European Review for Medical and Pharmacological Sciences 2014; 18: 3425-3434

Acute high dose-fentanyl exposure produces hyperalgesia and tactile allodynia after coronary artery bypass surgery

V. YILDIRIM[1], S. DOGANCI[2], S. CINAR[1], M.B. ESKIN[1], G. OZKAN[1], S. EKSERT[1], M.E. INCE[1], A. DOGRUL[3]

[1]Department of Anesthesiology and Intensive Care, Gulhane Military Academy of Medicine, Ankara, Turkey
[2]Department of Cardiovascular Surgery, Gulhane Military Academy of Medicine, Ankara, Turkey
[3]Department of Pharmacology, Gulhane Military Academy of Medicine, Ankara, Turkey

Abstract. – OBJECTIVE: Opioid-induced hyperalgesia is well known complication of acute high dose and chronic opioid therapy. In this study, we evaluated development of opioid-induced hyperalgesia following intraoperative short-term use of μ-opioid agonist fentanyl after coronary artery bypass surgery.

PATIENTS AND METHODS: 100 patients undergoing elective coronary artery bypass graft surgery is divided into two groups. In group I (low dose), anesthesia was induced with propofol 1-2.5 mg/kg and fentanyl 2 mcg/kg, in group II (high dose) fentanyl 40-70 mcg/kg was used. In group I, propofol 5-10 mg/kg/h, fentanyl 1-3 mcg/kg/h, in group II fentanyl 5-10 mcg/kg/h was used for maintenance of anesthesia. The tactile and thermal thresholds were measured before surgery and in 1st, 3rd and 7th postoperative days by using Von Frey filaments and a thermal source, respectively.

RESULTS: Tactile thresholds were significantly decreased at the first (6.08 ± 0.21 and 3.76 ± 0.13 g; $p < 0.001$) and third (6.76 ± 0.24 and 4.96 ± 0.16 g; $p < 0.001$) postoperative days compared to baseline preoperative values (7.72 ± 0.26, and 7.60 ± 0.21 g; $p = 816$) in two groups. Postoperative 1st(13.45 ± 0.33 and 10.05 ± 0.24 sec; $p < 0.001$) and 3rd day (14.77 ± 0.28 and 13.17 ± 0.26 sec; $p < 0.001$) assessments showed a statistically significant thermal hyperalgesia compared to the preoperative baseline values (16.67 ± 0.51 and 16.45 ± 0.42 sec; $p = 0.997$) in two groups. This decrease in both tactile and thermal thresholds returned to baseline control values at the 7th day of measurement.

CONCLUSIONS: Our results showed that patients undergoing coronary artery bypass surgery receiving fentanyl anesthesia developed postoperative tactile allodynia and thermal hyperalgesia and this was more prominent in high dose group.

Key Words:
Fentanyl, Opioid induced hyperalgesia, Tactile allodynia, Von Frey filaments.

Introduction

Opiates such as morphine and fentanyl are the primary agents used for conditions ranging from acute pain, postoperative pain to chronic pain[1,2]. Clinical use of this group of drugs is sometimes hindered by two opioid related phenomena. The first is antinociceptive tolerance that is defined as the decrease in the analgesic activity of a drug after a previous exposure to the same or a similar drug[3]. Thus, higher doses of the drug are required to elicit the same amount of pain relief. A second problem is a more recently recognized phenomenon of opioid-induced hyperalgesia. In this situation, prolonged or acute administration of opioids results in a paradoxic decrease of pain threshold and increase of atypical pain that appears to be unrelated to the original nociceptive stimulus[4,5].

It is known that opioid-induced paradoxical pain may be seen in animal models and in humans[6,7]. Animal studies show that acute and chronic opioid exposure cause hyperalgesia and tactile allodynia[8-10]. A similar hyperalgesia phenomenon has been described in human in former opioid addicts and postoperative patients who exposed to opioids during the surgery[11-13]. Indeed, it has been previously reported that the higher intraoperative opioid fentanyl or remifentanil doses, the greater postoperative pain level and morphine requirement[11,14].

Postoperative pain is still a serious problem although a variety of strong analgesics are available. Dolin et al[15] have reported that about 40% of all surgical patients experience different degree of pain after the surgery and among these patients, 24% were still experienced inadequate pain control. It has been suggested that the presence of

Corresponding Author: Suat Doganci, MD; e-mail: drvyildirim@yahoo.com

postoperative hyperalgesia has a major impact in the management of postoperative pain[16].

