Epidural fentanyl improves the onset and spread of epidural mepivacaine analgesia

Toshiharu Kasaba MD, Gotaro Yoshikawa MD,
Tomoko Seguchi MD, Mayumi Takasaki MD

Purpose: To determine the extent of enhanced blockade by the combined use of epidural fentanyl and mepivacaine. We compared the onset of hypoalgesia, analgesia and the threshold of pressure pain.

Methods: Thirty patients were randomly divided into three groups. The fentanyl group received 10 ml saline containing 0.1 mg fentanyl, mepivacaine group received 10 ml mepivacaine 1% and a mixed group received 10 ml mepivacaine 1% with 0.1 mg fentanyl. All solutions, without epinephrine, were injected through an epidural catheter at T₅₋₆ to T₆₋₇. The change in sensation, loss of pin-prick and pain threshold sensation, measured by pressure algometer, were assessed at 2.5-min intervals for 15 min at the T₄ dermatome. Spread of analgesia was determined at 15 min.

Results: Loss of pinprick was more rapid in the mixed, 11.0 ± 2.7 (SD) min, than in the mepivacaine group, 15.0 ± 2.9 min, ($P < 0.05$), although there was no difference in change of sensation. Pressure pain threshold increased with time in the mepivacaine ($P < 0.05$) and mixed ($P < 0.05$) groups. It was higher in the mixed than in the fentanyl and mepivacaine groups at 5, 7.5 and 10 min ($P < 0.05$). The lower level of analgesia was lower in the mixed than in the mepivacaine groups ($P < 0.05$). Blood pressure was unchanged in the three groups, but heart rate decreased at 7.5, 10, 12.5, and 15 min in the mepivacaine and mixed groups ($P < 0.05$).

Conclusions: The addition of fentanyl to mepivacaine accelerates the onset of analgesia and enhances the analgesic effect of epidural block.

Key words

ANAESTHETIC TECHNIQUE: epidural;
ANAESTHETICS, LOCAL: mepivacaine;
ANALGESICS: fentanyl;

From the Department of Anesthesiology, Miyazaki Medical College, Kiyotake-Cho, Miyazaki, Japan.

Address correspondence to: Dr. T. Kasaba, Department of Anesthesiology, Miyazaki Medical College, Kiyotake-Cho, Miyazaki, 889-16, Japan.

Phone: 81-985-85-2970. Fax: 81-985-85-7179.

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Objectif: Déterminer l'importance de la facilitation du bloc épidural produite par la combinaison du fentanyl et de la mépivacaïne. Ont été comparés le début de l'hypoalgésie, l'analgésie et le seuil de la douleur à la compression.

Méthodes: Trente patients étaient répartis aléatoirement entre trois groupes. Le groupe fentanyl recevait 10 ml de sol.phys. contenant fentanyl 0,1 mg, le groupe mépivacaïne recevait mépivacaïne 1% 10 ml et un groupe mixte recevait mépivacaïne 1% 10 ml avec fentanyl 0,1 mg. Toutes ces solutions non adrénalinées étaient injectées par un cathéter épidural situé entre T₅₋₆ et T₆₋₇. Le changement de sensation, la perte de sensation à la piqûre et le seuil douloureux, mesurés par un algomètre à pression étaient évalués à des intervalles de 2-5 min pendant 15 min au dermatome T₄. Le niveau de l'analgésie était déterminé à la 15^e min.

Résultats: La perte de la sensation à la piqûre survenait plus rapidement dans le groupe mixte, 11,0 ± 2,7 (ET) min, que dans le groupe mépivacaïne, 15 ± 2,9 min, ($P < 0,05$), bien qu'aucune différence n'était notée sur le changement de sensation. Le seuil de la douleur à la compression augmentait avec le temps pour les groupes mépivacaïne ($P < 0,05$) et mixte ($P < 0,05$). Il était plus élevé dans le groupe mixte que dans le groupe fentanyl et mépivacaïne à 5, 7,5 et 10 min ($P < 0,05$). Le niveau inférieur d'analgésie était plus bas dans le groupe mixte que les groupes mépivacaïne ($P < 0,05$). La pression artérielle était inchangée dans les trois groupes mais la fréquence cardiaque diminuait à 7, 5, 10, 12,5 et 15 min dans les groupes mépivacaïne et mixte ($P < 0,05$).

Conclusion: L'addition de fentanyl à la mépivacaïne accélère le début de l'analgésie et renforce l'effet analgésique du bloc épidural.

