

Clonidine Added to a Continuous Interscalene Ropivacaine Perineural Infusion to Improve Postoperative Analgesia: A Randomized, Double-Blind, Controlled Study

Brian M. Ilfeld, MD*, Timothy E. Morey, MD*, Lisa J. Thannikary, MD*, Thomas W. Wright, MD†, and F. Kayser Enneking, MD*†

Departments of *Anesthesiology and †Orthopaedics and Rehabilitation, University of Florida, Gainesville, Florida

Although clonidine has been shown to increase the duration of local anesthetic action and prolong postoperative analgesia when included in single-injection nerve blocks, the only controlled investigation of the efficacy of this practice to improve analgesia for continuous perineural local anesthetic infusion failed to discern any clinically relevant benefits. For this study, we used a larger dose of clonidine in an attempt to improve analgesia. Patients ($n = 20$) undergoing moderately painful orthopedic surgery of the shoulder received an interscalene brachial plexus block (40 mL of mepivacaine 1.5%, epinephrine 2.5 $\mu\text{g}/\text{mL}$, and clonidine 50 μg) and a perineural catheter before surgery. After surgery, ropivacaine 0.2% or ropivacaine 0.2% plus clonidine 2 $\mu\text{g}/\text{mL}$ was delivered via the catheter for 3 days (basal rate, 5 mL/h; patient-controlled bolus, 5 mL; lockout,

1 h). Investigators and patients were blind to random group assignment. The primary outcome variable was designated as the most intense pain during the day after surgery. Secondary end-points included additional pain scores, patient-controlled bolus doses, oral analgesic use, sleep quality, and catheter- or infusion-related complications. There were no statistically significant differences between groups for any of the variables investigated. We conclude that adding clonidine 2 $\mu\text{g}/\text{mL}$ to a ropivacaine interscalene perineural infusion does not decrease breakthrough pain intensity the day after surgery. For the additional end-points, our negative findings are only suggestive of a lack of effect and require further study for verification.

(Anesth Analg 2005;100:1172–8)

Local anesthetic infused via a perineural catheter provides postoperative analgesia and decreases opioid requirements, opioid-related side effects, and sleep disturbances (1–3). However, even with perineural infusion, most patients experience pain and require supplemental opioids (4,5). In an attempt to improve analgesia while avoiding an insensate extremity and muscular weakness, investigators have added clonidine to long-acting local anesthetic (1–2 $\mu\text{g}/\text{mL}$) for continuous perineural femoral (6), anterior lumbar plexus (7–9), interscalene (10), and popliteal (11) infusions. Although clonidine has been demonstrated to

increase the duration of single-injection nerve blocks (12), the only controlled investigation of adding clonidine to a continuous ropivacaine infusion (1 $\mu\text{g}/\text{mL}$) failed to reveal any clinically relevant benefits (13). Therefore, the primary objective of this randomized, double-blind, controlled study was to determine whether doubling the dose of clonidine to 2 $\mu\text{g}/\text{mL}$ would provide a clinically relevant improvement in postoperative analgesia. To this end, the primary outcome variable was designated as the worst pain experienced the day after surgery.

In addition, for ambulatory perineural infusion in which there is a limited local anesthetic reservoir volume, minimizing local anesthetic consumption allows for increased infusion duration and, therefore, prolonged analgesia (14). Attempts to simply decrease the basal rate of interscalene ropivacaine perineural infusions to reduce local anesthetic consumption have resulted in a concomitant decrease in analgesia and other infusion benefits (5). If the addition of clonidine to a basal ropivacaine infusion improves analgesia, patient-controlled bolus doses may be decreased,

Supported by the University of Florida Department of Anesthesiology and an unrestricted educational grant from Arrow International (Reading, PA). BMI has performed consulting work for Arrow International.

Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, NV, October 26, 2004.

Accepted for publication September 3, 2004.

Address correspondence and reprint requests to Brian M. Ilfeld, MD, Department of Anesthesiology, PO Box 100254, 1600 S.W. Archer Rd., Gainesville, FL 32610-0254. Address e-mail to bilfeld@ufl.edu.

