J Anesth (2012) 26:746–751
DOI 10.1007/s00540-012-1416-4

ORIGINAL ARTICLE

# Buprenorphine added to levobupivacaine enhances postoperative analgesia of middle interscalene brachial plexus block

**Astrid Behr · Ulderico Freo · Carlo Ori · Brigitte Westermann · Fernando Alemanno**

Received: 31 August 2011 / Accepted: 7 May 2012 / Published online: 29 May 2012


**Abstract**
*Purpose* The aim of this study was to assess whether addition of epineural buprenorphine prolonged postoperative analgesia of middle interscalene brachial plexus block (MIB) with levobupivacaine.
*Methods* One hundred and fifty consenting adult patients, scheduled for shoulder arthroscopic surgery for a rotator cuff tear under MIB with 29.5 ml of 0.75 % levobupivacaine, were randomized to receive additionally either saline or intramuscular buprenorphine 0.15 mg or epineural buprenorphine 0.15 mg. Onset of sensory and motor blocks, duration of postoperative analgesia, and consumption of postoperative analgesics were compared among the groups.
*Results* There were significant ($P < 0.05$) differences in the onset and the duration of the sensory block and in the duration of postoperative analgesia. Duration of both sensory block and postoperative analgesia was longer ($P < 0.05$) in patients who had received epineural buprenorphine (856.1 ± 215.2 and 1,049.7 ± 242.2 min) than in patients who had received intramuscular buprenorphine (693.6 ± 143.4 and 820.3 ± 335.3 min) or saline (488.3 ± 137.6 and 637.5 ± 72.1 min). Requirement of postoperative rescue analgesics was lower in the epineural buprenorphine group than in the other two groups. Few complications occurred from MIB (<1 %) and none from buprenorphine.
*Conclusions* Epineural buprenorphine prolonged postoperative analgesia of MIB more effectively than intramuscular buprenorphine, which suggests that buprenorphine acts at a peripheral nervous system site of action.

**Keywords** Brachial plexus block · Buprenorphine · Postoperative analgesia

A. Behr · U. Freo (✉) · C. Ori
Department of Pharmacology and Anesthesiology, University of Padova, Via C. Battisti 267, 35121 Padua (PD), Italy
e-mail: ulderico.freo@unipd.it

B. Westermann · F. Alemanno
Department of Anesthesia and Pain Therapy, San Camillo Hospital, 25123 Brescia (BS), Italy

## Introduction

Since the first successful reports at the turn of the 19th century, upper extremity nerve block has gained progressively wider popularity to become the most common nerve block in current anesthesiology practice [1, 2]. In the past two decades, the efficacy and safety of nerve blocks have improved as a result of important technical advances: needles are less traumatic, nerve localization more precise, and local anesthetics safer [2].

We recently reported on a new anatomical approach for brachial plexus anesthesia, the middle interscalene block (MIB) [3–5] carried out with levobupivacaine [5]. Levobupivacaine is a long-acting local anesthetic with an efficacy profile similar to that of bupivacaine but with a safer profile [6]. Depending on dose and concentration, and the number and site of injections, levobupivacaine provides a widely variable duration of postoperative analgesia that does not, however, completely prevent postoperative pain [3, 6, 8]. A substantial prolongation of postoperative analgesia is achieved with continuous catheters and a moderate prolongation with a variety of adjuvants (i.e., $\alpha_2$-agonists, benzodiazepines, cholinergics, epinephrine, opioids, and steroids) admixed to the local anesthetic [7–11]. Lack of homogeneous cohorts and appropriate control groups and lack of basic comprehension on how the

opioids work on the peripheral nervous system (PNS) undermine available evidence in favor of epineural opioids [9–11]. In fact, the benefits of adding an opioid to local anesthetics decline when a control group is included [9–11]. In the subclavian perivascular plexus block, however, when buprenorphine 0.3 mg is added to a mixture of mepivacaine, tetracaine, and epinephrine, the duration of postoperative analgesia triples (i.e., 17.4 vs. 5.3 h) [7]. When added to bupivacaine for sciatic nerve blockade, however, buprenorphine enhances post-block analgesia less than when it is added to mepivacaine and tetracaine for brachial plexus block [7, 12]. The findings suggest that factors such as features of local anesthetics, block technique, and nerve anatomy may be relevant to the efficacy of adjuvant opioids.

