Addition of Fentanyl to Bupivacaine Prolongs Anesthesia and Analgesia in Axillary Brachial Plexus Block

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Background and Objectives: To evaluate the analgesic and anesthetic effects of 40 mL bupivacaine 0.25%, 40 mL bupivacaine 0.25% plus fentanyl 2.5 μg/mL, and 40 mL bupivacaine 0.125% plus fentanyl 2.5 μg/mL for axillary brachial plexus block.

Methods: Sixty patients were randomly allocated to 3 groups and received axillary brachial plexus block with 40 mL bupivacaine 0.25% (group B), 40 mL bupivacaine 0.25% with fentanyl 2.5 μg/mL (group BF), or 40 mL bupivacaine 0.125% with fentanyl 2.5 μg/mL (group DBF). The onset times and the duration of sensory and motor blocks, duration of analgesia, hemodynamic parameters, and adverse events were noted.

Results: The mean duration of sensory block and analgesia were longer in group BF (10.1 hours and 20.9 hours) than group B (6.9 hours and 11.6 hours) and DBF (5.9 hours and 12.0 hours) ($P < .01$, $P < .001$, respectively). The mean duration of motor block was also longer in group BF (10.7 hours) than group B (4.9 hours) ($P < .01$). Only 2 patients experienced motor block in group DBF. The frequency of successful block was 35% in group DBF ($P < .01$). Hemodynamic parameters were similar in all groups. In group B, only 1 patient experienced dizziness. Nausea was observed in 1 patient in each fentanyl group.

Conclusion: The addition of 100 μg/mL fentanyl to 0.25% bupivacaine almost doubles the duration of analgesia following axillary brachial plexus block when compared with 0.25% bupivacaine alone. *Reg Anesth Pain Med 2001;26:434-438.*

Key Words: Axillary brachial plexus block, Opioid, Fentanyl, Local anesthetic, Bupivacaine.

Since the demonstration of opioid receptors in the peripheral nervous system,[1] the use of opioids alone or in combination with local anesthetics for peripheral nerve blocks has aroused interest. However, the results of investigations about combinations of opioids with local anesthetics remain controversial. Opioid receptors have been discovered on immune cells and peripheral neurons in animals.[2,3] Several studies have shown that the addition of opioids to local anesthetics in peripheral nerve blocks improved analgesia,[4-6] whereas others have not demonstrated improvement.[7,8]

It has been suggested that peripheral administration of opioids improves analgesia and reduces systemic side effects and total dose of local anesthetic required. The aim of our study was to evaluate the effect of fentanyl addition to bupivacaine 0.25% or 0.125% in axillary brachial plexus block on the quality, onset, and duration of block for elective upper extremity surgery.

Methods

After institutional ethics committee approval and written, informed consent, 60 patients, aged 18 to 60 years, weighing 50 to 100 kg, American Society of Anesthesiologists (ASA) I and II, undergoing elective surgery of the hand, forearm, or elbow under axillary brachial plexus block were enrolled in the study. Patients with a history of cardiac, respiratory, hepatic and/or renal failure, coagulopathy, local infection, and any reaction to local anesthetics were excluded.

Patients were not premedicated before the block. A 20-gauge intravenous cannula was inserted into the contralateral arm. Routine monitoring consisted of electrocardiogram, noninvasive measurement of arterial blood pressure, peripheral oxygen

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saturation, and respiratory rate monitoring. Axillary block was performed in the supine position with the upper arm abducted 90° and the elbow flexed at 110°. After shaving and draping the axilla with sterilized drapes, the axillary artery was fixed against the patient's humerus by 2 fingers of the anesthetist's left hand in the proximal part of the axilla. A nerve stimulator (StimuplexDig; Braun, Melsungen, Germany) and a 22-gauge insulated short beveled needle with extension tubing (StimuplexDig; Braun) were used to identify the brachial plexus. The needle was advanced towards the upper border of axillary artery until the axillary sheath was entered as evidenced by a click. Once the needle was placed subcutaneously, the nerve stimulator was set to deliver impulses of 2 Hz frequency and 2 mA intensity. When flexion of hand and wrist was observed in response to stimuli, the output of the nerve stimulator was reduced to 1 mA and then 0.5 mA. If muscle contractions persisted, 2 mL of local anesthetic solution was injected. If no motor response returned, and after aspiration to exclude intravascular placement, 40 mL local anesthetic solution was injected. If the motor response was not abolished in a few seconds, the needle was readvanced to again localize the brachial plexus for 2 more times using the same technique. All axillary blocks were performed by the same anesthetist.