DOI: 10.1097/01.ASN.0000145571.41015.D5

resulting in less anesthetic consumption, and a lengthening of the infusion duration and associated benefits. Therefore, secondary end-points included patient-controlled bolus dose use and total local anesthetic consumption, as well as supplemental opioid requirements, sleep disturbances, and patient satisfaction.

Methods

After University of Florida IRB approval, we prospectively enrolled adult patients scheduled for moderately painful ambulatory unilateral orthopedic surgery of the shoulder and who desired interscalene perineural catheter placement. Patients were required 1) to be able to understand the possible local anesthetic-related complications, study protocol, and care of the catheter and infusion pump system; and 2) to have a caretaker who would remain with them during the local anesthetic infusion. Exclusion criteria included any contraindication to interscalene nerve block, any known heart or lung disease (with the exception of mild mitral valve prolapse), baseline oxygen saturation of <96% on room air, a history of opioid dependence or allergy to study medications, current chronic analgesic therapy, known hepatic or renal insufficiency, peripheral neuropathy, and morbid obesity.

After obtaining written, informed consent, patients were placed supine with their head turned slightly away from the operative shoulder. Standard noninvasive monitors were applied, and oxygen was administered via a face mask. Intravenous midazolam and fentanyl were titrated for patient comfort while we ensured that patients remained responsive to verbal cues. All catheters were placed by using a technique described previously (5). Briefly, the area that would be subsequently covered by the catheter dressing was prepared with chlorhexidine gluconate and isopropyl alcohol (ChloroPrep One-Step; Medi-Flex Hospital Products, Inc., Overland Park, KS) and then shaved with a surgical safety razor, if necessary.

After sterile preparation and draping, a local anesthetic skin wheal was raised over the groove between the anterior and middle scalene muscles at the cephalad-caudad level of the cricoid cartilage. With the bevel directed anterolaterally, an 8.89-cm 17-gauge insulated needle (StimuCath; Arrow International, Reading, PA) was inserted with the long axis of the needle 45° to the parasagittal, transverse, and coronal planes. This needle was connected to a nerve stimulator (Stimuplex-DIG; B. Braun Medical, Bethlehem, PA) initially set at 1.2 mA, 0.1 ms, and 2 Hz. Once the needle tip was through the skin and immediate underlying fascia, the stylet was removed to allow for identification of a penetrated vessel. The needle was

redirected as needed until deltoid or biceps motion was elicited with a current between 0.30 and 0.70 mA.

The 19-gauge catheter was then placed through the length of the needle, and the nerve stimulator was transferred from the needle to the catheter, which had a conducting wire through its length that delivered current to its tip. The stimulating current was increased to 0.80 mA, and the catheter was advanced 3–5 cm beyond the needle tip. If biceps or deltoid motion decreased as the stimulating catheter was advanced, then the catheter was withdrawn into the needle, the needle was redirected or rotated, and the catheter was readvanced. If there was resistance during catheter withdrawal, the needle was withdrawn until the catheter resistance resolved. If resistance impeded catheter advancement after 10 attempts, the catheter was removed from the needle, and 20 mL of preservative-free normal saline was injected after a negative aspiration. The catheter was advanced 3–5 cm past the needle tip if the resistance had resolved, without muscle motion as a guide. If the catheter could not be placed after this maneuver or if the catheter could not be placed within 30 min, then the patient was withdrawn from the study.

Once a catheter had been successfully advanced 3–5 cm past the needle tip, the needle itself was withdrawn over the catheter, the catheter stylet was removed, and the catheter was tunneled subcutaneously toward the sternal notch by using the included needle stylet and a 17-gauge insulated needle (15). The injection port was attached to the end of the catheter, the nerve stimulator was attached to the injection port, and the minimum current resulting in muscle contraction was noted. The catheter was secured with sterile liquid adhesive, an occlusive dressing, and an anchoring device (StatLock; Venetec International, San Diego, CA) to affix the catheter hub to the patient.

