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SHORT COMMUNICATION

# Comparisons of two different doses of fentanyl for procedural analgesia during epidural catheter placement: a double-blind prospective, randomized, placebo-controlled study

**Takeshi Yano · Shigeaki Okubo · Hiroaki Naruo · Tatsuma Iwasaki · Isao Tsuneyoshi**

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**Abstract** The purpose of this study was to investigate the effect of fentanyl on analgesic properties and respiratory responses during an epidural procedure. Sixty patients premedicated with oral brotizolam 0.25 mg were allocated to receive procedural analgesia with saline or 25 or 50 μg of fentanyl. Five minutes after administration, an epidural procedure was started. Pain assessments were made immediately after the epidural catheter placement using a visual analog scale. The lowest $SpO_2$ levels during the procedure were recorded to evaluate respiratory depression, and cardiovascular complications were also recorded. The pain scores were significantly lower in the 25 and 50 μg fentanyl groups than in the placebo group ($P < 0.01$). There was no difference in pain assessment between the 25 and 50 μg fentanyl groups. The lowest $SpO_2$ value of the 50 μg fentanyl group was significantly lower than those of the other groups ($P < 0.001$). Seven of 20 cases in the 50 μg fentanyl group needed oxygen administration because of a decreased $SpO_2$ value (<94%). No cardiovascular complications were observed in any group during the entire study period. Thus, intravenous fentanyl at a dose of 25 μg provides effective procedural analgesia without the risk of hypoxemia during an epidural procedure in a patient with preanesthetic medication.

**Keywords** Procedural pain · Epidural anesthesia · Fentanyl · Procedural analgesia

T. Yano (✉) · I. Tsuneyoshi
Department of Anesthesiology, School of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan
e-mail: plant9458@yahoo.co.jp

S. Okubo
Department of Anesthesiology, Miyazaki Medical Association Hospital, Miyazaki, Japan

H. Naruo
Department of Anesthesiology, Miyazaki Prefectural Nichinan Hospital, Miyazaki, Japan

T. Iwasaki
Department of Anesthesiology, National Hospital Organization Miyakonojo Hospital, Miyazaki, Japan

A patient's fear of pain during the epidural anesthetic procedure is strong [1], and, as a result, some patients may refuse epidural anesthesia [2]. Analgesic agents such as ketamine, parecoxib, and opioids are known for their efficacy as procedural sedatives [3–5]. Although 50 μg of fentanyl administered intravenously prior to an epidural puncture can provide adequate sedation during an epidural procedure, it does not contribute to the reduction of pain, and it may cause respiratory depression [3]. Safe and effective dosages of fentanyl to decrease epidural procedural pain are uncertain; however, lower doses of fentanyl (25 μg) are, in our clinical settings, frequently useful for procedural analgesia during an epidural puncture. We therefore hypothesized that 25 μg of fentanyl administered intravenously with light preanesthetic medication would be sufficient to decrease the pain associated with an epidural procedure without serious complications. The aim of this study was to investigate the dose-related responses to 25 and 50 μg of fentanyl: analgesic and sedative properties, safety profile, and respiratory effects.

This randomized, double-blind, controlled study was approved by the institutional review board (Clinical Study Committee of the National Miyakonojo Hospital), and written informed consent was obtained from each participant. Sixty adult surgical, urological, and gynecological

patients with an American Society of Anesthesiologists physical status of 1–2 who were scheduled for laparotomy as elective surgery under combined general-epidural anesthesia were investigated. Patients were randomly assigned to one of three groups receiving normal saline (control), 25 μg of fentanyl (F25), or 50 μg of fentanyl (F50), according to a random number table. Each drug solution was diluted to 2 ml with saline by an investigator not involved with subsequent patient assessments to facilitate blinding. The criteria for exclusion were as follows: pregnancy, obesity (body mass index of 30 or greater), severe scoliosis, spinal or neuronal diseases, psychiatric or mental disorder, systemic treatment with steroids, opioids, or nonnarcotic analgesics, treatment with an antipsychotic or antidepressant agent, hypersensitivity to fentanyl, a severe cardiovascular, pulmonary, or systemic disorder, or a percutaneous measurement of oxygen saturation ($SpO_2$) by pulse oximetry of ≤96% at the time of either preanesthetic evaluation or the measurement of initial vital signs before drug administration.