Patients were randomly assigned to receive either 40 mL of bupivacaine 0.25% (group B, n = 20), 40 mL of bupivacaine 0.25% with fentanyl 2.5 μg/mL (group BF, n = 20), or 40 mL bupivacaine 0.125% with 2.5 μg/mL (group DBF, n = 20) in a randomized, double-blinded fashion. When the injection was completed, the arm was adducted and distal pressure was applied to prevent the distal flow of the local anesthetic solution. All blocks were performed by one of the authors, who was unaware of the injected solution, and another observer unaware of group performed assessment of the axillary block.

Both sensory and motor components of the block were assessed every 5 minutes for 30 minutes and thereafter on arrival in the postoperative care unit and on discharge from the hospital. The onset time of the sensory block, defined as the time between injection and the complete ablation of the pinprick test (normal, impaired, or absent sensation), was evaluated in median, ulnar, radial, and musculocutaneus nerves in both the arm and the forearm. Motor block was evaluated by using hand grip with a modified Bromage scale: normal, impaired, or absent motor function.[8,9] Duration of sensory block was defined as the time from complete block to return of the paresthesia. Motor block duration time was defined as the time of complete motor block to the restoration of full hand and wrist mobility. Patients were questioned about duration of analgesia (time from axillary block to the onset of pain; i.e., Visual Analogue Scale [VAS] $\geq$ 4) every hour for the first 2 hours, and thereafter every 4 hours for the rest of the study. Thirty minutes after local anesthetic injection, patients were permitted to be prepared for surgery and approximately 45 minutes after the axillary block, surgery was begun.

If the block was inadequate for surgery, additional local anesthetic infiltration was performed with 1% prilocaine. Successful block was declared if additional local anesthetic (1% prilocaine) infiltration was not needed. If the patient experienced discomfort during the operation, fentanyl 1 μg/kg and/or midazolam 0.05 mg/kg was given. General anesthesia was planned when these treatment modalities failed, and these patients were excluded from the study.

Heart rate, peripheral oxygen saturation, respiratory rate, and blood pressure were measured before the axillary block and 5, 10, 20, 30, 45, and 60 minutes after the axillary block and thereafter every 60 minutes for 2 hours postoperatively. Additional adverse events (bradycardia, dizziness, nausea and vomiting, and sedation) were recorded.

Descriptive variables were analyzed using Mann-Whitney U test and χ^2 test as appropriate. Sedation levels were analyzed using the χ^2 test. A P value less than .05 was considered to be statistically significant. Values are expressed as mean ± SEM.

Results

There was no significant difference between groups in age, weight, or sex (Table 1). Duration of surgery in group DBF was significantly shorter than the other groups ($P < .001$). The distrubition of the surgical types among groups are shown in Table 2, and there was no difference in the number of hand, forearm, or elbow surgery in groups.

Onset times of sensory and motor block were

Table 1. Patient Characteristics

	Group B (n = 20)	Group BF (n = 20)	Group DBF (n = 20)
Age (yr)	41.5 ± 3.8	38.7 ± 2.5	47.8 ± 2.6
Weight (kg)	69.3 ± 2.8	71.3 ± 2.6	73.0 ± 3.3
Sex (M/F)	9/11	10/10	9/11
Duration of surgery (min)	73.4 ± 10.0	64.1 ± 13.3	34.4 ± 4.0*
Onset of surgery	44.6 ± 1.5	42.6 ± 1.8	41.1 ± 1.4

NOTE. Values are expressed as mean ± SD. Group B, axillary bupivacaine 0.25%; group BF, axillary bupivacaine 0.25% plus 2.5 μg/mL fentanyl; group DBF, axillary bupivacaine 0.125% plus 2.5 μg/mL fentanyl.

*$P < .01$ compared with groups B or BF.

Table 2. Types of Surgery

	Group B (n = 20)	Group BF (n = 20)	Group DBF (n = 20)
Tendon transfers or repair	10	9	9
Internal fixation	8	5	6
Hardwire removal	1	3	3
Contracture releasing	1	3	2

NOTE. Group B, axillary bupivacaine 0.25%; group BF, axillary bupivacaine 0.25% plus 2.5 μg/mL fentanyl; group DBF, axillary bupivacaine 0.125% plus 2.5 μg/mL fentanyl.

similar in all groups (Table 3). The duration of sensory block and analgesia were longer in group BF than the other groups ($P < .01$, $P < .001$, respectively) (Table 3). In the DBF group, only 2 patients (10%) experienced motor block, and duration of motor block was not assessed in group DBF. Complete motor block was achieved 50% in both groups B and BF, and the incidence of complete motor block in groups B and BF was higher than group DBF ($P < .05$). The duration of motor block in group BF was significantly longer than group B ($P < .01$). The success rate of each nerve trunk is shown in Table 4.

