Intraoperative high dose fentanyl induces postoperative fentanyl tolerance

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Purpose: In a randomized, double-blind clinical trial, we compared the postoperative analgesic effect and dose consumption of fentanyl after intraoperative high dose and low dose fentanyl administration.

Methods: Sixty ASA class I to II female patients undergoing total abdominal hysterectomy (TAH), were randomly allocated to receive either 1 $\mu g \cdot kg^{-1}$ (low dose group, n = 30) or 15 $\mu g \cdot kg^{-1}$ (high dose group, n = 30) fentanyl during induction of anesthesia. Anesthesia depth was maintained with inhalation of halothane in the low dose group, or combined with 100 $\mu g \cdot hr^{-1}$ fentanyl *iv* in the high dose group. Postoperative pain was treated with an intravenous patient-controlled analgesia system and was assessed with a visual analog pain score at rest.

Results: Patients in the high dose group had higher pain intensity at four and eight hours postoperatively, more fentanyl consumption and a greater incidence of emesis in the postoperative period of 16 hr than those in the low dose group ($P < 0.05$). Heart rate, blood pressure, and respiratory rate were similar between the two groups.

Conclusion: Our results suggest that acute fentanyl tolerance develops after administration of high dose fentanyl during surgery and, consequently, results in a higher postoperative pain intensity and greater fentanyl consumption.

Objectif : Comparer, dans un essai clinique randomisé, à double insu, l'effet analgésique postopératoire et la consommation de fentanyl après l'administration peropératoire de forte et faible dose de fentanyl.

Méthode : Soixante patientes de classes I et II ASA devant subir une hystérectomie abdominale totale (HAT) ont été réparties au hasard et ont reçu, soit 1 $\mu g \cdot kg^{-1}$ (groupe de faible dose, n = 30), soit 15 $\mu g \cdot kg^{-1}$ (groupe de forte dose, n = 30) de fentanyl pendant l'induction de l'anesthésie. La profondeur de l'anesthésie a été maintenue avec l'inhalation d'halothane dans le groupe à faible dose, ou en combinaison avec 100 $\mu g \cdot h^{-1}$ de fentanyl *iv*, dans le groupe à forte dose. La douleur postopératoire a été soulagée avec une analgésie intraveineuse contrôlée par la patiente et évaluée, au repos, à l'aide d'une échelle visuelle analogue.

Résultats : Les patientes qui ont reçu la forte dose ont connu des douleurs plus intenses quatre et huit heures après l'opération, ont pris davantage de fentanyl et ont eu une plus grande incidence de vomissements dans les 16 h qui ont suivi l'opération, que celles qui ont reçu une faible dose ($P < 0,05$). La fréquence cardiaque, la tension artérielle et le rythme respiratoire n'ont pas présenté de différence intergroupe.

Conclusion : Les résultats suggèrent qu'une tolérance soudaine au fentanyl se développe après l'administration peropératoire d'une forte dose et qu'elle entraîne, par conséquent, des douleurs postopératoires plus intenses et une plus grande consommation de fentanyl.

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FENTANYL, a synthetic Mu receptor agonist, has been used widely in clinical anesthesia. Its potent antinociceptive effect has made it a major component of modern balanced anesthesia. Some reports have suggested the use of fentanyl in large doses as a sole anesthetic in cardiovascular surgery.[1] However, the effect of intraoperative use of large dose of fentanyl on postoperative pain management is controversial. A study in humans suggested that the use of high dose morphine before induction of anesthesia preempted the hyperalgesia resulting from intraoperative intubation or surgical nociceptive stimulus, thereby decreasing the postoperative opioid consumption and pain intensity.[2] However, Fassoulaki *et al.* found that administration of 10 $\mu g \cdot kg^{-1}$ fentanyl before induction of anesthesia induced more pain during the first 120 min after hysterectomy than administration of fentanyl after peritoneal incision or removal of the uterus.[3] Further study failed to support a preemptive analgesic effect of preoperative alfentanil on postoperative pain management.[4] In this prospective, double blind study, we evaluated pain intensity and postoperative fentanyl consumption in patients undergoing total hysterectomy who received either a relatively high dose or low dose of fentanyl intraoperatively.

