The Addition of Fentanyl to Local Anesthetics Affects the Quality and Duration of Cervical Plexus Block: A Randomized, Controlled Trial

Radomir P. Sindjelic, MD, PhD,* Gordana P. Vlajkovic, MD, PhD,* Lazar B. Davidovic, MD, PhD,† Dejan Z. Markovic, MD,* and Miroslav D. Markovic, MD, PhD†

BACKGROUND: Cervical plexus block is frequently associated with unsatisfactory sensory blockade. In this randomized, double-blind, placebo-controlled trial, we examined whether the addition of fentanyl to local anesthetics improves the quality of cervical plexus block in patients undergoing carotid endarterectomy (CEA).

METHODS: Seventy-seven consecutive adult patients scheduled for elective CEA were randomized to receive either fentanyl 1 mL (50 μg) or saline placebo 1 mL in a mixture of 10 mL bupivacaine 0.5% and 4 mL lidocaine 2% for deep cervical plexus block. Superficial cervical plexus block was performed using a mixture of 10 mL bupivacaine 0.5% and 5 mL lidocaine 2%. Pain was assessed using the verbal rating scale (0–10; 0 = no pain, 10 = worst pain imaginable), and propofol in 20-mg IV bolus doses was given to patients reporting verbal rating scale >3 during the procedure. Rescue medication consumption during surgery and analgesia requirements over the next 24 hours, as well as onset of sensory blockade, were recorded. A P value <0.05 was regarded as statistically significant.

RESULTS: Fewer patients in the fentanyl group (4 of 38, 10.5%) required propofol compared with the placebo group (26 of 39, 66.7%; $P < 0.001$). In comparison with the placebo group, the fentanyl group consumed less propofol (median 0 [0–60] vs 60 [0–160] mg, respectively; $P < 0.001$), required postoperative analgesia less frequently (22 of 38 patients, 57.9% vs 35 of 39 patients, 89.7%, respectively; $P = 0.002$), and requested the first analgesic after surgery later (median 5.8 [1.9–15.6] vs 3.1 [1.0–11.7] hours, respectively; $P < 0.001$), whereas the onset time of sensory blockade was similar in both groups (median 12 [9–18] vs 15 [9–18] minutes, respectively; $P = 0.18$).

CONCLUSIONS: The addition of fentanyl to local anesthetics improved the quality and prolonged the duration of cervical plexus block in patients undergoing CEA. (Anesth Analg 2010;111:234–7)

Cervical plexus block is a widely used anesthetic technique for carotid endarterectomy (CEA), which allows direct monitoring of cerebral function throughout the procedure.[1] However, cervical plexus block often provides a suboptimal level of surgical anesthesia, with >50% of patients requiring IV analgesic supplementation and/or repeated local anesthetic infiltration for pain relief.[2–4]

Since the presence of opioid receptors on primary afferent nerve terminals was described[5] and activity of endogenously released opioid peptides at these sites documented,[6] substantial efforts have been made to confirm peripheral analgesic action of exogenous opioids applied perineurally either alone or in combination with local anesthetics. Although opioid-related peripheral antinociception has been reported in vitro,[7,8] the results of both animal and human studies are conflicting. Whereas some authors reported improved analgesia after perineural injection of opioids,[9–12] others failed to demonstrate such an effect.[13–15] One systematic review concluded that evidence regarding the analgesic benefit of perineural opioids was equivocal, and more evidence was required before their routine use could be recommended.[16]

There is little research on the addition of analgesic adjuncts to cervical plexus block, despite a high rate of unsatisfactory sensory blockade for CEA. Although fentanyl has not been approved for perineural application, it is widely used and accepted in clinical practice as an analgesic adjunct to local anesthetics. We hypothesized that the addition of fentanyl to a mixture of local anesthetics would improve the quality of cervical plexus block in patients undergoing CEA.