The incidence of successful block was lower in group DBF (35%) than group B (85%) and group BF (95%) ($P < .01$). The use of additional fentanyl or midazolam during operation was similar in all groups. Five patients in both groups B and BF required a single fentanyl dose. Two patients in group DBF required both single fentanyl and midazolam doses. General anesthesia was not needed in any patient in any group.

There were no significant differences between groups in hemodynamic variables, peripheral oxygen saturations, or respiratory rate.

Table 3. Onset and Duration of Anesthesia and Analgesia After Axillary Block

	Group B (n = 20)	Group BF (n = 20)	Group DBF (n = 20)
Onset of sensory block (min)	23.8 ± 1.8	27.3 ± 1.6	27.3 ± 2.7
Onset of motor block (min)	22.9 ± 1.7	25.1 ± 1.8	26.1 ± 2.7
Duration of sensory block (h)	6.9 ± 0.2	10.1 ± 0.7*	5.9 ± 1.4
Duration of motor block (h)	4.9 ± 0.6	10.7 ± 1.8†	—
Duration of analgesia (h)	11.6 ± 0.4	20.9 ± 0.4‡	12.0 ± 0.5

NOTE. Values are expressed as mean ± SD. Group B, axillary bupivacaine 0.25%; group BF, axillary bupivacaine 0.25% plus 2.5 μg/mL fentanyl; group DBF, axillary bupivacaine 0.125% plus 2.5 μg/mL fentanyl.
*$P < .01$ compared with groups B or DBF.
†$P < .01$ compared with group B.
‡$P < .001$ compared with groups B or DBF.

Table 4. Success Rate for Each Nerve Trunk

	Group B (n = 20)	Group BF (n = 20)	Group DBF (n = 20)
Median nerve	17/20	19/20	7/20
Ulnar nerve	17/20	19/20	7/20
Radial nerve	16/20	18/20	6/20*
Musculocutaneous nerve	12/20	13/20	3/20*

NOTE. Values are number of patients (%). Group B, axillary bupivacaine 0.25%; group BF, axillary bupivacaine 0.25% plus 2.5 μg/mL fentanyl; group DBF, axillary bupivacaine 0.125% plus 2.5 μg/mL fentanyl.
*$P < .05$ compared with groups B or BF.

One patient in group B experienced dizziness, and 1 patient in each fentanyl group developed mild nausea. Sedation was not observed in any group.

Discussion

The results of our study suggest that the addition of fentanyl 2.5 μg/mL to bupivacaine 0.25% for axillary brachial plexus block prolongs the duration of anesthesia and analgesia without increased side effects, whereas fentanyl 2.5 μg/mL with bupivacaine 0.125% did not provide any additional effect. Moreover, the combination of fentanyl 2.5 μg/mL and bupivacaine 0.125% resulted in more unsuccessful blocks, and required more local anesthetic supplementation.

In order to limit side effects, as well as the intensity of motor block, dilute local anesthetic solutions are often used, but the quality and duration of the analgesia obtained may be insufficient for surgery. Therefore, opioids are added to local anesthetics to improve anesthesia and prolong analgesia. In a previous study, it was shown that very dilute solutions of local anesthetic combined with fentanyl produced results comparable to a more concentrated solution of the same local anesthetic solution with minimal motor block during labor.[10] In our study, 2.5 μg/mL fentanyl and 0.125% bupivacaine, the success rate of block was diminished, and more additional local anesthetic infiltration was required.

There has been increasing interest in the combination of local anesthetics and opioids to improve the quality and duration of nerve blocks. It was noted that the onset is more rapid and anesthesia more complete and more prolonged when fentanyl is added to bupivacaine solutions for regional anesthesia.[11] Some receptors mediate nociception on peripheral sensory axons, and the peripheral administration of opioids has analgesic effects. The mechanisms of the analgesic effects of these drugs are unclear. Opioids may directly act on the nerves with local anesthetic action and/or synergistic ef-

fects with injected local anesthetics. Previous experimental electrophysiologic studies have also suggested that opioids might exert a nonspecific action by impairing sodium and potassium conductions or an increase in calcium conduction in the nerve fibers.[12,13] When injected near neurovascular sheaths, opioids may cause systemic effects by absorption to systemic circulation.[14] Furthermore, when opioids are perineurally injected, they are carried by opioid binding proteins to the dorsal horn neurons and may exert central effects.[15]