Methods

Sixty ASA I-II female patients undergoing total abdominal hysterectomy were recruited for the double-blind study. Approval was obtained from the Human Investigation Committee and informed consent was obtained from all patients. The patients were randomly equally allocated to receive either 1 $\mu g \cdot kg^{-1}$ fentanyl (low dose group, n = 30) or 15 $\mu g \cdot kg^{-1}$ fentanyl (high dose group, n = 30) by slow intravenous infusion over 20 min before induction of anesthesia under close supervision of an anesthesiologist, who did not participate in the postoperative evaluation and patient contact. Ventilation was assisted manually via a face mask. After administration of 5 $mg \cdot kg^{-1}$ thiopental and 0.1 $mg \cdot kg^{-1}$ vecuronium, the tracheal was intubated, and the lungs were ventilated with oxygen 50% in air. Inhalation of halothane was used to maintain anesthesia without further opioid supplementation during surgery in the low dose group; or combined with 100 $\mu g \cdot hr^{-1}$ fentanyl *iv* until the end of anesthesia in the high dose group. Hemodynamic variables were maintained within 20% of baseline, defined as the mean of three pre-anesthesia measurements. All patients were lying on a warming blanket to maintain core temperature at around 36°C. The ECG, direct intra-arterial pressure, and heart rate were continuously monitored throughout the operation and the first two hours postoperatively. Arterial blood was drawn for analysis during three different phases; phase I: period before induction of anesthesia; phase II: during surgery; and phase III: four hours after the end of anesthesia. At the end of anesthesia, neuromuscular blockade was reversed with 1.0 mg atropine and 2.0 mg neostigmine *iv*. All patients were then transported to the Post-anesthesia Care Unit (PACU) when they breathed spontaneously. At PACU, we administered oxygen via a nasal cannula or T-piece tube. The trachea was extubated when the patient was awake (eye opening or purposeful movement) and without compromised respiration (tidal volume $\geq$ 5 $mL \cdot kg^{-1}$). Meantime, a patient-controlled analgesia (PCA) system (Abbott Pain Management Provider) was connected to a peripheral intravenous route for pain relief with an on demand bolus dose of 15 µg and a lockout time of five minutes. The upper limit four hour dose was set at 300 µg fentanyl. The time for first fentanyl demand was defined as the duration from the end of the anesthesia to the first fentanyl demand by patient.

Measurements

Postoperative pain intensity at rest was evaluated by patients using a visual analogue pain score (VAS; 0 = no pain, 10 = unbearable pain) in each four hour interval for the first 16 hr postoperatively. Sedation level was assessed by nurses in our acute pain service team using a 0-3 scale as follows: 0, fully awake; 1, asleep with response to stimulus; 2, asleep without response to stimulus; 3, comatose. The duration of surgery and the occurrence of emesis were recorded. Postoperative heart rate, blood pressure, and fentanyl consumption every four hours were also recorded. Patients who had more than five episodes of vomiting per day received 5 mg prochlorperazine *im* every eight hours. Respiratory depression was defined as respiratory rates $\leq$ 8 bpm. The patients and surgeon were blinded to the treatment group. Patient data were recorded by the operative room nurses and the acute pain sisters, blinded to the treatment group allocation, followed up the postoperative data. The time to the first fentanyl demand was defined as the period from the end of anesthesia to the first demand for bolus dose delivery by the PCA.

Statistical analysis

The sample size (30 patients in each group) was calculated to detect a 25% reduction in fentanyl requirements with a Type I error of 0.05 and a power 80%. Demographic data, duration of surgery, arterial blood gas data, fentanyl consumption, and the time for first

TABLE I Demographic characteristics

	Low dose group (n = 30)	*High dose group (n = 30)*
Age (yr.)	44 ± 8	42 ± 6
Height (cm)	155 ± 9	142 ± 11
Weight (kg)	56 ± 10	54 ± 12
Duration of surgery (min)	150 ± 48	157 ± 30

Values given as means ± SD

TABLE II Hemodynamic outcomes and sedation scores during the first postoperative 16 hr

Hours postoperatively	*Low dose group (n = 30)*	*High dose group (n = 30)*
RR		
4	19 ± 3	18 ± 3
8	19 ± 2	20 ± 2
12	19 ± 1	20 ± 1
16	19 ± 2	20 ± 2
HR		
4	78 ± 8	83 ± 12
8	76 ± 13	87 ± 10
12	76 ± 10	82 ± 12
16	76 ± 10	82 ± 11
SBP		
4	119 ± 13	120 ± 16
8	125 ± 9	123 ± 16
12	118 ± 12	124 ± 14
16	122 ± 11	121 ± 12
DBP		
4	65 ± 10	76 ± 13
8	74 ± 8	78 ± 9
12	76 ± 9	81 ± 9
16	75 ± 11	78 ± 10
Sedation score		
4	0 (0-1)	1 (0-2)
8	0 (0-0)	0 (0-1)
12	0 (0-0)	0 (0-0)
16	0 (0-0)	0 (0-0)

Values given as means ± SD or medium (range)
RR: Respiratory rate, HR: Heart rate, SBP: Systolic blood pressure, DBP diastolic blood pressure.

fentanyl demand were analyzed using repeated measures analysis of variance (ANOVA) and un-paired Student's t test. Data on VAS and sedation scores were analyzed using the Mann-Whitney U test. The incidence of emesis and ASA status discrepancy was analyzed using Fisher's exact test or chi-squared test when suitable. Statistical analysis was performed using a computer and software SPSS for Windows, Release 7.0 (Statistic Product and Service Solutions, SPSS Inc.). A value of $P < 0.05$ was considered to be statistically significant.