Two hours before entering the operation room, all patients were premedicated with oral brotizolam 0.25 mg, and acetate Ringer's solution was intravenously infused at a rate of 100 ml/h via an 18-gauge (G) catheter inserted into a brachial vein. Once in the operation room, the patients underwent an electrocardiogram and noninvasive measurements of blood pressure and $SpO_2$. A decrease in heart rate of >50% or a heart rate of less than 45 beat/min was recorded as bradycardia, and reductions in systolic pressure to less than 90 mmHg were recorded as hypotension. Regarding the evaluation of respiratory depression according to fentanyl, the lowest $SpO_2$ value of each patient was recorded during the epidural procedure. Oxygen was provided if the patient's $SpO_2$ decreased below 94%. A record was also made of the patient's Ramsay score to evaluate sedative properties.

Epidural anesthesia was performed with the patient lying in the left lateral position. Five minutes after the administration of saline or 25 or 50 μg of fentanyl, epidural anesthetic procedures were started in a double-blind fashion by one of three staff anesthesiologists with 8–15 years of clinical experience. To prevent centesis pain, 1 ml of 1% lidocaine was slowly administered subcutaneously over 10 s, and 5 ml of 1% lidocaine was slowly administered in deep tissues for over 60 s for infiltration anesthesia.

A 26-G needle (B. Braun Melsungen AG, Melsungen, Germany) was used for this infiltration anesthesia. The epidural catheter (Perifix® Standard Epidural Catheter, B. Braun Melsungen AG, Melsungen, Germany) was placed between the fifth thoracic and the third lumbar vertebrae via an 18-G Tuohy needle (Perifix® Epidural Needle, B. Braun Melsungen AG, Melsungen, Germany), which was inserted with a median or paramedian approach, after confirming the epidural space using the loss-of-resistance technique. No epidural pilot local anesthetics were administered. If the procedure took >15 min (from the infiltration anesthesia to the catheter placements) or if the Tuohy needle needed to be inserted more than three times, the patient was excluded from the study.

For the quantitative analysis of epidural procedural pain, each patient rated their degree of pain by marking a 100 mm visual analog scale (VAS) line ranging from "no pain = 0" to "unbearable pain = 100." VAS measurements were performed after epidural catheter placement.

The data are presented as the mean ± SD. A three-group comparison was made by ANOVA, and, when any significant difference was observed, the comparison was subjected to a post hoc test by the Bonferroni method. The chi-square statistic was used to compare categorical variables. The level of significance was $P < 0.05$.

Sixty patients aged 24–75 years were included in the present study; there were no intergroup differences in the patient demographic data, including initial vital signs and details regarding the epidural catheter placement (Table 1). Further administration of 1% lidocaine (adding 1–4 ml) for infiltration anesthesia was needed in 4, 3, and 4 patients in the control, F25, and F50 groups, respectively. In all patients, an epidural procedure was completed by one or two needle insertions within 10 min. Ramsay's score in most patients was level 2 (patient cooperative, oriented, and calm [6]); however, level 1 (patient anxious and agitated or restless or both [6]) was observed in one patient in the control group and level 3 (patient responds to commands only [6]) in one patient in the F50 group.

The reported VAS scores (mean ± SD) regarding the procedural pain of the control, F25, and F50 groups were 34.9 ± 20, 19.5 ± 13, and 20.0 ± 15 mm, respectively (Fig. 1a). The VAS scores in the F25 and F50 groups were significantly lower than those of the control group. There was no significant difference in the VAS scores of the F25 and F50 groups.

The lowest $SpO_2$ values during the epidural procedures in the control, F25, and F50 groups were 97.1 ± 1.6, 96.9 ± 1.4, and 95.0 ± 1.9%, respectively. The lowest $SpO_2$ value of the F50 group was significantly lower than those of the other two groups (Fig. 1b). There was no significant difference between the control and the F25 group in the lowest $SpO_2$. Seven patients in the F50 group needed administration of oxygen because of a decreased $SpO_2$ value (<94%). After administration of oxygen, $SpO_2$ recovered to 99 or 100%. No adverse events, such as bradycardia, hypotension, or nausea/vomiting, were observed during the entire study period in all groups.