After negative aspiration, 40 mL of anesthetic solution was injected via the catheter with gentle aspiration between divided doses (3–5 mL per dose). The injectate contained mepivacaine 1.5%, epinephrine 100 µg, and preservative-free clonidine 50 µg. After 15 min, terminal nerve blockade was evaluated and was considered successful with an inability to abduct the arm at the shoulder. Specific nerve distributions and the degree of sensory/motor blockade were not formally evaluated. A general anesthetic was administered with propofol, isoflurane, and/or nitrous oxide. No additional opioids or benzodiazepines were administered after catheter placement.

After successful block and catheter placement, patients were randomly assigned to receive one of two possible postoperative catheter infusions: ropivacaine 0.2% or ropivacaine 0.2% combined with preservative-free clonidine 2 µg/mL. An investigational pharmacist using a computer-generated randomization table

performed group assignment and provided the investigational injectate (500 mL). Assignment was not revealed to the patients or any clinical personnel.

After surgery, patients were discharged home with a portable electronic infusion pump (CADD-Legacy; Smiths Medical, St. Paul, MN) that infused study solution via the interscalene catheter at a basal infusion rate of 5 mL/h (5-mL patient-controlled bolus doses; 1-h lockout). The patient and caretaker were given standard postoperative outpatient instructions, as well as verbal and written instructions, on the use of the pump and catheter. Telephone and pager numbers for physicians available at all times were given to each patient. Patients were given the following supplies: a medication log, a prescription for an oral analgesic (oxycodone 5 mg combined with acetaminophen 500 mg), a pair of nonsterile gloves, and a self-addressed and stamped padded envelope for pump return. As part of their postoperative education, patients self-administered one bolus from their infusion pump.

In the event of breakthrough pain, patients were instructed to first use the bolus function of the infusion pump. If the pain had not resolved after 20 min, patients were instructed to use oral analgesics and to record this use in their medication log.

Patients were telephoned beginning the night of surgery and each evening thereafter through the night after catheter removal (see Appendix 1 for questionnaire). Patients were also questioned about symptoms of local anesthetic toxicity, gross sensory and motor function, dyspnea, vertigo, and the appearance of the catheter site. If complete anesthesia of the surgical extremity was experienced at any time on or after the morning of postoperative day (POD) 1, patients were instructed to pause their infusion until they regained feeling in their extremity and then to restart the infusion.

On the evening of POD 2, patients' caretakers removed the catheters by using the pair of nonsterile gloves, with the physician in telephone contact throughout. The presence of a metallic catheter tip confirmed complete removal. Patients disposed of the catheter and any residual infusate. The pump was returned to the surgical center in the supplied padded envelope via the US Postal Service. Upon arrival at the surgical center, the infusion pump memory, containing all pump events with a date/time stamp (e.g., bolus activation), was downloaded to a desktop computer.

Sample size calculations were centered around our primary hypothesis that clonidine added to an interscalene ropivacaine perineural infusion (2 μ g/mL) decreases postoperative pain compared with ropivacaine alone. To this end, we chose the primary outcome variable "worst pain" on POD 1 to estimate a probable sample size and considered a 50% reduction in pain score to be clinically relevant (5). According to previous experience, we expected patients with a basal rate

of 4–5 mL/h to have a mean worst pain score of 8 on a verbal analog scale of 0 to 10 (5). Assuming an SD in each group of 3 (5), a two-sided Type I error protection of 0.05, and a power of 0.8, approximately 10 patients in each group were required to detect a 50% reduction in this pain score with the addition of clonidine to the ropivacaine infusion (StatMate 1.01; GraphPad Software, San Diego, CA).

Normality of distribution was determined by using the Kolmogorov-Smirnov test with the Lilliefors correction (SigmaStat 2.03; SPSS, Inc., Chicago, IL). Continuous parametric data are reported as mean \pm SD. Nonparametric data are graphically presented as median with 25th–75th percentile bars and 10th–90th percentile whiskers or are textually noted by using median (10th–90th percentile). For normally distributed data, single comparisons were tested with Student's *t*-test, whereas multiple comparisons were made by using repeated-measures analysis of variance with Tukey post hoc pairwise testing when appropriate. For nonparametric data, the Mann-Whitney ranked sum test or repeated-measures analysis of variance for ranks with Tukey post hoc pairwise testing was used, when appropriate. Categorical and nominal data were analyzed by using Fisher's exact test because some cells had fewer than five observations, and this would lead to significant error with χ^2 analysis. $P < 0.05$ was considered significant. Analysis was performed according to the intention-to-treat principle.