The use of epidural opioids for pain relief is well established.^{1,2} The combination of epidural bupivacaine and fentanyl is used widely for Caesarean section to improve the quality of perioperative analgesia.³⁻⁹ However, the onset time of analgesia in their reports was not affected by the addition of fentanyl to bupivacaine. The combination of other local anaesthetics such as mepivacaine, which is commonly used in our hospital, has not been clearly investigated. Boidin *et al.*¹⁰

reported that epidural fentanyl enhanced the quality of epidural blockade when combined with mepivacaine but the onset time of sensory analgesia was no different. Previously, Koganemaru *et al.*¹¹ reported that the combined use of fentanyl and mepivacaine in the epidural space produced a rapid onset and wide spread of analgesia. To examine more clearly whether epidural fentanyl with mepivacaine enhanced the onset of analgesia, we compared not only analgesia but also hypoalgesia and threshold of pressure pain.

This study was designed to investigate the analgesic interaction of a mixture of fentanyl and mepivacaine, compared with the analgesia produced by fentanyl or mepivacaine alone. The purpose of this study was to determine whether the addition of fentanyl to mepivacaine accelerated the onset of hypoalgesia and analgesia as assessed by pin-prick or increased the threshold of pressure pain.

Methods

The study was approved by the human research review committee of our institute, and informed consent was obtained from each patient. Thirty patients, ASA I or II, undergoing lobectomy or mastectomy were studied. They were randomly divided into three groups: a fentanyl group received 10 ml saline solution containing 0.1 mg fentanyl; a mepivacaine group received 10 ml mepivacaine 1%; a mixture group received 10 ml mepivacaine 1% with 0.1 mg fentanyl. All solutions administered in the epidural space contained no epinephrine. Demographic details are shown in Table I.

All patients received premedication with 0.5 mg benzodiazepine *po* 1.5 hr before induction of anaesthesia. With patients in the lateral decubitus position and after 2–3 ml lidocaine 1% for local anaesthesia, the epidural space was identified by loss of resistance to saline using a 17-gauge Tuohy needle at the T₅₋₆ or T₆₋₇ interspace. An epidural catheter was inserted 3 cm cephalad and the patient was turned supine. A test dose was not used. Each solution was injected epidurally over one minute.

The onset of cutaneous hypoalgesia and analgesia were observed at 2.5-min intervals using pin-prick at the mid-thoracic region at the T₄ dermatome. Fifteen minutes after the initial injection of opioid and/or local anaesthetic, the spread of analgesia was determined by pin-prick. Latency of onset was defined as the time between the extradural injection and the appearance of hypoalgesia or analgesia. Hypoalgesia was assessed subjectively by the patient as a decrease in pain to pin-prick, compared with pain produced by pin-prick at the shoulder as a reference. Analgesia was assessed as the loss of pain sensation by pin-prick. The threshold of

pressure pain was determined at 2.5-min intervals using a spring pressure algometer (Attukei, Igarashi-ika-kogyo, Tokyo, Japan) with a 50 mm² circular probe on the sternum at the T₄ dermatome. The loading rate was set at 0.5 kg·sec⁻¹ and the cut-off level at 6 kg. Systolic and diastolic blood pressures were measured by oscillometer at 2.5-min intervals, and heart rate was measured from the ECG. The haemodynamic data and haemoglobin oxygen saturation were displayed on a Nihon-koden BSM-8500 monitor (Nihon-koden, Tokyo, Japan) and recorded on a recorder (Nihon-koden, Tokyo, Japan). Side effects, such as respiratory depression, itching, nausea and vomiting were assessed. Oxygen was administered when haemoglobin oxygen saturation decreased <93%. The pH of each solution was determined with a pH-meter (accumet model 15, Fisher Scientific, USA).

After the studies, anaesthesia was induced in all patients with thiopentone (5 mg·kg⁻¹) and maintained with epidural block and nitrous oxide, oxygen and a low concentration of sevoflurane. Muscle relaxation was produced with vecuronium (0.15 mg·kg⁻¹) that facilitated tracheal intubation. The data were expressed as mean ± SD or median (range) (the level of analgesia). Groups were analyzed using analysis of variance (ANOVA) or chi squared analysis. Anaesthetic characteristics between mepivacaine group and mixture group were analyzed using the Mann-Whitney U test. Changes in the pressure pain were compared using the Kruskal-Wallis test. Changes in the haemodynamic values were compared using repeated-measures analysis of variance and post hoc Fisher's procedure for multiple comparisons. Analyses were performed using Stat View (Abacus, Berkeley, CA). *P* < 0.05 was considered statistically significant.