The mechanism underlying opioid-induced hyperalgesia is not exactly known. However, previous studies showed the involvement of L-type voltage dependent calcium channels, N-methyl-D-aspartate (NMDA)-receptors and kappa opioid receptors on the development of opioid-induced hyperalgesia in animal models[2,17,18]. Recent data provide evidence that use of ketamin and tramadol diminish the postoperative hyperalgesia[17,19].

The aim of this study was to evaluate the effect of intraoperative short-term high dose usage of μ-opioid agonist fentanyl on postoperative thermal hyperalgesia and tactile allodynia, and compare these effects with low dosages.

Patients and Methods

Patients

A total of 100 patients undergoing elective coronary artery bypass graft surgery (CABG) were enrolled in the study. Written informed consent was obtained from all subjects. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Gulhane Military Medical Academy Hospital in Ankara Turkey.

Patients were allocated randomly to one of two groups: group I (a conventional nonopioid-based anesthetic tecnique-low-dose fentanyl) (n=50) and group II (a conventional opioid-based anesthetic technique-high-dose fentanyl) (n=50). The night before surgery, all elective CABG patients were familiarized with the visual analog pain scoring (VAS) and were introduced to the patient-controlled analgesia (PCA) pump (Pain Management Provider™ pump, Abbott Laboratories, North Chicago, IL, USA) and instructed in its use and tactile threshold was performed with Von Frey filaments (Touch-Test™ Sensory Evaluator Instructions, North Coast Medical, Inc. San Jose, CA, USA) and thermal threshold was also performed with a modified thermal sensory analyzer to all patients. The criteria for exclusion were hepatic or renal dysfunction, known allergy, sensitivity, asthma, diabetes, contraindications to study drugs, history of peptic ulcer or bleeding diathesis, history of drug and alcohol abuse, severe thyroid, neuropatic diseases, a major psychiatric disorder, intake of opioid treatment for at least six months and nonsteroidal antiinflamatory drugs within seven days prior to operation, patients who were unable to cooperate/understand the operation of the PCA device, and pregnancy.

Anesthetic Protocol

All patients received intravenous midazolam (Dormicum, Roche, Istanbul, Turkey) 2.5 mg as premedication 1 h before surgery.

In group I (low dose), anaesthesia was induced with propofol (Propofol 1%, Fresenius, Istanbul, Turkey) 1-2.5 mg/kg and fentanyl (Talinat 0.5 mg/10 ml, Vem, Istanbul, Turkey) 2 mcg/kg. In group II high dose fentanyl 40-70 mcg/kg was used. In all patients muscle relaxation for tracheal intubation was facilated with vecoronium bromide (Norcuron 10 mg flacon, Organon Teknika, Istanbul, Turkey) 0.1 mg/kg. The lungs were mechanically ventilated with 8-10 mg/kg air/oxygen mixture, aiming for arterial carbondioxide tension ($PaCO_2$) of 35-40 mmHg during mechanical respiratory support. After intubation, anesthesia was maintained with continuous infusion of propofol, fentanyl and vecuronium. In group I, propofol 5-10 mg/kg/h, fentanyl 1-3 mcg/kg/h, in group II fentanyl 5-10 mcg/kg/h and in all patients vecuronium 0.1 mg/kg/h were used.

In addition to peripheral venous lines, all patients received one central venous line, and one radial artery line catheters upon induction of anesthesia under local anesthesia. For perioperative antibiotics prophylaxis, 1 g cefazolin (Cefamezin IM/IV 1000 mg flacon, Zentiva, Luleburgaz, Turkey) was used.

Initial heparinization was accomplished with 400 IU/kg body weight and was supplemented as required to maintain an activated clotting time longer than 400 seconds. To reverse the heparin effect, protamin was administered after discontinuation of CPB.

For cardioplegic cardiac arrest, St. Thomas solution (Plegisol, Hospira Inc. North Chicago, IL, USA) and intermittent cold blood cardioplegia was used. A non-pulsatile pump flow was maintained at 2.4 L/min/m^2 with a perfusion pressure 60 to 80 mmHg. CPB was initiated at moderate hypothermia (30-32°C).

Postoperative Procedure

At the end of surgery, patient were transferred to intensive care unit (ICU) intubated and mechanically ventilated using continuous positive pressure ventilation (Evita 2, Dräger AG, Lübeck, Germany) to maintain PaO_2 more than 70 mmHg and normocapnia. Patients were sedated postoperatively with a continuous infusion of

fentanyl and intermittent bolus administration of opioids until 60 min before extubation. Patients were extubated when they were awake, oriented and cooperative, with a stable circulation, a temperature >36.5°C, minimal chest drain loss, and after a 30 min trial of spontaneous ventilation from a T piece ($PaCO_2$ < 45 mmHg, SaO_2 > 93%). After extubation, patients were given an i.v. PCA pump.