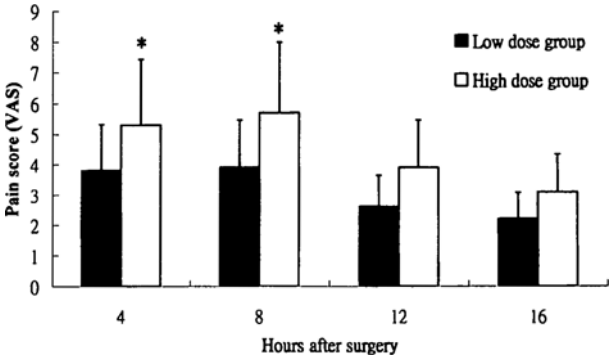

FIGURE 1 Postoperative visual analogue scores (VAS) (mean ± SD) during the first postoperative 16 hr. *: $P < 0.05$.

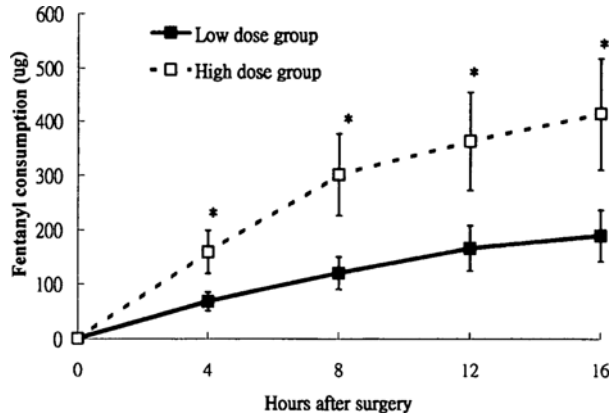

FIGURE 2 Postoperative accumulated fentanyl consumption (μg) (mean ± SD) during the first 16 hours after surgery. *: $P < 0.05$.

Results

Results were obtained for 60 patients; 30 in each group. The two groups were matched for age, weight, height, duration of surgery, and ASA status (Table I). Patients in the high dose group had higher VAS values at the 4th and 8th hr postoperatively (4th hour: 5.3 ± 1.1 *vs* 3.8 ± 0.9; 8th hr: 5.7 ± 1.5 *vs* 3.9 ± 0.8, $P < 0.05$) (Figure 1) and consumed more fentanyl (4th hr: 158.9 ± 42.1 μg; 8th hr: 301.1 ± 99.7 μg; 12th hr: 363.3 ± 118.5 μg; 16th hr: 413.3 ± 132.0 μg) than those in the low dose group (4th hr: 68.1 ± 23.5 μg; 8th hr: 120.0 ± 36.8 μg; 12th hr: 166.2 ± 56.4 μg; 16th hr: 189.8 ± 61.3 μg, $P < 0.05$) (Figure 2). There was an 18 - 50% increase in fentanyl requirements between 0-16 hr after surgery in the high dose group.

TABLE III Arterial blood gas data

	Low dose group (n = 30)			*High dose group (n = 30)*		
	Phase I	*Phase II*	*Phase III*	*Phase I*	*Phase II*	*Phase III*
PaO_2 (mmHg)	74.5 ± 8.2	224.1 ± 38.8	114.6 ± 18.0	68.9 ± 8.0	192.1 ± 36.0	104.0 ± 20.9
$PaCO_2$ (mmHg)	35.3 ± 5.6	30.1 ± 6.3	32.8 ± 4.2	34.1 ± 8.2	32.1 ± 8.1	37.8 ± 7.9
SaO_2 (%)	98 ± 1	99 ± 1	98 ± 1	97 ± 2	99 ± 1	97 ± 1
pH	7.448 ± 0.061	7.395 ± 0.085	7.402 ± 0.036	7.392 ± 0.050	7.412 ± 0.042	7.356 ± 0.038
$HCO3^-$ ($mmol \cdot L^{-1}$)	25.3 ± 4.1	20 ± 4.8	24.2 ± 3.9	25.0 ± 6.1	24.7 ± 3.0	22.8 ± 4.8

Values given as means ± SD

Phase I: Before anesthesia; phase II: During operation; phase III: Four hours after the end of the anesthesia.