METHODS

Patient Selection

After obtaining IRB approval and written informed consent, 80 consecutive adult patients, scheduled for elective CEA under cervical plexus block at a single center, were enrolled in the study. Exclusion criteria were refusal of or contraindications to regional anesthesia, age >80 years, body mass index >35 kg/m^2, history of allergy to anesthetics, and the use of opioids within 24 hours before the study. Patients were allocated randomly using a computer-generated table of random numbers to receive deep cervical plexus block with either fentanyl 1 mL (50 μg) or saline placebo 1 mL in a

From the *Institute of Anesthesia and Resuscitation and †Institute of Cardiovascular Diseases, Clinical Center of Serbia, Belgrade University Medical School, Belgrade, Serbia.

Accepted for publication March 26, 2010.

Supported by departmental sources.

Disclosure: The authors report no conflicts of interest.

Reprints will not be available from the author.

Address correspondence to Gordana P. Vlajkovic, MD, PhD, Institute of Anesthesia and Resuscitation, Clinical Center of Serbia, Belgrade University Medical School, Dr. Koste Todorovica 8, 11000 Belgrade, Serbia. Address e-mail to gvlajkov@eunet.rs.

DOI: 10.1213/ANE.0b013e3181e1e9ab

mixture of local anesthetics. The allocation sequence was prepared by an independent researcher and sealed in sequentially numbered, opaque envelopes that were opened before anesthesia. The day before surgery, each patient was instructed on how to report the intensity of pain using the verbal rating scale (VRS) (0–10; 0 = no pain, 10 = worst pain imaginable). The patients were blinded to the treatment group.

Anesthesia Procedures

All patients were premedicated with IM midazolam 0.03 mg/kg and atropine 0.01 mg/kg. A 20-gauge cannula was inserted in the contralateral radial artery for invasive arterial blood pressure measuring and blood gas sampling. Other monitoring included 5-lead electrocardiography (leads II and V5), noninvasive arterial blood pressure, and pulse oximetry. Oxygen at 4 L/min was administered via nasal cannula in all cases.

Deep cervical plexus block was performed by a 3-injection technique at the C2, C3, and C4 levels using a mixture of 10 mL bupivacaine 0.5% and 4 mL lidocaine 2% with the addition of either fentanyl 1 mL or saline placebo 1 mL, according to the randomization code. The sterile study solution was prepared immediately before use by an investigator who did not participate in the study. The superficial block was performed by injecting a mixture of 10 mL bupivacaine 0.5% and 5 mL lidocaine 2% subcutaneously along the posterior border of the sternocleidomastoid muscle in both caudal and cranial directions from the midpoint as well as along the inferior border of the mandible. All cervical plexus blocks were performed by the same anesthesiologist experienced in the technique. An observer who was unaware of the study medication tested sensory block every 3 minutes until 20 minutes after injection. Complete loss of pinprick sensation in the C2 to C4 dermatomes confirmed the onset of block. In case of blockade failure, conversion to general anesthesia followed, and the patient was excluded from further study. A single 2-mL aliquot of lidocaine 2% was applied topically onto the carotid sheath before carotid artery dissection in all patients. An intraluminal shunt was inserted if signs of inadequate cerebral perfusion occurred after carotid cross-clamping.

Observations

Pain was assessed using VRS at the following time points: skin incision (T1), spreading of surgical retractors (T2), carotid sheath dissection (T3), and skin closure (T4). Propofol in 20-mg IV bolus doses was given as a rescue adjuvant to patients reporting VRS score >3 at any time during the procedure. After surgery, the patients were observed for 24 hours and were given either IM ketorolac 30 mg or IM tramadol 50 mg to relieve pain scored >3 on the VRS. The choice of analgesic was left to the discretion of postanesthesia care unit and ward nurses.

The study's primary end point was the quality of anesthesia as measured by the proportion of patients requiring IV rescue medication during surgery. Secondary outcomes were the total amount of rescue adjuvant, the number of patients requiring postoperative analgesia, the time to first request for analgesia after surgery, and the onset of sensory blockade. Heart rate, mean arterial blood pressure, and peripheral oxygen saturation were measured continuously until the end of surgery. The level of sedation before carotid cross-clamping was assessed using the Observer Assessment of Alertness and Sedation score. Blood gas analyses were obtained at time points cited above. Episodes of bradycardia (heart rate <50 bpm), hypotension (mean arterial blood pressure <70 mm Hg), hypoxemia (oxygen saturation as measured by pulse oximetry <95%), and hypercapnia ($Paco_2$ >6.1 kPa) were noted. All other perioperative adverse events were also recorded.