At the end of the surgery, PCA infusions were immediately started through a peripheral vein using a special infusion set (Life care Provider Set; Abbott Laboratories, Donegal, Ireland). Group I and Group II patients were given fentanyl (50 mcg/mL) with an infusion rate of 1 mcg/kg/h and 10 mcg bolus; with a 5-minute lockout time for all groups. Postoperative data were recorded in the cardiac intensive care unit at 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours after extubation.

Pain was assessed by a VAS from 0 to 10 (0 = no pain, 10 = the worst pain imaginable) and sedation on a six-point scale described by Ramsay et al[20] (1 = anxious and agitated or restless or both; 2 = cooperative, oriented, tranquil; 3 = responds to commands only; 4 = brisk response to a light glabellar tap or loud auditory stimulus; 5 = sluggish response to a light glabellar tap or loud auditory stimulus; 6 = no response to light glabellar tap or loud auditory stimulus).

Patients with VAS scores of 3 or less were defined as adequate analgesia. If scores were greater than 3, per oral 100 mg diclofenac sodium (Voltaren 100 mg, Novartis, Istanbul, Turkey) was given.

The authors also analyzed time to extubation, patient's demand and bolus numbers administered in the 24-hour period, and patient's demand numbers at 4-hour intervals for 24 hours were recorded. Furthermore, opioid-related side effects (respiratory effects, itching, nausea and vomiting, bradycardia, etc.) were also evaluated.

On the first or second postoperative day, all patients were discharged from the ICU and transferred to postoperative care ward. Independent physicians who were not involved in the study procedure carried out the general treatments of the patients. None of the patients required reintubation of the trachea, bronchoscopy, or special respiratory therapy such as continuous or bilevel positive airway pressure via mask during the entire study period.

After renewed explanation of the PCA device, the patients were able to start and use the device for the following 3 days.

Measurements of all variables were recorded in the morning on the first, third and seventh postoperative days after CABG.

In addition, patients retrospectively assessed their postoperative pain management during the entire study period on a scale from 1 to 5 (very poor, poor, moderate, good, or excellent, respectively) at the end of the study.

Assessment of Tactile Allodynia

To test the tactile threshold required to elicit a verbal response to touch, the calibrated Von Frey filaments were used when testing for low threshold mechanoreceptive function. Previous studies have shown that this method is reliable[21-23]. The filaments were applied to the forearm of all patients. The up-and-down method with different sizes of filaments was used to detect a mechanical pain threshold (ranging from 26 to 300 g). The mechanical pain threshold was defined as a painful response, reported by the patient, to at least one out of three stimuli using a filament. The pinprick test was performed by briefly striking the patient's forearm twice using a standard desk pin. The patient's response to this stimulation was documented as painful or non-painful. Measurements were calculated as g/mm^2. The tactile thresholds were measured before the surgery, 1st, 3rd and 7th post operative days. The von Frey filament, pinprick tactile thresholds were measured before the surgery, 1st, 3rd and 7th post operative days.

Assessment of Thermal Hyperalgesia

Custom-constructed thermode (Gulhane Military Academy of Medicine Department of Biomedical Enginering, Ankara, Turkey) was used in this study. The baseline temperature for the thermode was set at +32°C. The rate of temperature change was 1 °C/s, and cut off + 50 °C to avoid tissue injury.

A thermal source was applied to the forearm of all patients. To detect heat pain threshold, patients were instructed to stop stimulation when they first perceived pain sensation, as temperature ascended from the temperature of 32°C. The temperature at which the patient stopped the stimulation was recorded as threshold temperature (°C).

Statistical Analysis

Data was given as mean ± SD. One way repeated measures of ANOVA followed by Dunnet test was used to assess statistically difference be-

Table I. Demographic data of the patients.

	Low dose group (n=50)	High dose group (n=50)
Age (year)	68 ± 9	67 ± 11
Weight (kg)	78 ± 12	80 ± 11
M/F (n)	35/15	38/12
ASA physical status (II/III) (n)	32/18	30/20
Previous myocardial infarction	11	13
COPD	6	5
Medication		
β-blockers	41	44
Calcium channel blockers	42	43
ACE inhibitors	16	15
Nitrates	15	14
Diuretics	40	39
Antiarrhythmic agents	19	20
Platelet aggregation inhibitors	43	45

M/F: Male/Female, ASA: American Society of Anesthiology, COPD: Chronic Obstructive Pulmonary Disease, ACE: Angiotensin Converting Enzyme

tween groups using Graphpad Prism 3. Statistical significance was determined with $p < 0.05$.

