_2$ in "T" group was significantly low compared with the basal value. The early postoperative gasometric readings were within acceptable values in both groups (Table 3).

Verbal pain score (VPS) showed no significant differences between both groups in the first 6 postoperative hours. However, significant increases in VPS-compared with first hour reading-were recorded in the fifth and fourth hours in "T" and "F" groups respectively (Fig. "1"). Pain free patients (VPS=0)-one hour postoperatively-were 73.3% and 66.6% in "T" and "F" groups respectively and these ratios decreased until reached 20% and 6.7% in "T" and "F" groups respectively after 3 hours (Table 4). Only one case in "T" group showed complete failure of analgesia (VPS = 3 on recovery). Patients that needed analgesics (VPS$\geq$2) were 46.7% and 40% in "T" and "F" groups respectively. Nausea and vomiting couldn't be evaluated because of presence of Ryle's tube. No signs of respiratory depression were recorded in "T" group as evidenced by normal $PaCO_2$ (Table 3) and normal respiratory rate (Table 4). Only one case in "F" group showed a respiratory rate of 10/min. for 15 min. after recovery but with accepted blood gasometric variables.

Table (1) : Demographic and clinical data of the studied patints. Values are number or mean ± SD (range)

	Tramadol group "T" (n=15)	Fentanyl group "F" (n=15)
Age (Yr)	45.5 ± 13	46.8 ± 12
	(24-58)	(31-59)
Sex (M/F)	10/5	8/7
Weight (Kg)	70.0 ± 11	67.7 ± 12
	(54-100)	(55-90)
Surgery time (min.)	177 ± 31	162 ± 28
	(120-280)	(130-240)
Type of surgery:		
- Colorectal cancer	6	5
- Gastric oper.	4	6
- Biliary surgery	1	3
- Malignant Int. obst	2	-
- Ulcerative colitis	1	-
- Pseudopancreatic cyst	1	1

Table (2): Heart rate (HR) and mean arterial blood pressure (MBP) in Tramadol "T" and Fentanyl "F" groups. Values are mean ± SD.

	HR (bpm)		MBP (mmHg)	
	"T"	"F"	"T"	"F"
• Basal	88 ± 14	91 ± 18	95 ± 9	101 ± 12
• Postinduction:				
- 15 min.	88 ± 10	87 ± 14	99 ± 9	94 ± 13
- 30 min.	82 ± 11	79 ± 12*	97 ± 10	88 ± 10*
- 60 min.	80 ± 11	77 ± 11*	96 ± 10	88 ± 9*
- 120 min.	81 ± 10	81 ± 12	95 ± 10	88 ± 10*
• At recovery:	91 ± 11	86 ± 16	101 ± 11	87 ± 11
• Postoperative:				
- 30 min.	87 ± 10	89 ± 12	98 ± 10	93 ± 12
- 60 min.	85 ± 8	91 ± 12	96 ± 10	93 ± 11
- 120 min.	86 ± 8	91 ± 11	91 ± 16	92 ± 14

* Significant changes as compared with the basal value ($P < 0.05$)

Table (3) : Blood gasometric variables of Tramadol "T" and Fentanyl "F" groups. Values are mean ± SD.

	PaO_2 (mmHg)		SaO_2 (%)		pH		$PaCO_2$ (mmHg)		HCO_3^- ($mmol.L^{-1}$)	
	"T"	"F"	"T"	"F"	"T"	"F"	"T"	"F"	"T"	"F"
Preoperative	97.2 ±5	96.2 ±7	95.4 ±2	96.3 ±2	7.41 ±0.1	7.39 ±0.1	39.9 ±4	40.0 ±4	22.8 ±2	22.3 ±2
1hr. postinduction	187.1* ±21	170.5* ±25	97.7 ±1	98.2 ±1	7.39 ±0.1	7.38 ±0.1	34.8* ±2	37.7 ±3	21.9 ±2	21.1 ±2
1hr. postoperative	92.4 ±7	89.1 ±7	94.9 ±2	95.3 ±1	7.39 ±0.04	7.37 ±0.03	39.0 ±5	42.8 ±4	21.7 ±2	21.8 ±2

* Significant changes as compared with the basal value ($P < 0.05$)

Table (4): Postoperative outcome in Tramadol "T" and Fentanyl "F" groups. Values are number, range or (percentage)

	Tramadol "T"	Fentanyl "F"
• Pain free patients: (VPS= 0)		
1 st hour :	11 (73.3%)	10 (66.6%)
2nd hour :	6 (40%)	4(26.7%)
3rd hour :	3(20%)	1 (6.7%)
• Patients requiring analgesia: (VPS>2)	7 (46.7%)	6 (40%)
• Postoperative consumption of analgesia/ptn.	30-100 mg	35-90µg
• Adverse events:		
- Itching	0	0
- Resp. rate/min	14-22	10-20