Results

There were no differences in the distributions of sex, age, weight, height and baseline variables among the three groups (Table I). The pH of the solution used in the fentanyl group (5.1 ± 0.04) was lower than that in the mepivacaine (6.34 ± 0.05) or mixture group (6.33 ± 0.04) (*P* < 0.05).

Anaesthetic characteristics after epidural injection of fentanyl, mepivacaine or the mixture are shown in Table II. No hypoalgesia and analgesia was induced in the fentanyl group. The onset of analgesia was more rapid in the mixture than in the mepivacaine group (*P* < 0.05). The lower levels of analgesia were different between the mepivacaine and mixture groups (*P* < 0.05).

The threshold of pressure pain (1.2 ± 0.4 kg in the fentanyl group, 1.6 ± 0.8 kg in the mepivacaine group, 1.5 ± 0.6 kg in the mixture group) increased at 10 ($3.1 \pm$

TABLE I Demographic details in three groups (mean $\pm$ SD)

	Fentanyl (n = 10)	Mepivacaine (n = 10)	Mixture (n = 10)
Sex - M:F	6:4	6:4	8:2
Age - yr	59 $\pm$ 17	55 $\pm$ 11	64 $\pm$ 13
Weight - kg	53 $\pm$ 9	55 $\pm$ 6	58 $\pm$ 7
Height - cm	157 $\pm$ 9	157 $\pm$ 6	161 $\pm$ 11
BP - mmHg	132/69 $\pm$ 21/12	124/65 $\pm$ 12/9	134/74 $\pm$ 21/12
HR - mmHg	78 $\pm$ 12	80 $\pm$ 12	81 $\pm$ 9

No significant differences among groups.

TABLE II Anaesthetic characteristics after fentanyl, mepivacaine or mixture

	Fentanyl (n = 10)	Mepivacaine (n = 10)	Mixture (n = 10)
Hypoalgesia - min	-	8.8 $\pm$ 4.0	7.0 $\pm$ 2.0
Analgesia - min	-	15.0 $\pm$ 2.9	11.0 $\pm$ 2.7*
Upper level analgesia	-	T ₃ (T ₁ -T ₄)	T ₃ (T ₂ -T ₃)
Lower level analgesia	-	T ₁₀ (T ₇ -T ₁₂)	T ₁₂ (T ₁₀ -L ₅)*

Values mean $\pm$ SD or median (range).

* $P < 0.05$ vs mepivacaine group.

1.9 kg), 12.5 (4.4 $\pm$ 1.9 kg) and 15 (5.1 $\pm$ 1.2 kg) min in the mepivacaine group ($P < 0.05$) and at 5 (3.1 $\pm$ 0.8 kg), 7.5 (4.2 $\pm$ 1.5 kg), 10 (5.1 $\pm$ 1.3 kg), 12.5 (5.8 $\pm$ 0.1 kg), and 15 (6.0 $\pm$ 0.0 kg) min in the mixture group ($P < 0.05$), but remained unchanged in the fentanyl group (Figure 1). The threshold was higher in the mixture group than in the fentanyl and mepivacaine groups at 5, 7.5, and 10 min ($P < 0.05$). At 12.5 and 15 min, the threshold was higher in the mepivacaine and mixture groups than in the fentanyl group ($P < 0.05$), but no difference was found between the mepivacaine and mixture groups.

No changes in systolic and diastolic blood pressures were observed in the three groups (Figure 2). The heart rate decreased at 7.5 (70 $\pm$ 12, 74 $\pm$ 12 $\cdot$ min⁻¹), 10 (68 $\pm$ 12, 73 $\pm$ 12 $\cdot$ min⁻¹), 12.5 (68 $\pm$ 12, 72 $\pm$ 12 $\cdot$ min⁻¹), and 15 (69 $\pm$ 12, 68 $\pm$ 12 $\cdot$ min⁻¹) min in the mepivacaine and mixture groups ($P < 0.05$), respectively, but remained unchanged in the fentanyl group. There was no difference in heart rate between the mepivacaine and mixture groups. Additional low flows of oxygen were administered in three patients in the mixture group during the study, because haemoglobin oxygen saturation decreased $<93\%$. Itching was seen in one patient in the fentanyl group; other side effects, such as nausea and vomiting were not seen.