Results

There were no significant differences in patient characteristics, which were summarized in Table I. There were no statistically significant differences in aortic cross clamp time, cardiopulmonary bypass time, and anesthesia and surgery times. However, there were significant differences in mechanical ventilation and prolonged mechanical ventilation times. These data were showed in Table II. Postoperative hearth rate, mean arterial blood pressure, and respiratory rate were not different between groups at all the measured times (Table III).

Table II. Intra and postoperative data.

	Low dose group (n=50)	High dose group (n=50)
Intraoperative data		
Cross-clamp time (min)	30.2 ± 10.8	28.9 ± 8.5
CPB time (min)	64.4 ± 15.6	62.3 ± 13.4
Duration		
Anesthesia (min)	201.8 ± 19.1	209.8 ± 22.4
Surgery (min)	176 ± 14.7	171.9 ± 16.5
Postoperative data		
Mechanical ventilation, h	4,1 ± 2,7	9.1 ± 1.2*
Prolonged mechanical ventilation (>12 h), n (%)	2 (4)	12 (24)*
ICU stay, h (min-max)	48 (17-24)	44 (17-24)
Prolonged hospitalization (>7 d), n (%)	4 (8)	6
Death at 30 days, n	0	0

*$p < 0.001$
CPB: Cardiopulmonary bypass, min: minute, h: hour, d: day, ICU: Intensive Care Unit
min-max: minimum-maximum

Table III. Postoperative Heart Rate, Mean Arterial blood pressure, and Respiratory Rate.

Hours after operation	Low dose group (n=50)	High dose group (n=50)	*p* values
Baseline			
HR (beats/min)	87.1 ± 16.3	86.9 ± 16.5	NS
MAP (mmHg)	102.2 ± 19.1	98.7 ± 18.1	
RR (breaths/min)	17.1 ± 1.9	16.2 ± 1.8	
1st Hour			
HR (beats/min)	86.6 ± 15.3	85.2 ± 15.1	NS
MAP (mmHg)	96.7 ± 17.1	97.3 ± 16.7	
RR (breaths/min)	16.4 ± 1.6	16.3 ± 1.7	
3rd Hour			
HR (beats/min)	83.1 ± 13.2	82.3 ± 11.8	NS
MAP (mmHg)	99.8 ± 10.1	98.3 ± 10.6	
RR (breaths/min)	15.9 ± 1.3	16.4 ± 1.4	
6th Hour			
HR (beats/min)	84.2 ± 12.1	80.3 ± 12.7	NS
MAP (mmHg)	96.2 ± 14.1	96.8 ± 14.5	
RR (breaths/min)	15.3 ± 1.2	15.4 ± 1.1	
12th Hour			
HR (beats/min)	84.1 ± 11.6	81±12.1	NS
MAP (mmHg)	94.1 ± 12.8	93.4 ± 13.5	
RR (breaths/min)	15.3 ± 1.2	15.6 ± 1.2	
24th Hour			
HR (beats/min)	83.4 ± 11.3	79.7 ± 12.4	NS
MAP (mmHg)	92.1 ± 12.1	91.7 ± 13.2	
RR (breaths/min)	15.1 ± 1.1	15.2 ± 1.0	
2nd Day			
HR (beats/min)	82.1 ± 12.3	78.2 ± 11.7	NS
MAP (mmHg)	90.9 ± 12	89.6 ± 12.1	
RR (breaths/min)	14.2 ± 1.3	14.4 ± 1.2	
3rd Day			
HR (beats/min)	81.3 ± 11.9	79.1 ± 11.0	NS
MAP (mmHg)	89.4 ± 11.7	88.2 ± 11.8	
RR (breaths/min)	14.3 ± 1.1	14.2 ± 1.2	
7th Day			
HR (beats/min)	80.6 ± 10.1	79.9 ± 10.4	NS
MAP (mmHg)	90.1 ± 11.2	89.2 ± 10.3	
RR (breaths/min)	13.9 ± 1.0	14.1 ± 1.0	

HR: Heart rate, MAP: Mean Arterial Pressure, RR: Respiratory rate, NS: Non significant.