The present randomized, double-blind study investigated the effects of adding intramuscular or epineural buprenorphine 0.15 mg to MIB with levobupivacaine 0.75 % for patients undergoing arthroscopic rotator cuff repair. Our primary outcome was the duration of postoperative analgesia.

## Materials and methods

After obtaining the approval of the Institutional Ethics Committee and informed written consent, 150 adult patients, aged 18–80 years, ASA physical status classification 1–2, and scheduled for arthroscopic rotator cuff repair were enrolled in this double-blind, prospective, single-center randomized trial. Patients who were either ASA physical status classification >3, or were suffering from cardiac, coagulative, neurological, respiratory, hepatic, or renal disease, or were pregnant women, or patients with a personal history of opioid abuse or allergy to local anesthetics were excluded from the study. All procedures were carried out in a standardized fashion by the same surgical team. Patients were randomized according to a computer-generated list of random numbers that were placed in an opaque envelope and concealed from the investigators.

On arrival at the operating room, all patients had an 18-gauge venous access in the contralateral arm. A standard noninvasive monitoring (i.e., ECG, $SpO_2$, noninvasive blood pressure) was established, and oxygen was delivered via face mask. Intravenous midazolam and fentanyl were titrated for patient comfort, while ensuring that patients remained responsive to verbal cues.

Drugs were prepared according to the randomization list by an anesthesiology nurse who was not further involved in the care of the study patient. A second anesthesiologist unaware of the treatment assessed the onset of the sensory and motor block.

MIBs were carried out as previously described by an anesthesiologist with at least 4 years experience with the technique [4, 5]. Briefly, with the patient in the beach chair position, the subclavian artery pulse, the midpoint of the clavicle, and the spinous process of C7 are identified as surface landmarks. After aseptically preparing and infiltrating the skin with 5 ml of 2 % lidocaine, a 35-mm, 24-gauge, Teflon-coated needle, connected to a nerve stimulator, is inserted laterally close to the subclavian artery pulse following a straight line which from the midpoint of the clavicle is posterolaterally tangent to the subclavian artery pulse; the needle has to follow in depth the transverse plane of C7 in a horizontal or slightly cephalad direction. Stimulation parameters were initially set as follows: frequency 2 Hz, duration of stimulation pulse 0.1 ms, intensity 0.5 mA. After an appropriate motor response was elicited, the stimulus intensity was reduced. The placement of the needle was considered correct when deltoid or biceps contractions were evoked with an intensity of 0.3 mA.

Patients were randomly assigned to receive one of the following treatments consisting of a mixture of two drugs given epineurally for MIB and of a third drug given intramuscularly in the contralateral deltoid:

1. Group CONTROL: received MIB using 29.5 ml of 0.75 % levobupivacaine [Chirocaine, Abbott, Campoverde di Aprilia (LT), Italy] plus 0.5 ml of saline solution and intramuscular deltoid injection of 0.5 ml of saline solution
2. Group IMB: received MIB using 29.5 ml of 0.75 % levobupivacaine plus 0.5 ml of saline solution and deltoid injection of 0.5 ml of buprenorphine 0.15 mg.
3. Group ENB: received MIB with 29.5 ml of levobupivacaine 0.75 % plus 0.5 ml of buprenorphine 0.15 mg and deltoid injection of 0.5 ml of saline.

After evidence of a successful MIB, the patient was taken to the operating room for surgery. The anesthesiological plan was to proceed with general anesthesia in case the block has been unsuccessful at 30 min after MIB. Following surgery, patients were transferred to the post-anesthesia care unit or to the orthopedic ward and monitored for quality and duration of postoperative analgesia, complications, and side effects.