Discussion

This study demonstrated that the addition of 0.1 mg

FIGURE 1 Changes in pressure threshold (mean $\pm$ SD). Empty square = fentanyl group, empty circle = mepivacaine group, and filled circle = mixture group. * $P < 0.05$ vs baseline values; † $P < 0.05$ vs fentanyl group; ‡ $P < 0.05$ vs mepivacaine group.

FIGURE 2 Haemodynamic changes (mean $\pm$ SD). (upper figure) changes of systolic and diastolic BP, (lower figure) change of HR. Empty square = fentanyl group, empty circle = mepivacaine group, and filled circle = mixture group. * $P < 0.05$ vs baseline values.

fentanyl to mepivacaine 1% accelerated the onset of analgesia and increased the threshold of pressure pain during epidural analgesia without any haemodynamic changes.

Koganemaru *et al.*¹¹ also demonstrated that fentanyl accelerated the onset of analgesia by about four minutes compared with mepivacaine alone. They used mepivacaine 2% with 0.1 mg fentanyl and measured the onset time at one-minute intervals. However, Boidin *et al.*¹⁰ could not demonstrate the acceleration of the onset of analgesia by the addition of fentanyl. They used mepi-

vacaine 2% with 0.05 mg fentanyl and measured the onset time every five minutes. One reason for the difference may be the interval between measurements. Although we could not demonstrate acceleration of the onset of hypoalgesia, testing at one-minute intervals may have detected a difference. The dose ratio between mepivacaine and fentanyl may be another important reason for acceleration of the onset of analgesia. Boidin *et al.*¹⁰ used a ratio of 1 mg: 0.25 µg, while Koganemaru *et al.*¹¹ used a ratio of 1 mg: 0.33 µg for mepivacaine and fentanyl. Although the optimum dose ratio of local anaesthetics and opioids has not been determined, we used a ratio of 1 mg: 1 µg. The dose ratio of epidural bupivacaine and fentanyl reported previously was 1 mg: 4 µg by Cooper and Turner¹² and 1 mg: 5 µg by George *et al.*¹³ Considering the potency ratio of bupivacaine and mepivacaine (4:1), the dose ratio of epidural mepivacaine and fentanyl in our study may be suitable.

In this study, pressure pain threshold increased rapidly in the mixture group although it remained unchanged in the fentanyl group. Many sensory components such as touch, pressure and pain are stimulated by a pressure algometer. Epidural opioids act on receptors in the spinal cord and block pain pathways selectively.^{14,15} Opioids inhibit neuronal activity in the dorsal horn evoked by C fibres more strongly than that evoked by Aδ fibres, whereas neuronal activity evoked by Aβ fibres is unaltered.^{16,17} Touch and pressure stimuli are conducted through Aβ fibres which inhibit A and C fibres.¹⁸ Local anaesthetics easily block Aδ and C fibres, which conduct pain sensation, but at this time Aβ fibres remain unblocked. The rapid onset of analgesia and increase of pressure pain threshold observed in this study is, therefore, likely the results from inhibitory effect of Aβ fibres to Aδ and C fibres.

Alkalinization of local anaesthetic solutions has been shown to produce a more rapid onset and improved quality of sensory and motor blocks although clinical studies with alkalinized local anaesthetic solutions have produced controversial results.¹⁹ In this study addition of fentanyl to mepivacaine did not change the pH of the mepivacaine solution. Therefore, enhancement of analgesic efficacy is probably due to the analgesic effect of fentanyl.

We did not use test doses because the test dose itself blocks the sensory nerve at the T₄ dermatome which affects the onset of analgesia and pressure pain. In this study, no changes in systolic or diastolic blood pressures were observed in the three groups, although the heart rate decreased in the mepivacaine and mixture groups. The haemodynamic changes following epidural mepivacaine and fentanyl were similar to those following mepi-

vacaine alone. Thus, the addition of fentanyl to local anaesthetics would not affect haemodynamics during epidural anaesthesia.

In conclusion, the addition of 0.1 mg fentanyl to mepivacaine 1% accelerated the onset of analgesia and increased pressure pain threshold during epidural analgesia. Epidural injection of a mixture of local anaesthetic and fentanyl may be advantageous in clinical practice, when a rapid onset of epidural analgesia is required.

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