VAS scores for pain in the preoperative period were similar in two groups. After the operation, pain scores were significantly higher in high dose group than low dose group at the 72nd hour (Table IV). Sedation scores were similar in low dose group and high dose group for all the measured times.

Total fentanyl consumption, PCA requirements and demand numbers, and diclofenac sodium usage were significantly less in the low dose group compared to the high dose group (Table V). Total fentanyl consumption in two groups were 883.6 ± 74.0 and 8126.0 ± 725.9; $p < 0.001$, PCA need (19.1 ± 0.3 and 29.9 ± 3.3; $p < 0.001$), PCA demand (22.5 ± 3.3 and 32.5 ± 3.3; $p < 0.001$), and rescue analgesic requirement were significantly higher in high dose group ($p < 0.001$).

Table IV. Postoperative pain scores in two groups.

	1 h	3 h	6 h	12 h	24 h	2nd day	3rd day	7th day
Low dose group (n=50)	2.1±0.8	1.8±0.6	1.5±0.6	1.1±0.7	2.8±0.7	1.9±0.6	1.7±1.1*	1.6±1.2
High dose group (n=50)	2.0±0.8	1.8±0.6	1.4±0.6	0.9±0.7	3.3±0.6	2.4±0.5	3.4±1.2	1.7±0.8

*72h; $p = 0.02$, h: hour

Table V. Fentanyl use in two groups.

	Low dose group (n=50)	High dose group (n=50)
Total fentanyl consumption	883.6±74.0	8126.0±725.9*
PCA requirements (number of bolus doses)	19±0.3	29.9±3.3*
PCA demand number	22.5±3.3	32.5±3.3*
Diclofenac sodium number	16.8±3.2	28.6±3.1*

*$p < 0.001$
PCA: Patient controlled analgesia.

Frequent side effects noted during the study period were nausea, vomiting, dizziness, somnolence, pruritus, diarrhea, constipation, urinary retention, and respiratory depression (Table VI). Incidence of nausea, vomiting and somnolence was significantly ($p < 0.05$) higher in high dose group; there was no difference in incidence of other adverse effects between the groups.

Figure 1 shows the tactile thresholds in the patients undergoing CABG surgery. The tactile thresholds were significantly decreased at the first (6.08 ± 0.21 and 3.76 ± 0.13 g; $p < 0.001$) and third (6.76 ± 0.24 and 4.96 ± 0.16 g; $p < 0.001$) postoperative days compared to the baseline preoperative values (7.72 ± 0.26 and 7.60 ± 0.21 g; $p = 816$) in two groups. Tactile thresholds were significantly less at 24 h and third postoperative day in the high-dose fentanyl group than low-dose fentanyl group ($p < 0.001$). This decrease returned to the baseline values at the 7th day of the measurement (7.56 ± 0.23 and 7.12 ± 0.17 g; $p = 0.129$).

Pre- and post-operative thermal threshold values were given in Figure 2. Postoperative 1st and 3rd day assessments showed a statistically significant hyperalgesia compared to the preoperative baseline values in two groups (13.45 ± 0.33 and 10.05 ± 0.24 sec; $p < 0.001$ and 14.77 ± 0.28 and 13.17 ± 0.26 sec; $p < 0.001$: respectively first day

Table VI. Incidence of adverse effects encountered through study in two groups.

	Low dose group (n=50)	High dose group (n=50)
Nausea	7*	14
Vomiting	5*	10
Dizziness	1	2
Somnolence	-	-
Pruritus	6*	11
Diarrhea	-	-
Constipation	2	3
Urinary retention	-	-
Respiratory depression	-	-