In this study, intravenous 25 μg of fentanyl had a significant analgesic effect without complications in patients receiving epidural catheter placement. In contrast, 50 μg of

**Table 1** Demographic data, initial vital signs, and details of epidural puncture of patients

| | Control ($n = 20$) | F25 ($n = 20$) | F50 ($n = 20$) | $P$ value |
|---|---|---|---|---|
| Age (year) | 59.8 ± 13 | 58.3 ± 12 | 55.0 ± 13 | 0.484 |
| Weight (kg) | 60.6 ± 13 | 63.1 ± 7 | 59.9 ± 15 | 0.682 |
| Height (cm) | 159 ± 6.6 | 162 ± 9.2 | 158 ± 9.3 | 0.551 |
| Gender (male/female) | 14/6 | 12/8 | 8/12 | 0.149 |
| Initial vital signs (baseline) | | | | |
| Systolic blood pressure (mmHg) | 132 ± 19 | 140 ± 19 | 137 ± 19 | 0.328 |
| Heart rate (beat/min) | 68.3 ± 10 | 73.8 ± 14 | 69.0 ± 13 | 0.334 |
| $SpO_2$ (%) | 98.2 ± 1.1 | 98.1 ± 1.2 | 98.4 ± 0.9 | 0.766 |
| Site of epidural puncture ($n$) | | | | |
| Thoracic/lumbar | 16/4 | 15/5 | 15/5 | 0.911 |
| Approach to the epidural space ($n$) | | | | |
| Median/paramedian | 9/11 | 10/10 | 10/10 | 0.935 |
| Depth of loss of resistance (cm) | 4.98 ± 1.1 | 4.93 ± 0.8 | 4.95 ± 0.8 | 0.979 |
| Catheter in the epidural space (cm) | 4.25 ± 0.4 | 4.43 ± 0.4 | 4.33 ± 0.4 | 0.516 |
| Volume of 1% lidocaine (ml) | 6.70 ± 1.5 | 6.28 ± 0.9 | 6.65 ± 1.3 | 0.380 |

Continuous data are presented as mean ± SD

$n$, number of patients

fentanyl had a significant respiratory depressant effect; however, its analgesic effect was the same as that of 25 μg of fentanyl.

Although both 25 and 50 μg fentanyl were able to reduce procedural pain in this study, Oda et al. [3] reported that intravenous 50 μg of fentanyl did not affect the VAS score (mean value in control 27.7 mm, fentanyl 28.9 mm) in patients with an epidural puncture. Vadalouca et al. reported that 40 mg of parecoxib (a nonsteroidal anti-inflammatory drug) administered intravenously reduced the VAS score in an epidural procedure (control 62.4 mm, parecoxib 37.1 mm); however, the VAS value of the control group in their study seemed higher than that obtained in this study [5]. The differences between this and previous studies might be caused by the difference in the preanesthetic medication. In the two previous studies, no preanesthetic medication was used. Since fentanyl may act synergistically on other sedatives [7], it was considered that 0.25 mg of oral brotizolam might affect a patient's pain sensation. In addition, it is possible that the epidural procedural pain might have been influenced by the use of the infiltration anesthetic technique, especially regarding the injection pressure [8]. In this study, the speed of the injection of the local anesthetics was controlled to average that of the initial invasive procedure; however, the techniques used for infiltration anesthesia were not described in previous studies. Differences in the VAS values in each control group among this and previous reports may support our speculations above.

In volunteers and patients, the range of the plasma fentanyl concentration providing analgesia without clinically significant respiratory depression is 0.6–2 ng/ml [9, 10]. According to the pharmacokinetics calculation (TIVA Trainer Version 8, Frank Engbers, Leiden, The Netherlands), a bolus of 25 and 50 μg of fentanyl administered intravenously may retain its steady plasma concentration at 0.4 and 0.9 ng/ml for more than 10 min in a patient with an average physique in the F25 and F50 groups, respectively [11]. In a previous study, 10% of the patients who received 50 μg of fentanyl intravenously required the administration of oxygen because of a decreased $SpO_2$ value (<90%) [3]. These findings indicated that 50 μg of fentanyl may frequently cause a hypoxemic event in a patient receiving an epidural catheter placement.