Results

Of the 28 patients enrolled, in 8 cases the catheter could not be placed in <30 min, and the patients were removed from the study. Of the remaining 20 patients, all experienced a successful interscalene block as defined by this study (inability to abduct at the shoulder). These 20 subjects were randomized to receive either ropivacaine ($n = 10$) or ropivacaine plus clonidine ($n = 10$). There were no statistically significant differences between these groups in demographics or surgical procedures (Tables 1 and 2).

There were no statistically significant differences between groups for any of the variables investigated (Table 3, Figs. 1–3). Two patients in the clonidine/ropivacaine group and one patient in the ropivacaine-only group experienced a complete lack of sensation in the surgical extremity from surgery through the morning of POD 1 that resolved after a 1- to 3-h discontinuation of local anesthetic infusion ($P = 0.77$). Three patients, all in the clonidine/ropivacaine group, reported minor vertigo unassociated with standing ($P = 0.12$). Three patients from each group experienced mild dyspnea that partially resolved with positional changes. There were no inadvertent catheter dislodgements, and all catheters were safely removed at home by patient caretakers.

Table 1. Demographic, Block, and Surgical Information

Variable	Clonidine/ ropivacaine	Ropivacaine only
Age (yr)	50 ± 15	47 ± 17
Sex (F/M)	6/4	4/6
Height (cm)	171 ± 8	174 ± 10
Weight (kg)	88 ± 20	89 ± 19
IV fentanyl (μg) ^a	200 (100-250)	200 (166-234)
IV midazolam (mg) ^a	4.0 (3.0-4.5)	4.0 (2.0-5.5)
Minimum current via needle (mA)	0.60 ± 0.12	0.56 ± 0.14
Minimum current via catheter (mA)	0.68 ± 0.38	0.54 ± 0.28
Surgery duration (min)	130 ± 50	95 ± 51

Values are reported mean ± SD or median (10th-90th percentiles) for parametric and nonparametric data, respectively. There were no statistically significant differences between the measurements of these two study groups.
^a Sedation only for preoperative block placement.

Table 2. Surgical Procedures for Each Study Group

Variable	Clonidine/ ropivacaine	Ropivacaine only
Open rotator cuff repair	1	3
Arthroscopic rotator cuff repair	2	1
Arthroscopic Mumford and SAD	3	3
Arthroscopic Mumford or SAD	3	2
Arthroscopic capsulectomy and débridement	1	1

There were no statistically significant differences between groups.
SAD = subacromial decompression.

Table 3. Infusion Profile by Study Group

Variable	Clonidine/ ropivacaine	Ropivacaine only
Bolus doses attempted (n)	15 (4-60)	15 (6-100)
Bolus doses delivered (n)	14 (2-29)	13 (5-32)
Bolus doses delivered/24 h (n)	7 (1-13)	6 (2-14)
Infusion duration (h) ^a	186 ± 92	179 ± 90
Unused local anesthetic (mL)	53 (50-56)	54 (26-56)

Values are reported mean ± SD or median (10th-90th percentiles) for parametric and nonparametric data, respectively. There were no statistically significant differences between the measurements of these two study groups.

^a Infusion was stopped in the evening of Postoperative Day 2 regardless of the local anesthetic volume remaining in reservoir.

Six patients (30%) had a nonscheduled contact with the on-call physician during the course of their infusion. These contacts involved surgical issues (four patients) or an insensate extremity the morning of POD 1 (two patients). There were no pump malfunctions or alarms, and all infusion pumps were returned to the surgical center via the postal service.