*$p < 0.05$

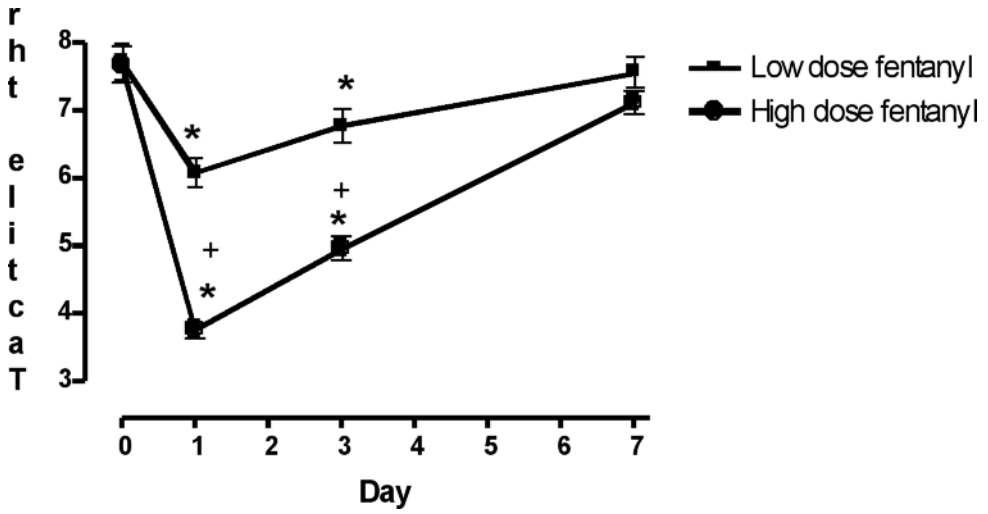

Figure 1. Pre- and post-operative tactile thresholds of 50 patients undergoing coronary artery bypass graft surgery. Tactile thresholds was measured by Von Frey filaments. *Statistical difference from baseline values, $p < 0.05$. + Statistical difference from low fentanly dose, $p < 0.05$.

and third day v.s. preoperative values, 16.67 ± 0.51 and 16.45 ± 0.42 sec; $p = 0.997$). Thermal thresholds were significantly less at 24 h and third postoperative day in the group II than group I ($p < 0.001$). Similar to the tactile thresholds, the thermal hyperalgesia disappeared at the 7th day of assessment (15.83 ± 0.3 and 15.39 ± 0.25 sec; $p = 0.228$).

Discussion

Our results showed that administration of acute high dose fentanyl causes thermal hyperalgesia and tactile allodynia at early postoperative stage in the patients undergoing CABG surgery. This change returned to the normal values at about one week after the operation.

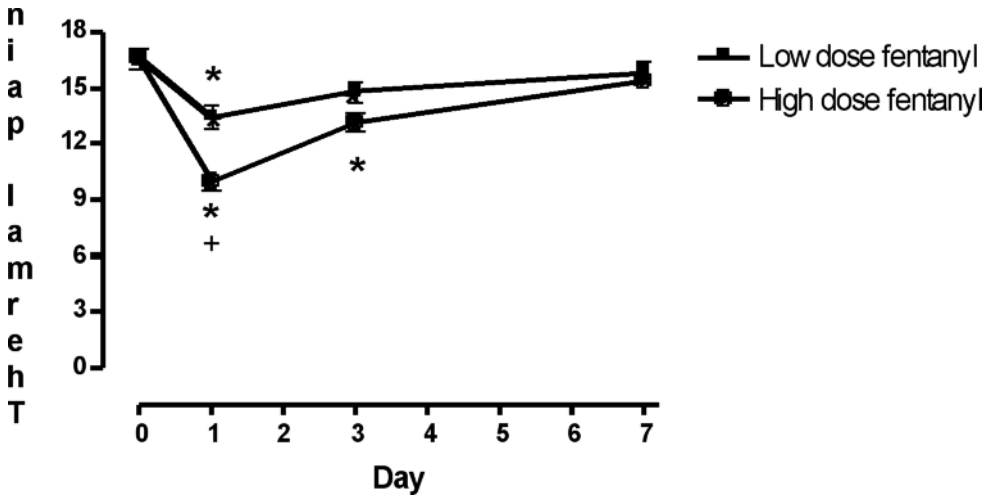

Figure 2. Pre- and post-operative thermal pain latencies of 50 patients undergoing coronary artery bypass graft surgery. Thermal pain threshold was measured by custom-made thermode. *Statistical difference from baseline values, $p < 0.05$. +Statistical difference from low fentanly dose, $p < 0.05$.

In some patients to maintain adequate analgesia, we need to increase the opioid dose over time due to the development of tolerance to the analgesic effects of opioids. However, the loss of analgesic efficacy can also be the result of opioid-induced hyperalgesia. Opioid-induced hyperalgesia and analgesic tolerance are two distinct pharmacologic phenomena that can result in similar effect on opioid dose requirements[24]. Angst et al[25] reported that the occurrence of tolerance is commonly inferred from the need to increase the dose to maintain a therapeutic effect. In many instances tolerance does develop in the contex of chronic therapy. Acute tolerance to opioids is more controversial than the tolerance with chronic use. A study by Joly et al[26], directly measured the development of secondary wound hyperalgesia after acute intraoperative opioid exposure. The authors found that high-dose intraoperative exposure to the potent, ultrashort-acting μ-opioid agonist remifentanil increased peri-incisional wound allodynia and hyperalgesia compared with low-dose intraoperative remifentanil in patients undergoing major abdominal surgery. They also pointed out that exposure to high intraoperative opioid doses may results in increased postoperative opioid consumption and/or pain. These findings could alternatively be explained by the development of acute opioid-induced hyperalgesia.