After performance of MIB, an anesthesiologist blind to patient treatment group assessed onset of sensory and motor blocks of the axillary, musculocutaneous, median, radial, and ulnar nerves every 5 min in the first 30 min. After surgery, nursing staff unaware of patient allocation recorded, at 2, 4, 6, 8, 12, 24, and 36 h postoperatively, the following variables: intensity of pain at rest and of sensory block, time to first analgesic and analgesic consumption, postoperative nausea and vomiting (PONV), sedation, heart

rate, and arterial blood pressure. Sensory block was assessed by asking the patient to compare the pinprick sensation in the primary innervation areas in the anesthetized arm with the contralateral arm as reference. Onset and duration of sensory block were considered as the times of initial loss of the pinprick sensation in any dermatome until the complete recovery of function. Successful sensory block was defined as an absence of sensation in the entire surgical territory. Motor block was determined using a modified Lovett scale ranging from 6 (normal strength) to 0 (complete paralysis) for motor response typical of the axillary, musculocutaneous, median, radial, and ulnar nerves. Onset of motor block was the time to first loss of motor power. Intensity of postoperative pain and of PONV were assessed on a 10-cm linear visual analogue scale (VAS) ranging from 0 (no pain or no nausea) to 10 (severe pain or severe PONV). Patients were instructed to call in case of pain (i.e., VAS $> 3$) and were given intramuscular ketorolac 30 mg or intravenous tramadol 100 mg in 100 ml of saline solution in case of pain, respectively, of moderate (i.e., VAS $> 3 \leq 6$) or severe (i.e., VAS $\geq 7$) intensity. In case of nausea (i.e., VAS $> 3$) or vomiting, patients were given intravenous levosulpiride 25 mg in 100 ml of saline solution. Times of calls and types and doses of drugs were recorded along with complications and side effects.

Based on a pilot study on 10 patients, we determined that a sample size of 44 patients would be sufficient to detect a 30 % difference in postoperative analgesia with a power of 0.9 and significance level of 0.05. To account for larger SD and possible dropouts, 50 patients per group were included. The projected duration of postoperative analgesia in the CONTROL (levobupivacaine alone) group was 621 ± 265 min.

Statistical analysis was performed using Statistica software version 9.0 (StatSoft Italia, Vigonza, Padova, Italy). Definitional statistics for continuous variables are presented as means ± standard deviation (SD), and for nominal variables as numbers and percentages. Statistically significant intergroup differences were assessed using analysis of variance (ANOVA) and a Bonferroni multiple comparison test. Categorical variables were analyzed with Yates correct $\chi^2$ test. The nature of significant testing was two tailed. A $P$ value $< 0.05$ was considered statistically significant.

## Results

There was no difference in the demographic data among groups (Table 1); there were significant ($P < 0.05$) group differences in the onset and duration of sensory block and in the duration of postoperative analgesia (Table 1). Compared to levobupivacaine alone, epineural buprenorphine and intramuscular buprenorphine shortened the onset of sensory block ($P < 0.035$), prolonged the sensory block ($P < 0.001$) and postoperative analgesia ($P < 0.001$) (Fig. 1), and reduced the postoperative requirement of analgesic drugs (Table 2).

MIBs were completed in <25 min in all patients. In the ENB patient group, mean postoperative analgesia was prolonged (1,049.7 ± 242.2 min) compared to that of both the IMB group (820.3 ± 335.3 min) and the CONTROL group (637.5 ± 72.1 min) (Fig. 1).

PONV occurred in four ENB and six IMB patients, hypotension in one patient each in the ENB and IMB groups, respiratory depression in two IMB patients,

**Table 1** Patient clinical features, and anesthesia and surgery times

| Group | CONTROL ($n = 50$) | IMB ($n = 50$) | ENB ($n = 50$) | $P$ value |
|---|---|---|---|---|
| Gender (male) | 20 (40) | 24 (48) | 20 (40) | 0.588 |
| Age (years) | 56.3 ± 12.6 | 56.8 ± 10.8 | 55.3 ± 10.6 | 0.798 |
| Height (cm) | 166.1 ± 7.6 | 165.1 ± 10.1 | 167.7 ± 7.8 | 0.313 |
| Weight (kg) | 74.7 ± 12.6 | 72.1 ± 13.7 | 73.4 ± 13.4 | 0.619 |
| ASA PS I/II | 35/15 | 38/12 | 31/19 | 0.749 |
| Duration of surgery (min) | 77.8 ± 13.9 | 82.3 ± 19.3 | 85.7 ± 22.5 | 0.115 |
| Onset of sensory block (min) | 6.3 ± 1.3 | 5.7 ± 1.7 | 5.5 ± 1.2 | 0.035*,† |
| Onset of motor block (min) | 10.3 ± 2.2 | 9.7 ± 2.1 | 9.5 ± 1.4 | 0.101 |
| Duration of sensory block (min) | 488.3 ± 137.6 | 693.6 ± 143.4 | 856.1 ± 215.2 | <0.001*,†,§ |