Although safe epidural insertions in an anesthetized patient have been reported previously [12], there is an important limitation; namely, that epidurals should be placed in awake or mildly sedated patients capable of providing feedback to the individual placing the block, in order to avoid any neurologic injury related to epidural anesthesia [13, 14]. The sedative levels of patients in the F25 group were sufficient for them to be able to provide feedback when they perceived irradiation pain during the epidural procedure. Severe complications were not observed in any of the study patients. Moreover, no patients required oxygen in the F25 group; 25 μg of fentanyl administered intravenously may be adequately safe as an analgesic agent for pain reduction during an epidural procedure. However, Ueta et al. [15] reported that 23 adult patients (53%) undergoing elective abdominal surgery complained of nausea, sleepiness, dizziness, sensation of

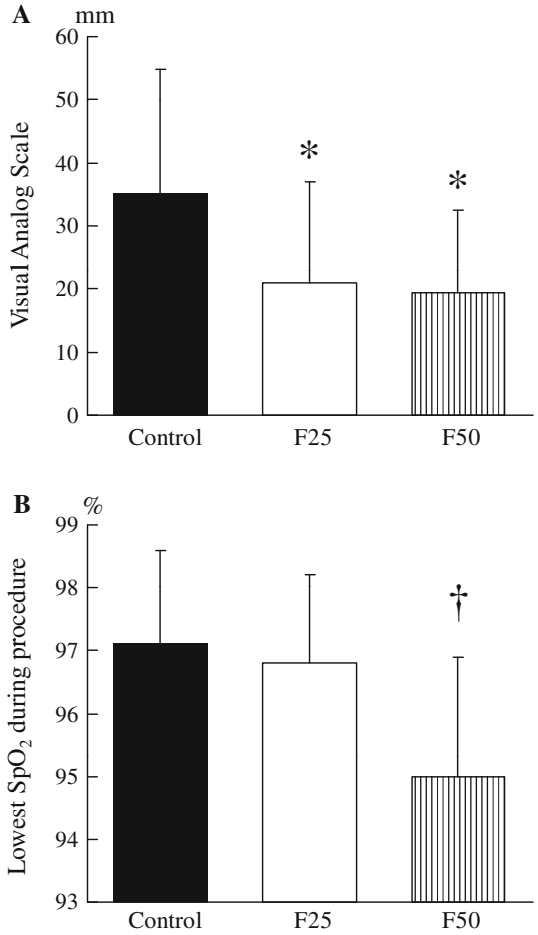


**Fig. 1** Pain scores from the visual analog scale (**a**) and lowest $SpO_2$ values (**b**) in the control, F25, and F50 groups during epidural catheter placement. The pain scores were significantly lower in the F25 and F50 groups than in the control group ($^*P < 0.01$). In contrast, the lowest $SpO_2$ value of the F25 group was the same as that of the control group; however, the F50 group had a significantly lower value than the control and F25 groups ($^\dagger P < 0.001$)

warmth, and other symptoms after intravenous administration of 50 μg of fentanyl immediately before induction of general anesthesia. The possibility of the occurrence of complications should be a concern after fentanyl administration even when the concentration is low. Further study focusing on the safety, effectiveness, and demand for analgesia, including the administration of analgesic agents and the innovation of techniques for the anesthetic procedure, is required.

In conclusion, intravenous fentanyl at a dose of 25 μg rather than 50 μg poses less risk of hypoxemia, and has an equivalent analgesic effect, in patients who have received oral brotizolam premedication. Consideration should be given by the anesthesiologist to a patient who fears pain with regard to regional anesthetic procedures in order to safely provide procedural analgesia. For safe and effective analgesia, we recommend the use of a low dose, 25 μg or less, of fentanyl when its use is planned due to a patient's request for analgesia during an epidural procedure.

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