Two prospective controlled clinical studies by Chia et al[27] and Guignard et al[11] have reported the increased postoperative pain despite increased postoperative opioid use in patients who received high doses of intraoperative opioids. A separate study[28] of women undergoing cesarean section found that the intraoperative exposure to intrathecal fentanyl also leads to a similar finding of increased postoperative opioid consumption without improved analgesia, compared with women who received placebo intrathecal saline injections.

These findings are contradicted by other studies that did not show an effect of intraoperative opioid dose on postoperative pain sensitivity. Cortinez et al[29] after high-dose intraoperative remifentanil exposure in patients undergoing elective gynecologic surgery did not find an increase in pain or postoperative opioid consumption. Lee et al[30] also failed to show a significant difference in postoperative pain or opioid consumption in patients who received intraoperative remifentanil compared with 70 % nitrous oxide, after colorectal surgery. Hensen et al[31] also failed to show a significant difference in postoperative pain or opioid consumption. They showed a significant increase in VAS score in remifentanil group compared to placebo during the immediate postoperative period that is suggestive of opoid-induced hyperalgesia, this difference was no longer significant 2 hours after surgery or during the remainder of the 24-hour observation period. The failure to observe an effect of intraoperative opioid exposure on postoperative pain and opioid consumption in these studies may be related to the lower total intraoperative opioid exposure in the cases of Cortinez et al[29] and Lee et al[30] reports when compared to the positive results of Guignard et al[11]. Our findings were also similar with those studies.

Hyperalgesia can be detrimental in the early postoperative period and results either in an increased sensitivity to pain, an aggravation of pre existing pain or the expression of novel pain symptoms[32]. More pain means more stress for patient and chronic pain may develop following this condition. Hyperalgesia after surgery may be due to surgical intervention via nervous system sensitization or opioid treatment especially with the use very high and escalating doses of opioids[16].

Large number of animal researches shows that chronic[2,5,10] and acute[9,11] exposure to opioids may cause hyperalgesia. Mao et al[33] reported that opioid induced tolerance and hyperalgesia may develop. In our study, we also found that fentanyl-induced hyperalgesia and tactile allodynia developed despite the patients were still on opioid-based pain management treatment.

After repeated applications of fentanyl Celerier et al[34] found that fentanyl can cause not only a decrease in the analgesic response but also a dose dependent reduction of pain thresholds in rats. This effect lasts only one day with low dose fentanyl (80 μg/kg) but they found that the hyperalgesia could still be observed after five days with high dose fentanyl (400 μg/kg) in a rat model. Similar to the animal models, studies in human shows that acute high dose (15 μg/kg) but not low dose fentanyl administration during surgery cause analgesic tolerance to the drug and result in increase of postoperative pain and lead to greater opioid consumption after surgery[27]. Similar to the aforementioned works, our patients in group II were also exposed to high doses (40-70 μg/kg fentanyl) for induction and maintenance (5-10 μg/kg/h fentanyl) of the anesthesia and as a result we observed decreases in tactile and thermal thresholds in 1st and 3rd days. Additionally we found that fentanyl-induced hyperal-

gesia lasted long time and returned to normal about one week after the surgery. In group I, there were also some decreases in the threshold levels, these decreases were not as prominent as in group II.

The significantly higher PCA requirement and demand observed immediately after surgery in patients receiving fentanyl may indicatethe development of acute opioid tolerance and opioid induced hyperalgesia. These findings were similar with the changes in tactile threshold and thermal pain latency. Furthermore, these two different findings may be accepted ascross-checks for each other.