Discussion

This randomized, double-blind, controlled study provides evidence that the addition of clonidine (2 μg/

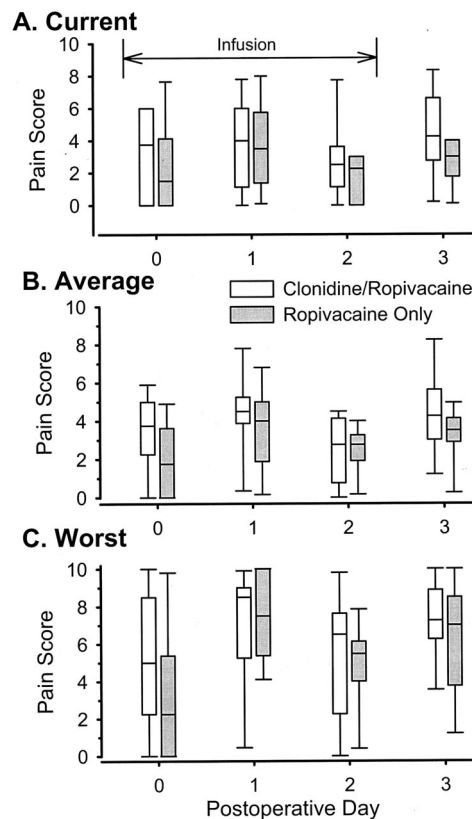


Figure 1. Effects of the addition of clonidine to interscalene perineural ropivacaine infusion on current (A), average (B), and worst (C) pain after moderately painful shoulder surgery (scale of 0-10). The infusions were discontinued in the evening of postoperative Day 2, as indicated by the horizontal bar. Data are expressed as median (horizontal bar) with 25th-75th (box) and 10th-90th (whiskers) percentiles for patients randomly assigned to ropivacaine 0.2% or ropivacaine 0.2% plus clonidine 2 μg/mL (basal rate, 5 mL/h; bolus dose, 5 mL; lockout, 1 h). There were no statistically significant differences between study groups.

mL) to an interscalene perineural ropivacaine infusion does not provide a clinically relevant improvement in breakthrough pain intensity the day after moderately painful shoulder surgery. Furthermore, local anesthetic consumption, opioid requirements, sleep quality, and satisfaction scores did not improve with the addition of clonidine. However, because these additional variables were secondary end-points, our negative findings are only suggestive of a lack of effect and require further study for verification.

As noted previously, the single controlled investigation of the efficacy of this practice to improve analgesia for continuous perineural local anesthetic infusion failed to discern a clinically relevant benefit (13). In that study, we identified two possible causes for a Type II error—failing to detect a difference between two treatments when there is one—that we corrected for in this investigation. First, for that study, 1 μg of clonidine was added to each milliliter of infused ropivacaine because all but one study (6) that added

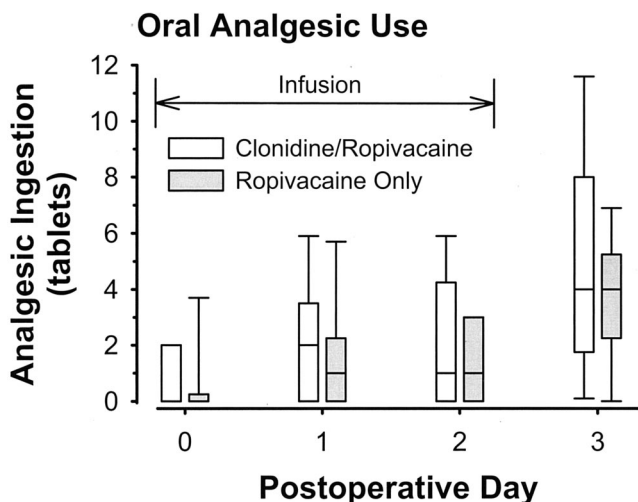


Figure 2. Effects of the addition of clonidine to interscalene perineural ropivacaine infusion on oral analgesic use (oxycodone and acetaminophen). This secondary end-point consisted of the number of analgesic tablets consumed. The infusions were discontinued in the evening of postoperative Day 2, as indicated by the horizontal bar. Data are expressed as median (horizontal bar) with 25th–75th (box) and 10th–90th (whiskers) percentiles for patients randomly assigned to ropivacaine 0.2% or ropivacaine 0.2% plus clonidine 2 $\mu\text{g}/\text{mL}$ (basal rate, 5 mL/h; bolus dose, 5 mL; lockout, 1 h). For tightly clustered data (e.g., postoperative Day 0; ropivacaine-only group), the median approximated the 10th and 25th percentile values. In this case, the median is 0.0, and only the 75th and 90th percentiles are noted. There were no statistically significant differences between study groups.