There are conflicting results in clinical studies concerning the benefit of opioids and local anesthetics for peripheral nerve blocks. Fletcher et al[16] showed no clinical benefit adding 100 μg of fentanyl to 1.5% lidocaine with 1:200,000 epinephrine for axillary brachial plexus block, although a faster onset time of anesthesia was noted. Similarly, Flory et al[7] demonstrated no improvement in quality of analgesia after 5 mg of morphine was added to 0.5% bupivacaine 40 mL for supraclavicular block. Although interscalene brachial plexus block may take 30 minutes to be fully established, in the latter study, all patients underwent general anesthesia 15 minutes after the block, and assessing the efficacy of the block is difficult during the intraoperative period. In another study, supraclavicular block with fentanyl 75 μg added to mepivacaine 1.5% and epinephrine 5 μg/mL was shown to have no clinical benefit when compared with a systemic fentanyl group.[17] Interestingly, Gormley et al[8] claimed that alfentanil added to lidocaine with epinephrine has no postoperative analgesic effect; yet they also reported that duration of the sensory and motor functions were significantly prolonged in the alfentanil group. Bazin et al[5] found that the addition of morphine 75 μg/kg, buprenorphine 3 μg/kg, or sufentanil 0.2 μg/kg to 2 mg/kg of lidocaine 1% and 1 mg/kg of bupivacaine 0.5% mixture with 1:200,000 epinephrine lengthened the duration of analgesia. Nishikawa et al[18] suggested that the addition of fentanyl to lidocaine for axillary brachial plexus block delayed onset of analgesia, but the success rate of block was improved.

A systematic review of analgesic adjunts for brachial plexus block demonstrated that evidence regarding the analgesic effects of opioid adjunts remains equivocal, and more evidence is required before recommending use.[14] Similar to these studies, our results showed that fentanyl 2.5 μg/mL with bupivacaine 0.25% provided more prolonged and effective analgesia than the bupivacaine alone. The lack of a systemic fentanyl group can be taken as a weakness of our study. However, Gormley et al[8] have shown that opioid injection near the neurovascular sheath provided insufficient plasma concentration to produce systemic effects.

The reason for such varied results may be that certain opioids are not able to penetrate layers of axonal myelin. It is also possible that the prepared local anesthetic and opioid solutions (sometimes with epinephrine) may alter the quality and onset of block by changes in pH of the solution. It is known that pH of the local anesthetic solution plays an important role in the onset of anesthesia. Our results showed that the addition of fentanyl to bupivacaine caused no significant clinical difference on the onset of sensory or motor block in axillary block, but duration of analgesia lasted twice that produced by bupivacaine alone. Sensory and motor block were also prolonged with fentanyl and bupivacaine combination. These results suggest that the prolongation in sensory and motor block may be the result of the local anesthetic action of fentanyl affecting both sensory and motor neurons in the axillary sheath.

Different study designs, the use of different local anesthetics or opioids (high or low lipid solubility), the different site of the block (axillary, supraclavicular, interscalene), addition or ommission of epinephrine to the block solution, and the pH differences of the combined solutions may be other reasons for such varied results. Another major problem concerns the lack of dose response studies for these peripheral opioid trials. Considering that the majority of studies have found no improvement by combining an opioid and local anesthetic in peripheral nerve blocks, it is remarkable that our study shows the most significant results ever published. This may be caused either by the fortuitous doses used, the agents chosen, or both. Although fentanyl and bupivacaine have not previously been reported for axillary brachial plexus block, the most remarkable methodologic difference of our study is that in order to avoid any possible peripheral analgesic effects, we have chosen to use the local anesthetic at the minimum effective concentration. This is in sharp contrast with other and mostly contradictory studies in which the local anesthetic concentration used was at the higher end of the effective concentration range. In previous studies, the concentration of the local anesthetic agent used in opioid was 0.5% for bupivacaine,[5,7] 1.5% for lidocaine,[8,16,18] and 1.5% for mepivacaine.[17] The recommended minimum and maximum local anesthetic concentrations are 0.25 to 0.5% bupivacaine, 1% to 2% lidocaine and mepivacaine.[19] These findings suggest that higher local anesthetic concentrations may mask the opioid effect, and choice of the anesthetic concentration may be important in demonstrating synergistic effect.

In conclusion, our study demonstrated prolongation of sensory and motor block with the addition of fentanyl 2.5 μg/mL to bupivacaine 0.25% for axillary brachial plexus block. However, no improvement in the onset of anesthesia was achieved with this admixture. Dilute bupivacaine with fentanyl is not a recommended mixture for axillary brachial plexus block due to the high incidence of unsuccessful block rate.

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