Conclusions

Patients undergoing CABG surgery developed signs of postoperative thermal hyperalgesia and tactile allodynia following fentanyl administration (40-70 μg/kg for induction and 5-10 μg/kg/h for maintenance). At the same time, intraoperative high dose opioids induce higher pain scores and opioid consumption when compared to low dose therapy. The exact mechanism of opioid-induced hyperalgesia remained to be clarified.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mammucari M, Lazzari M, Maggiori E, Gafforio P, Tufaro G, Baffini S, Maggiori S, Palombo E, de Meo B, Sabato AF; On Behalf of the Steering Committee of Italian Society of Mesotherapy (SIM), Italy. Role of the informed consent, from mesotherapy to opioid therapy. Eur Rev Med Pharmacol Sci 2014; 18: 566-574.
2) King T, Ossipov MH, Vanderah TW, Porreca F, Lai J. Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? Neurosignals 2005; 14: 194-205.
3) Dupen A, Shen D, Ersek M. Mechanisms of opioid-induced tolerance and hyperalgesia. Pain Manag Nurs 2007; 8: 113-121.
4) Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006; 7: 43-48.
5) Sjøgren P, Thunedborg LP, Christrup L, Hansen SH, Franks J. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration? Six case histories. Acta Anaesthesiol Scand 1998; 42: 1070-1075.
6) Singla A, Stojanovic MP, Chen L, Mao J. A differential diagnosis of hyperalgesia, toxicity, and withdrawal from intrathecal morphine infusion. Anesth Analg 2007; 105: 1816-1819.
7) Suzuki R, Porreca F, Dickenson AH. Evidence for spinal dorsal horn hyperexcitability in rats following sustained morphine exposure. Neurosci Lett 2006; 407: 156-161.
8) Célèrier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. J Neurosci 2001; 21: 4074-4080.
9) Laulin JP, Maurette P, Corcuff JB, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg 2002; 94: 1263-1269.
10) Vanderah TW, Ossipov MH, LAI J, Malan TP jr, Porreca F. Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin. Pain 2001; 92: 5-9.
11) Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D, Chauvin M. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000; 93: 409-417.
12) Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. Pain 2001; 90: 91-96.
13) Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage 2000; 20: 237-245.
14) Fletcher D, Pinaud M, Scherpereel P, Clyti N, Chauvin M. The efficacy of intravenous 0.15 versus 0.25 mg/kg intraoperative morphine for immediate postoperative analgesia after remifentanil-based anesthesia for major surgery. Anesth Analg 2000; 90: 666-671.
15) Dolin sj, Cashman Jn, Bland Jm. Effectiveness of acute postoperative pain management: I. Evidence from published data. Br J Anaesth 2002; 89: 409-23.
16) Wilder-Smith OH, Arendt-Nielsen L. Postoperative hyperalgesia: its clinical importance and relevance. Anesthesiology 2006; 104: 601-607.
17) Angst Ms, Koppert W, Pahl I, Clark Dj, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106: 49-57.
18) Dogrul A, Bilsky EJ, Ossipov MH, Lai J, Porreca F. Spinal L-type calcium channel blockade abolishes opioid-induced sensory hypersensitivity and antinociceptive tolerance. Anesth Analg 2005; 101: 1730-1735.
19) Kamerman P, Koller A, Loram L. Postoperative administration of the analgesic tramadol, but not the

selective cyclooxygenase-2 inhibitor parecoxib, abolishes postoperative hyperalgesia in a new model of postoperative pain in rats. Pharmacology 2007; 80: 244-248.

20) Ramsay Ma, Savege Tm, Simpson Br, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br J Med 1974; 2: 656-659.

21) Nakanishi O, Amano Y, Ishikawa T, Azuma M, Imamura Y. Effects of midazolam on pain sensations in the face. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 84: 11-15.

22) Ellermeier W, Westphal W. Gender differences in pain ratings and pupil reactions to painful pressure stimuli. Pain 1995; 61: 435-439.

23) Chen L, Malarick C, Seefeld L, Wang S, Houghton M, Mao J. Altered quantitative sensory testing outcome in subjects with opioid therapy. Pain 2009; 143: 65-70.

24) Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain 2008; 24: 479-496.

25) Angst MS, Chu LF, Tingle MS, Shafer SL, Clark JD, Drover DR. No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. Pain 2009; 142: 17-26

26) Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology 2005; 103: 147-155.

27) Chia YY, Liu K, Wang JJ, Kuo MC, Ho ST. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46: 872-877.

28) Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? Br J Anaesth 1997; 78: 311-313.

29) Cortínez LI, Brandes V, Muñoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. Br J Anaesth 2001; 87: 866-869.

30) Lee LH, Irwin MG, Lui SK. Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. Anesthesiology 2005; 102: 398-402.

31) Hansen EG, Duedahl TH, Rømsing J, Hilsted KL, Dahl JB. Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand 2005; 49: 1464-1470.

32) Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. Best Pract Res Clin Anaesthesiol 2007; 21: 65-83.

33) Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. J Neurosci 1994; 14: 2301-2312.

34) Célèrier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology 2000; 92: 465-472.