clonidine to local anesthetic perineural infusions used the smaller dose (7–11). This may have been an inadequate dose to provide a clinically relevant improvement in analgesia, so the dose was doubled for this study. Second, inaccurate catheter placement in the previous study could have confounded the results. In that study, the initial local anesthetic bolus was administered via the introducing needle, and a non-stimulating catheter was subsequently advanced without further guidance. This did not allow confirmation of accurate catheter placement. For this study, a stimulating catheter was used; this allowed the introduction of the initial local anesthetic bolus via the catheter after placement and allowed confirmation of accurate catheter tip placement adjacent to the brachial plexus.

The pain scores, opioid requirements, and sleep disturbances reported in this study were all higher than in a similar study of interscalene perineural ropivacaine infusion (1). However, in the previous investigation, patients received a ropivacaine basal infusion of 8 mL/h. A subsequent dose-response study demonstrated that by decreasing the ropivacaine interscalene basal infusion from 8 to 4 mL/h, the associated benefits of the ropivacaine infusion decreased as well, even if large patient-controlled bolus doses were provided (5). Patients in this study received a basal infusion of 5 mL/h, and it is notable that they reported remarkably similar pain scores, opioid requirements,

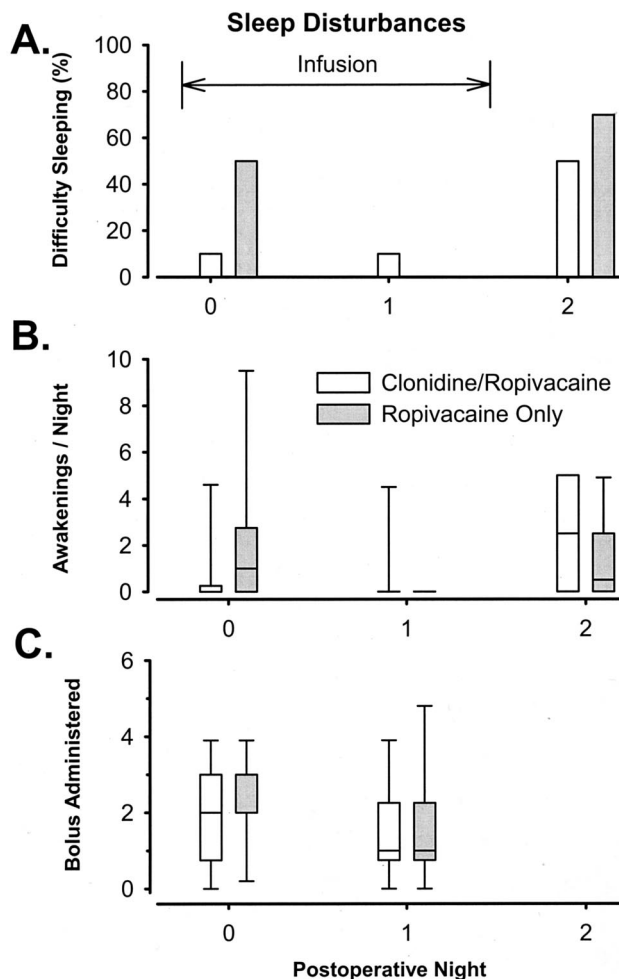


Figure 3. Effects of the addition of clonidine to interscalene perineural ropivacaine infusion on sleep disturbances after moderately painful shoulder surgery. End-points included the percentage of each group reporting difficulty sleeping because of pain (A), number of awakenings because of pain (B), and number of bolus doses self-administered between 11:00 PM and 7:00 AM (C). The infusions were discontinued in the evening of postoperative Day 2, as indicated by the horizontal bar. A, Data are expressed as the fraction of patients reporting difficulty sleeping because of pain. B and C, Data are expressed as median (horizontal bar) with 25th–75th (box) and 10th–90th (whiskers) percentiles for patients randomly assigned to ropivacaine 0.2% or ropivacaine 0.2% plus clonidine 2 $\mu\text{g}/\text{mL}$ (basal rate, 5 mL/h; bolus dose, 5 mL; lockout, 1 h). For tightly clustered data (e.g., Panel B, postoperative Day 1, clonidine/ropivacaine group), the median approximated the 10th, 25th, and 75th percentile values. In this case, the median is 0.0, and only the 90th percentile is clearly noted. There were no statistically significant differences between study groups.

and satisfaction scores compared with patients receiving 4 mL/h in the previous dose-response study (5). The available data therefore lead us to recommend a basal infusion for interscalene perineural ropivacaine infusions of at least 8 mL/h after moderately painful surgery of the shoulder. Related to this, because more boluses were attempted than delivered (Table 3), the basal rate of 5 mL/h that was used for this investigation may also have affected the results.