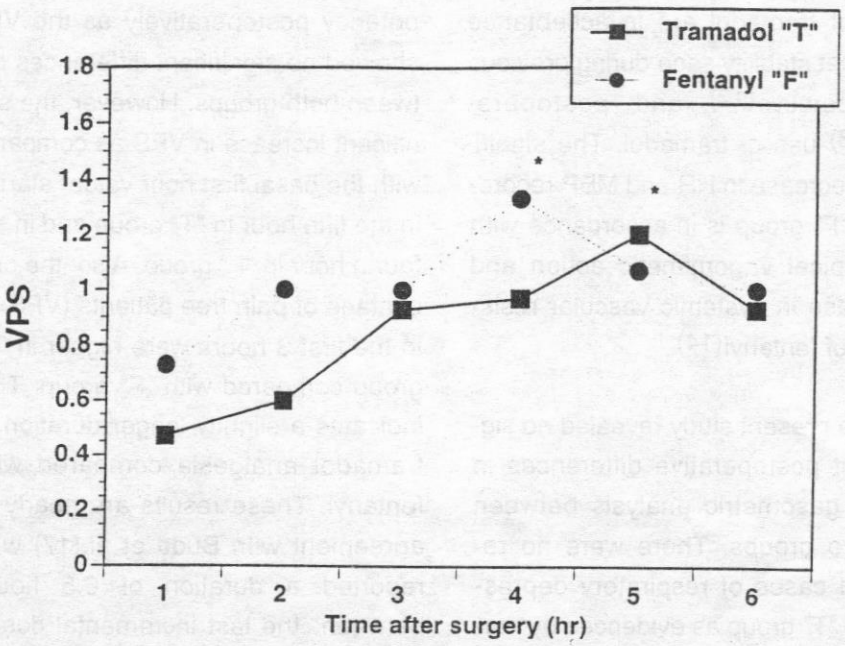

Fig. (1) : The mean verbal pain score (VPS) in Tramadol "T" and Fentanyl "F" groups during postoperative period.

* Sig. change as compared with basal value in each group ($P < 0.05$).

DISCUSSION

The present report shows that I.V. infusion of either tramadol or fentanyl can provide adequate intraoperative analgesic supplementation and-to some extent-considerable postoperative analgesia in patients undergoing major abdominal surgery. Also, the incidence of complications was nearly abscent in both groups.

It has been suggested that tramadol, N_2O, enflurane anaesthesia lead to 65% incidence of awareness(4). However, a recent report(11) found that tramadol in doses up to 200 mg during stable light N_2O-isoflurane anaesthesia did not lead to clinically significant lightening of anaesthesia. Although we did not assess the level of awareness during general anaesthesia with both groups, we think that the used regimen was enough to suppress awareness as evidenced by stable haemodynamic parameters, no need for further bolus doses of analgesics or to increase concentration of halothane. The haemodynamic find-

ings of tramadol are in acceptance with that stability seen during previous intraoperative[12] and postoperative[13] use of tramadol. The significant decrease in HR and MBP recorded in "F" group is in accordance with the typical vagomimetic action and decrease in systemic vascular resistance of fentanyl[14].

The present study revealed no significant postoperative differences in blood gasometric analysis between the two groups. There were no recorded cases of respiratory depression in "T" group as evidenced by normal respiratory rate and $PaCO_2$, a finding goes in parallel with the fact that tramadol has minimal[5] or even no respiratory depressant action[15]. The dual mechanism of action is the accepted explanation for its negligable effect on respiration despite its analgesic potency[16]. Only one case in "F" group showed slow respiratory rate (10/min) after recovery but with acceptable blood gases values and without requirement of naloxone. This indicate that fentanyl also in the given regimen was a safe short acting analgesics.

The two comparable drugs in this study showed nearly equal analgesic potency postoperatively as the VPS showed no significant differences between both groups. However, the significant increase in VPS-as compared with the basal first hour value- started in the fifth hour in "T" group and in the fourth hour in "F" group. Also, the percentage of pain free patients (VPS=0) in the first 3 hours were higher in "T" group compared with "F" group. This indicates a slightly longer duration of tramadol analgesia compared with fentanyl. These results are nearly in agreement with Budd et al.(17) who reported a duration of 6.5 hours between the last incremental doses of tramadol and time at which the patient required further analgesia. Moreover, James et al.(18) reported that a single I.V. dose of 150 mg tramadol provided postoperative analgesia compared to that of epidural morphine in the early postoperative 6 hours.

It is clear that both analgesics-in the given regimen-have nearly the same potency with slightly longer duration of action of tramadol than fentanyl. Tramadol-given by the infusion technique-appears to be a promising drug for intra-and postoperative pain relief with respiratory and haemodynamic stability.

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مقارنة تأثير كل من عقارى الترامادول والفنتانيل بالتسريب الوريدى أثناء التخدير على ديناميكية الدورة الدموية، تسكين الألم، وحاله المريض بعد العملية

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أجريت هذه الدراسة العشوائية لتقارن بين عقارى الترامادول والفنتانيل عند إستخدامها بطريقة التسريب الوريدى من حيث درجة التسكين وحاله المريض بعد العملية. وشملت هذه الدراسة ثلاثون مريضاً ستجرى لهم جراحة عظمى بالبطن. وتم تقسيم المرضى الى مجموعتين على حسب نوع المسكن المستخدم : مجموعة الترامادول (١٥ مريضاً) ومجموعة الفنتانيل (١٥ مريضاً) ... وتم إعطاء نفس نوع التخدير العام للمجموعتين .

وقد تم تسجيل ومتابعه كل من ديناميكية الدورة الدموية، متغيرات غازات الدم الشريانى، درجة تسكين الألم وجرعة المسكن المستخدم بعد العملية وكذلك المضاعفات الممكن حدوثها خلال هذه الفترة .

وقد أوضحت الدراسة عدم وجود أى فرق ذات مغذى إحصائى فى ديناميكية الدورة الدموية، متغيرات غازات الدم الشريانى أو درجة تسكين الألم. ولكن أظهرت الدراسة أن مدة تسكين الألم بالترامادول أطول قليلاً من الفنتانيل .

من هذه الدراسة نستخلص أن عقار الترامادول عندما يعطى بالتسريب الوريدى له قوة تسكينية للآلام معادلة للفنتانيل ... ويمكن القول أنه مسكن واعد بدون مضاعفات بالجهاز الدورى أو التنفسى.