Furthermore, the incidence of postoperative emesis was higher in the high dose group than in the low dose group (52% *vs* 12%, $P = 0.02$). There were no differences in respiratory rate, heart rate, systolic, diastolic blood pressure, and sedation scores postoperatively (Table II). The time of the first PCA demand was similar in the two groups (low dose group, 0.7 ± 0.3 hour; high dose group, 0.9 ± 0.3 hour, $P = 0.253$). The respiratory rates of patients in both groups were similar and > 10 bpm. Arterial blood gas analyses were similar in the two groups (Table III). The average dose of intraoperative fentanyl was 22 ± 3 $\mu g \cdot kg^{-1}$ in the high dose group, 20 times the dose administered in the low dose group (1 $\mu g \cdot kg^{-1}$).

Discussion

Our results indicate that preoperative administration of 15 $\mu g \cdot kg^{-1}$ followed by intraoperative administration of 100 $\mu g \cdot hr^{-1}$ fentanyl induces greater consumption of fentanyl and higher pain intensity after surgery than preoperative administration of 1 $\mu g \cdot kg^{-1}$ fentanyl. The comparable data in terms of respiratory rate, heart rate, systolic and diastolic pressure suggests similar cardiopulmonary effects of the two doses of fentanyl. Meanwhile, patients in the high dose group experienced a higher incidence of emesis than those in the low dose group patients did.

Opioids are commonly used in modern anesthesia and pain management. For most physicians and patients, the development of tolerance to opioids which leads to greater than expected consumption of opioids, is of concern. Tolerance to opioids may develop in a few days, hours, or even minutes after administration and has been classified as "chronic" or "acute" tolerance depending on the duration between treatment and the development of tolerance.[5] Previous animal studies described the characteristics of acute morphine tolerance as an acute decreased analgesic effect following repeated bolus or continuous administration of morphine.[6] In human, it leads to an increased use of opioids or/and decreased analgesic effect.[7] Patients in our study receiving 15 $\mu g \cdot kg^{-1}$ fentanyl before surgery followed by infusion of 100 $\mu g \cdot hr^{-1}$ consumed more fentanyl postoperatively, as demonstrated by higher pain intensity and similar cardiopulmonary effects as those receiving a lower dose of fentanyl (1 $\mu g \cdot kg^{-1}$). This implies that acute tolerance develops concerning postoperative analgesic and cardiopulmonary depressive effects of fentanyl.

Hovav *et al.* showed that repeated bolus doses of 4 or 10 $mg \cdot kg^{-1}$ morphine, estimated to produce > 70% of the maximal depressive effect to respiratory rate, heart rate and mean blood pressure, produces the acute morphine tolerance. Whereas, a smaller dose of 2 $mg \cdot kg^{-1}$ morphine with less than 25 % maximal effect leads to enhanced depressive effect instead of tolerance.[8] We anticipated difficulty in defining and measuring the maximal perioperative analgesic effect of fentanyl in humans, because previous studies have demonstrated that a four- to six-fold interindividual variation regarding postoperative therapeutic plasma concentrations[9] and many factors may affect the opioid consumption such as age, culture, race, sex, surgical area, and the differences in individual pharmacokinetic and pharmacodynamic behaviour of opioids.[10] However, a previous study demonstrated that 2 $\mu g \cdot kg^{-1}$ fentanyl *iv* depressed respiration in 50% of volunteers in the absence of nociceptive stimulation.[11] Whilst 10 $\mu g \cdot kg^{-1}$ fentanyl parentally in dogs induces severe apnea.[12] Hence, in our study, a dose of 15 $\mu g \cdot kg^{-1}$ at induction of anesthesia combined with maintenance doses of 100 $\mu g \cdot hr^{-1}$ hour in the high dose group was intended to provide over 70% of the maximal perioperative analgesic effect. A dose of 1 $\mu g \cdot kg^{-1}$ at induction of anesthesia in the low dose group without further opioid administration was expected to provide an analgesic effect of much lesser magnitude. McQuay *et al.* reported that at the end of an intravenous bolus dose of 10 $\mu g \cdot kg^{-1}$ fentanyl followed by three-hour's infusion of 100 $\mu g \cdot hr^{-1}$ fen-