Data are expressed as means ± SD, or as numbers of patients (percent)

All patients received epineural 29.5 ml of 0.75 % levobupivacaine and additional saline (CONTROL) or intramuscular buprenorphine 0.15 mg (IMB) or epineural buprenorphine 0.15 mg (ENB)

$P$ values are determined by $\chi^2$ test (gender, ASA PS) and Bonferroni-corrected analysis of variance (ANOVA) (age, height, weight, block onset and duration, duration of surgery)

* $P < 0.05$ IMB versus CONTROL; † $P < 0.05$ ENB versus CONTROL; § $P < 0.05$ ENB versus IMB

laryngeal nerve block in one CONTROL and two IMB patients, and arterial puncture in one CONTROL patient (Table 2). Pruritus did not occur in any patient.

## Discussion

The use of buprenorphine as either an intramuscular or epineural adjunct prolonged the postoperative analgesia of MIB with levobupivacaine 0.75 % for arthroscopic rotator cuff repair. Buprenorphine was more effective when given epineurally than intramuscularly, which suggests that its primary site of action is the PNS.

The action of opioids on the PNS was shown more than 30 years ago [10]. Since then, several authors have tested the analgesic efficacy of peripheral opioids and obtained conflicting results [9–11]. Buprenorphine is of interest because, in comparison to other opioids, it is more lipophilic and likely to access PNS opioid receptors [13, 14]. Gobeaux and Landais [15] reported that fentanyl and meperidine reduce the lidocaine dose for a complete brachial plexus block by stimulating opioid receptors in the PNS. Viel and coworkers [16] showed that, added to local anesthetics for brachial plexus block, buprenorphine 3 μg/kg produced longer postoperative analgesia than morphine 50 μg/kg. Both studies, however, were limited by lack of control groups. Given its long half-life, the authors could not rule out a systemic effect of buprenorphine. More recently, Candido and coworkers evaluated the effects of buprenorphine 0.3 mg added to local anesthetics for interscalene and axillary brachial plexus blocks [7, 8]. The latter approach should minimize drug diffusion to the central nervous system (CNS) [8]. In the first study, addition of epineural buprenorphine prolonged the duration of postoperative analgesia more than three fold in comparison to a block with only local anesthetics [7]. In the second study, the same authors demonstrated that epineural buprenorphine also prolongs pain relief in comparison to systemic buprenorphine (>80 %) [8]. Consistently with those by Candido et al., our findings confirm that buprenorphine is more effective when given epineurally than intramuscularly and suggest that the PNS is the site of action of epineural buprenorphine.

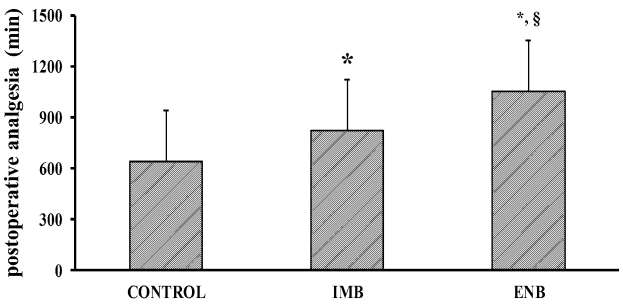


**Fig. 1** *Bars* represent mean postoperative analgesia (±SD) after middle interscalene brachial plexus block (MIB) with levobupivacaine given with additional either saline (*CONTROL*), or intramuscular buprenorphine 0.15 mg (*IMB*) or epineural buprenorphine 0.15 mg (*ENB*). *Significantly different from CONTROL group; †significantly different from IMB; $P < 0.001$