Table 1. Demographic and Surgical Data for the Fentanyl Group and the Placebo Group

Variable	Fentanyl group (n = 38)	Placebo group (n = 39)
Age, years*	66.2 (63.5–69.0)	65.8 (63.0–68.7)
Gender, M/F†	26/12 (68%/32%)	21/18 (54%/46%)
Weight, kg*	74.4 (71.0–77.9)	73.2 (69.5–76.9)
Duration of surgery, min*	82.4 (76.0–88.8)	87.2 (80.5–93.9)
Carotid cross-clamping time, min*	15.3 (13.3–17.2)	16.5 (14.3–18.8)
Use of shunt, n*	2 (5.3%)	2 (5.1%)

Values are *mean (95% confidence interval) or †number (%).

Statistical Analysis

Statistical analyses were performed with the MedCalc software program (Version 10.4.8.0, ©1993–2009, Frank Schoonjans). Data are presented as mean (95% confidence interval), median (range), and number (%). Between-groups comparisons were made using Student t test, the Mann-Whitney U test, and Fisher exact test, as appropriate. A P value <0.05 was considered statistically significant. On the basis of previous reports, we assumed that approximately 65% of patients would require IV rescue medication during surgery.[2] According to a power analysis, a sample size of 38 patients per group would have a power of 90%, at a significance level of 0.05, to detect a reduction in rescue adjuvant administration from 65% to 30%.

RESULTS

Of the 80 patients recruited, 78 met the inclusion criteria to enter the study. Two patients were excluded, one for refusing to accept regional anesthesia and the other for body mass index >35 kg/m^2. One patient who experienced an intraoperative cerebrovascular accident was withdrawn from further evaluation. Thus, 77 patients remained for analysis, 38 in the fentanyl group and 39 in the placebo group. The 2 groups were comparable ($P > 0.05$) with respect to demographic and surgical characteristics (Table 1).

VRS scores at all times were significantly lower in the fentanyl group than in the placebo group (Fig. 1).

Rescue adjuvant consumption during surgery, as measured by the number of patients receiving propofol and the total amount of propofol given, was lower in the fentanyl group than in the placebo group ($P < 0.001$) (Table 2). The same was true for analgesia requirements over the first 24 hours after surgery. Significantly fewer patients in the

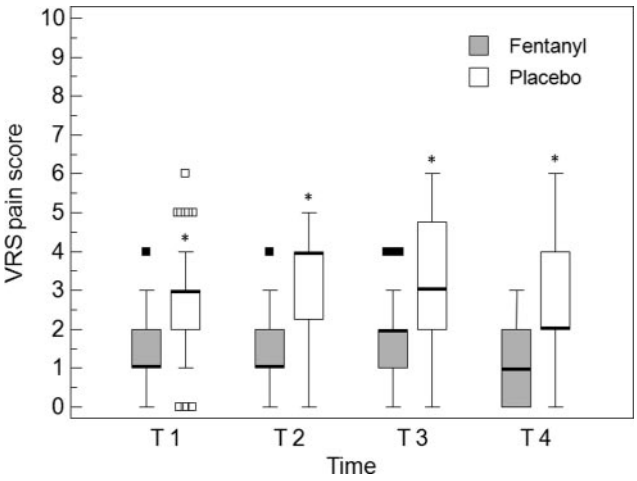

Figure 1. Verbal rating scale (VRS) pain scores at skin incision (T1), spreading of surgical retractors (T2), carotid sheath dissection (T3), and skin closure (T4). Values are shown as median (thick solid line), interquartile range (box plot), 100% of range (whisker), and outliers for the fentanyl group (■) and the placebo group (□). *$P <$ 0.001 fentanyl group versus placebo group.