tanyl, the plasma concentration of fentanyl was 3.4 ± 0.6 ng·ml^{-1}; and three hours after discontinuation of administration, the plasma level was 2.6 ± 0.5 ng·ml^{-1}.[7] Whilst the plasma fentanyl concentration in patients who had received only 1.5 μg·kg^{-1} fentanyl was 0.1-0.4 ng·ml^{-1}. They found that acute fentanyl tolerance to analgesia developed in the former group. In our study, total fentanyl dosage during surgery in patients in the high dose group was > 22 μg·kg^{-1} while that in the low dose was 1 μg·kg^{-1}. This very different dose might induce a greater difference in plasma fentanyl concentrations than in McQuay's report. The major differences in plasma concentrations may remain even during the postoperative period because, after a large bolus dose of fentanyl followed by a continuous infusion, the equilibration between plasma and other tissues, such as muscle and fat tissue, is established. Fentanyl accumulates as a result of its slow release by liver metabolism, and redistribution is less effective in removing fentanyl from its site of action, such as in the central nerve system.[19] Hence, lacking great decrease in plasma concentrations after discontinuation of a bolus and infusion dose of fentanyl and consuming more fentanyl for postoperative analgesia in the high dose group, further supported the hypothesis that acute fentanyl tolerance occurred.

A previous animal study observed that the depressive effect of fentanyl on respiration, heart rate, and blood pressure occurred at 10-15 min after its administration, declined in the next 20-30 min, and disappeared 75 min later.[8] Askitopoulou and colleague also found that acute tolerance to the depressive effects of fentanyl on arterial pressure and heart rate actually developed in anesthetized dogs within three hours after administration.[13] In our results, the mean duration of surgery was 150.2 ± 48.8 and 156.9 ± 30.2 min in the high and low dose patients, respectively, and there no operation taken for < 75 min. Therefore, all patients had sufficient duration of exposure for the development of fentanyl tolerance during the operation.

Parker *et al.* reported that patients who received postoperative continuous morphine infusion consumed more opioid medication than did those who received repeated bolus infusion.[14] Thornton *et al.* had similar findings.[15] It was assumed that postoperative continuous infusion of morphine induces the development of acute tolerance to analgesia, which therefore leads to increased postoperative morphine consumption. In our study, postoperative PCA was set to deliver an intermittent bolus fentanyl of 15 μg to avoid the disturbance of the postoperative development of fentanyl tolerance. Our results revealed that patients who received a high dose of fentanyl consumed more fentanyl for postoperative pain management and experienced greater pain severity. This suggests that the development of acute fentanyl tolerance occur during anesthesia.

Vaccarino *et al.* found that the analgesic effect of morphine to tail-flick test or formalin test does not lead to tolerance after repeated bolus dose of morphine for three days in the rats with the presence of formalin-induced pain, while the same dose of morphine did produce tolerance in the rats without formalin pain.[16] This suggests that acute tolerance to opioids may be prevented in the presence of continuing nociceptive stimulation. Our patients in both groups experienced intraoperative surgical and postoperative wound pain stimulation, but analgesic tolerance to fentanyl still occurred. The mechanism is unclear. It is possible that the pathway of surgical nociceptive input is partially or totally inhibited by halothane during inhalation anesthesia, thus the excessive amount of fentanyl in the high dose group tended to induce the development of acute tolerance. This is partially supported by the previous studies that halothane depressed the activity of cells and lamina V and slightly decreases the activity of cells in lamina I in a dose-dependent manner,[17] and that halothane suppresses the expression of c-Fos protein evoked by noxious somatic stimulation in the deeper layer of the spinal cord in the rat.[18] However, this needs further exploration.

In this study, a higher incidence of emesis was observed in the high dose group than in the low dose group: no acute tolerance to fentanyl induced emesis occurred. Postoperative respiratory rate was not different between the two groups from 4 to 16 hr postoperatively, and no patient experienced the respiratory depression in both groups. Only four cases (13.3%) in the high dose group had a respiratory rate from 11-14 bpm and increased arterial partial carbon dioxide pressure to 45 mmHg during the post-anesthesia recovery period (within two hours after the end of the anesthesia). This further delayed weaning from the endotracheal tube. In one case, even, the trachea was intubated *in situ* with T-piece wean trial three hours after the end of the anesthesia due to insufficient respiratory drive (tidal volume < 5 mL·kg^{-1}). The trachea was extubated at last four hours after the end of the anesthesia.

In summary, the preoperative administration of 15 μg·kg^{-1} fentanyl followed by intraoperative infusion of 100 μg·hr^{-1} fentanyl results in increased postoperative fentanyl consumption and pain severity when compared with the preoperative administration of 1 μg·kg^{-1} fentanyl, and leads to an increased incidence of fentanyl induced emesis. This suggests that acute tolerance to fentanyl's analgesia occurs after a relatively large dose fentanyl during surgery.

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