Duration of local anesthesia depends on several factors (i.e., type, concentration and volume of the anesthetic, method of nerve localization and drug injection), making studies difficult to compare. Here, however, the levobupivacaine MIB determines duration of anesthesia and analgesia comparable to those reported using similar doses of levobupivacaine with different approaches to the brachial plexus block [17, 18]. Also, in our patients a satisfactory postoperative analgesia after MIB with levobupivacaine and buprenorphine is virtually identical to that reported by Candido et al. (i.e., 17.5 vs. 17.4 h) using a mixture of local anesthetics (i.e., mepivacaine 1 %, tetracaine 0.2 %), epinephrine, and a double dose of buprenorphine (i.e., 0.15 vs.

**Table 2** Postoperative analgesic drug consumption, complications, and side effects

| Group | CONTROL ($n = 50$) | IMB ($n = 50$) | ENB ($n = 50$) | $P$ value |
|---|---|---|---|---|
| Respiratory depression | 0 | 2 (4) | 0 | 0.131 |
| Laryngeal nerve block | 1 (2) | 1 (2) | 0 | 0.602 |
| Artery puncture | 1 (2) | 0 | 0 | 0.602 |
| PONV | 1 (2) | 6 (10) | 4 (10) | 0.155 |
| Ketoralac | 22 (44) | 12 (24) | 7 (14) | 0.018† |
| Tramadol | 31 (56) | 17 (34) | 12 (24) | <0.003*,† |

Data are expressed as numbers of patients (percent)

All patients received epineural 29.5 ml of 0.75 % levobupivacaine and additional saline (CONTROL) or intramuscular buprenorphine 0.15 mg (IMB) or epineural buprenorphine 0.15 mg (ENB)

$P$ values are determined by $\chi^2$ test

*PONV* postoperative nausea and vomiting

* $P < 0.05$ IMB versus CONTROL, † $P < 0.05$ ENB versus CONTROL, § $P < 0.05$ ENB versus IMB

0.3 mg) [7]. This rather unexpected result could be caused by the doses and the characteristics of drugs used in this study. In the first place, instead of a mixture of mepivacaine, tetracaine, and epinephrine, we used a high dose of levobupivacaine, which is characterized by a long half-life [6]. In comparison to other local anesthetics, levobupivacaine alone determines a 50 % longer analgesic effect than the combination of mepivacaine and tetracaine (i.e., 637 vs. 318 min) [7]. The dose of levobupivacaine used here is similar to those of previous studies and within the safety range [19, 20]. In the second place, the efficacy of buprenorphine is not correlated to its dose in a linear manner. Although most opioids present an hyperbolic dose–effect curve, the analgesic activity of buprenorphine in relation to dose is better described by a bell-shaped curve, because buprenorphine is an opioid mixed agonist–antagonist with high binding affinity to ORL1 receptors [21].

Rates of complications related to both buprenorphine and MIB are low. Including the present work, we have employed MIB in more than 1,000 studied patients, and important clinical complications (i.e., arterial puncture hematoma, laryngeal nerve block, respiratory depression) occurred in less than 1 % of patients; further, there was no case of pneumothorax or subarachnoid or vertebral artery injection [3–5].

The study has limitations. First, all MIBs were performed only by very experienced regional anesthesiologists. This approach seems advantageous in terms of a high success rate and low complication rate of MIB. It is possible, however, that the high success rate of MIB observed in this study would not generalize to our setting with less experienced anesthesiologists [22]. Also, the numbers of patients are too small for any firm conclusion on MIB safety [22]. Second, the relatively large volumes of local anesthetic (i.e., 29.5 ml of 0.75 % levobupivacaine) used in this study are consistent with clinical practice [19, 20]. However, the findings of this study cannot be extrapolated to other concentrations and volumes of local anesthetics. Also, the use of ultrasound to guide MIB could add to precision. Future studies will investigate whether the MIB dose of epineural buprenorphine can be further diminished by administration under ultrasound control. Finally, with regard to data collection, we were limited to assessing pain at 12-h intervals at 12, 24, and 36 h postoperatively; it is quite possible that we were unable to determine fluctuating pain levels in times between these three assessments.