Table 2. Perioperative Analgesia Requirements in the Fentanyl Group and the Placebo Group

Variable	Fentanyl group (n = 38)	Placebo group (n = 39)	P value
Patients requiring propofol during surgery, n	4 (10.5%)	26 (66.7%)	<0.001
Total amount of propofol, mg	0 (0–60)	60 (0–160)	<0.001
Patients requiring analgesia in the first 24 h after surgery, n	22 (57.9%)	35 (89.7%)	0.002
Time to first request for postoperative analgesia, h	5.8 (1.9–15.6)	3.1 (1.0–11.7)	<0.001

Values are number (%) or median (range).

fentanyl group required analgesia in that period and, of those who were administered pain medication, patients in the fentanyl group requested first analgesia later than patients in the placebo group ($P < 0.001$).

Median onset of sensory blockade did not differ in the fentanyl group (12 [9–18] minutes) and the placebo group (15 [9–18] minutes; $P = 0.18$). Patients who received fentanyl had higher median Observer Assessment of Alertness and Sedation scores before carotid cross-clamping than those who received placebo (5 [3–5] vs 4 [2–5], respectively; $P = 0.02$). Bradycardia occurred in 2 patients (5.3%) in the fentanyl group compared with 1 patient (2.6%) in the placebo group ($P = 0.61$). Hypercapnia was recorded in 4 patients, 3 of whom (7.9%) received fentanyl, whereas 1 (2.6%) received placebo ($P = 0.36$). No episodes of hypotension or hypoxemia were recorded in any patient. No other opioid-related or anesthesia-related adverse events were observed in either group. No other patient needed to be converted to a general anesthesia. All patients had an uneventful recovery and were discharged home 1 to 3 days after surgery.

DISCUSSION

The present study demonstrated that the addition of fentanyl to a mixture of local anesthetics enhanced the quality and the duration of cervical plexus block in patients undergoing CEA.

Several studies have investigated the analgesic benefit of a variety of opioids, including fentanyl, coadministered with local anesthetics to produce regional anesthesia. Karakaya et al.[11] found that fentanyl 2.5 μg/mL, in combination with bupivacaine 0.25%, almost doubled the duration of analgesia after axillary brachial plexus block. The same concentration of fentanyl, administered with lidocaine 1.5%, significantly increased the success and prolonged the duration of sensory brachial plexus block, but delayed the onset of analgesia.[12] However, brachial plexus block quality was not improved when fentanyl 1 μg/mL was added to ropivacaine 0.75%.[13] The conflicting findings may be attributed to differences in liposolubility, concentrations and doses of both opioids and local anesthetics used, sites of administration and techniques of nerve blockade chosen, as well as methodological differences in study design.

Cervical plexus block is associated with a frequent incidence of patient anxiety, discomfort, and pain during CEA because of irregular innervation of the operative field.[2,17] To improve patients' comfort and cooperation, supplemental IV analgesia and/or sedation is often administered, which may impair mental status evaluation and compromise respiratory and cardiovascular function.[4]

In our study, 66.7% of patients who were given plain anesthetic mixture for cervical plexus block required rescue medication during surgery, which was in agreement with previously reported data.[2,3] The addition of fentanyl to cervical plexus block significantly reduced both the need for propofol supplementation and total propofol consumption. As a result, the level of sedation before carotid cross-clamping was lower in the fentanyl group, which is of particular importance for close neurological monitoring in this type of surgery. Furthermore, the addition of fentanyl almost doubled the time to first request for postoperative analgesia, which may have a beneficial analgesic-sparing effect in clinical practice. In comparison with other investigations, higher concentrations of fentanyl (3.3 μg/mL) were used, because the penetration of a drug into nerve roots and, thus, the success of nerve blockade is affected by the concentration of perineurally deposed drug solution.[17,18] In addition, peripheral analgesic effects of low concentrations of opioids may be masked by high local anesthetic concentrations required for adequate anesthesia.[11]

One methodological weakness of our study is the lack of a control group receiving systemic fentanyl. Therefore, the interpretation of the results with regard to possible mechanisms of analgesic action of perineurally injected fentanyl must be made with caution.

A local anesthetic-like action of fentanyl, which has been shown in vitro when very high concentrations (50 μg/mL) of the drug were used,[7] is unlikely in the present study as a much lower concentration of the drug was used. Centripetal spreading of fentanyl into the adjacent epidural and subarachnoid spaces is possible,[6] but to prove the antinociceptive effect at the spinal cord, spinal fluid concentrations of the drug

should be measured.[12] Finally, central opioid-related analgesia due to systemic uptake of local anesthetics after cervical plexus block cannot be excluded.[2,3]

In summary, the results of the present study indicate that the addition of fentanyl to local anesthetics improved the quality and prolonged the duration of cervical plexus block for CEA. Further research is needed to determine the most effective dose of the drug and a potential local anesthetic-sparing effect.

REFERENCES

1. Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. Br J Anaesth 2007;99:159–69
2. Merle JC, Mazoit JX, Desgranges P, Abhay K, Rezaiguia S, Dhonneur G, Duvaldestin P. A comparison of two techniques for cervical plexus blockade: evaluation of efficacy and systemic toxicity. Anesth Analg 1999;89:1366–70
3. Pandit JJ, Bree S, Dillon P, Elcock D, McLaren ID, Crider B. A comparison of superficial versus combined (superficial and deep) cervical plexus block for carotid endarterectomy: a prospective, randomized study. Anesth Analg 2000;91:781–6
4. Krenn H, Deusch E, Jellinek H, Oczenski W, Fitzgerald RD. Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block. Br J Anaesth 2002;89:637–40
5. Fields HL, Emson PC, Leigh BK, Gilbert RF, Iversen LL. Multiple opiate receptor sites on primary afferent fibers. Nature 1980;284:351–3
6. Stein C. Peripheral mechanisms of opioid analgesia. Curr Opin Pharmacol 2009;9:3–8
7. Gissen AJ, Gugino LD, Datta S, Miller J, Covino BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. Anesth Analg 1987;66:1272–6
8. Power I, Brown DT, Wildsmith JA. The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. Reg Anesth 1991;16:204–8
9. Mays KS, Lipman JJ, Schnapp M. Local analgesia without anesthesia using peripheral perineural morphine injections. Anesth Analg 1987;66:417–20
10. Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. Anaesthesia 2006;61:932–7
11. Karakaya D, Büyükgöz F, Bariçs S, Güldoğuçs F, Tür A. Addition of fentanyl to bupivacaine prolongs anesthesia and analgesia in axillary brachial plexus block. Reg Anesth Pain Med 2001;26:434–8
12. Nishikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A. Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesth Analg 2000;91:384–7
13. Fanelli G, Casati A, Magistris L, Berti M, Albertin A, Scarioni M, Torri G. Fentanyl does not improve the nerve block characteristics of axillary brachial plexus anaesthesia performed with ropivacaine. Acta Anaesthesiol Scand 2001;45:590–4
14. Bouaziz H, Kinirons BP, Macalou D, Heck M, Dap F, Benhamou D, Laxenaire MC. Sufentanil does not prolong the duration of analgesia in a mepivacaine brachial plexus block: a dose response study. Anesth Analg 2000;90:383–7
15. Gormley WP, Murray JM, Fee JPH, Bower S. Effect of the addition of alfentanil to lignocaine during axillary brachial plexus block. Br J Anaesth 1996;76:802–5
16. Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuncts for brachial plexus block: a systematic review. Anesth Analg 2000;90:1122–8
17. Umbrain VJ, van Gorp VL, Schmedding E, Debing EE, von Kemp K, van der Brande PM, Camu F. Ropivacaine 3.75 mg/mL, 5 mg/mL, or 7.5 mg/mL for cervical plexus block during carotid endarterectomy. Reg Anesth Pain Med 2004;29:312–6
18. Taboada Muniz M, Rodriguez J, Bermudez M, Valino C, Blanco N, Amor M, Aguirre P, Masid A, Cortes J, Alvarez J, Atanassoff PG. Low volume and high concentration of local anesthetic is more efficacious than high volume and low concentration in Labat's sciatic nerve block: a prospective, randomized comparison. Anesth Analg 2008;107:2085–8