In conclusion, our study in patients undergoing rotator cuff repair with MIB shows that epineural buprenorphine is effective in prolonging analgesia and sparing postoperative analgesics. Buprenorphine, given epineurally, is effective at lower doses than previous studies reported, indicating that it acts on PNS neurons.

**Acknowledgments** This study was supported only by departmental funds.

## References

1. Hall RJ. Hydrochlorate of cocaine. N Y Med J. 1884;40:643–6.
2. Neal JM, Kopacz DJ, Liguori GA, Beckman JD, Hargett MJ. The training and careers of regional anesthesia fellows: 1983–2002. Reg Anesth Pain Med. 2005;30:226–32.
3. Alemanno F. A novel approach to brachial plexus. Minerva Anestesiol. 1992;58:403–6.
4. Alemanno F, Gretter R, Di Leo Y, Bellini L. Alemanno's brachial plexus block ten years later: topographic study of the anesthetised areas. Minerva Anestesiol. 2003;69:575–81.
5. Alemanno F, Capozzoli G, Egarter-Vigl E, Gottin L, Bartoloni A. The middle interscalene block: cadaver study and clinical assessment. Reg Anesth Pain Med. 2006;31:563–8.
6. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs. 2000;59:551–79.
7. Candido KD, Franco CF, Khan MA, Winnie AP, Raja D. Buprenorphine added to the local anesthetic for brachial plexus block to provide postoperative analgesia in outpatients. Reg Anesth Pain Med. 2001;26:167–72.
8. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD. Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. Reg Anesth Pain Med. 2002;27:162–7.
9. Axelsson K, Gupta A. Local anaesthetic adjuvants: neuraxial versus peripheral nerve block. Curr Opin Anaesthesiol. 2009;22:649–54.
10. Carstens E, Tulloch I, Zieglgänsberger W, Zimmermann M. Presynaptic excitability changes induced by morphine in single cutaneous afferent C- and A-fibers. Pflugers Arch. 1979;379:143–7.
11. Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuncts for brachial plexus block: a systematic review. Anesth Analg. 2000;90:1122–8.
12. Candido KD, Hennes J, Gonzalez S, Mikat-Stevens M, Pinzur M, Vasic V, Knezevic NN. Buprenorphine enhances and prolongs the postoperative analgesic effect of bupivacaine in patients receiving infragluteal sciatic nerve block. Anesthesiology. 2010;113:1419–26.
13. Kabirullah L, Cowan A. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2:395–402.
14. Kabirullah L. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. J Neurosci. 2003;23:10331–7.
15. Gobeaux D, Landais A. Utilisation de deux morphiniques dans le bloc du plexus brachial. Cah Anesthesiol. 1988;36:437–40.
16. Viel EJ, Eledjam JJ, de la Coussaye JE, D'Athis F. Brachial plexus block with opioids for postoperative pain relief: comparison between buprenorphine and morphine. Reg Anesth Pain Med. 1989;14:274–8.
17. Esmaoglu A, Yegenoglu F, Akin A, Turk CY. Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg. 2010;111:1548–51.
18. Piangatelli C, De Angelis C, Pecora L, Recanatini F, Cerchiara P, Testasecca D. Levobupivacaine and ropivacaine in the infraclavicular brachial plexus block. Minerva Anestesiol. 2006;72:217–21.
19. Liisanantti O, Luukkonen J, Rosenberg PH. High-dose bupivacaine, levobupivacaine and ropivacaine in axillary brachial plexus block. Acta Anaesthesiol Scand. 2004;48:601–6.

20. Borgeat A, Ekatodramis G, Blumenthal S. Interscalene brachial plexus anesthesia with ropivacaine 5 mg/mL and bupivacaine 5 mg/mL: effects on electrocardiogram. Reg Anesth Pain Med. 2004;29:557–63.
21. Pick CG, Peter Y, Schreiber S, Weizman R. Pharmacological characterization of buprenorphine, a mixed agonist-antagonist with kappa 3 analgesia. Brain Res. 1997;744:41–6.
22. Brull R, McCartney CJ, Chan VW, El-Beheiry H. Neurological complications after regional anesthesia: contemporary estimates of risk. Anesth Analg. 2007;104:965–74.