Also notable in this study was the removal of eight patients (29%) before randomization because of the inability to insert their catheter in <30 minutes. A previous study by the same investigators using the same equipment and technique reported a failure rate of only 4% (5). Accounting for this difference is the fact that in the previous investigation, no time limitation for catheter placement was defined, whereas the present study specified a 30-minute maximum.

A bolus of clonidine may precipitate hypotension and sedation when introduced by one of a number of possible routes (16), including perineural injection as part of a peripheral nerve block (17). However, these two complications have not been reported with a perineural infusion of clonidine $\leq 10 \mu\text{g}/\text{h}$ (7-11) or with an epidural infusion of $40 \mu\text{g}/\text{h}$ (16). In patients receiving an epidural bolus of clonidine $4 \mu\text{g}/\text{kg}$ followed by a $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ infusion, plasma clonidine concentrations decreased over 24 hours (18). In our previous study of perineural infusion involving the addition of $1 \mu\text{g}$ of clonidine to each milliliter of ropivacaine, no patients reported vertigo. However, in the present study, 3 patients with $2 \mu\text{g}$ of clonidine added to each milliliter of ropivacaine reported vertigo, compared with none who received only ropivacaine. Although this difference was not statistically significant ($P = 0.12$), it does represent a trend that should be taken into consideration by health care providers if the larger dose of clonidine is used.

In this study, there were no medical complications attributable to the initial regional block, catheter placement, or perineural infusion. However, the small number of patients does not permit us to draw definite conclusions about its relative safety. Because not all patients desire, or are capable of accepting, the extra responsibility that comes with the catheter and pump system, appropriate patient selection is crucial for safe ambulatory local anesthetic infusion. Interscalene catheters were used in this study. It is possible that clonidine would improve analgesia if infused with local anesthetic in another anatomic location or at a larger dose, or it may allow for a smaller concentration of ropivacaine to be used. Finally, clonidine may interact differently with local anesthetics used for continuous perineural infusion other than ropivacaine, although we believe that this is unlikely for long-acting local anesthetics on the basis of the results of one investigation involving single-injection interscalene blocks with bupivacaine (17).

Appendix 1. Nightly Questionnaire

Pain Scores (POD 0-3)

"Please answer the following questions regarding your surgical pain since the last time we spoke using a scale of 0 to 10, 0 being no pain at all and 10 being the worst pain you can imagine."

"What was the worst pain you have felt?"

"What is the current pain that you are feeling?"

"While you were resting, what was the average pain you have felt?"

Sleep Quality (POD 1-3)

"Did you awaken last night because of pain?" (no = 0)

If "yes": "How many times did you awaken last night because of pain?" (if more than nine awakenings or insomnia, score = 10)

Satisfaction (POD 2)

"How satisfied are you with your pain control following your operation on a scale of 0-10, 0 being very dissatisfied and 10 being very satisfied?"

Related Side Effects (POD 0-2)

"Have you felt dizzy or short-of-breath?" (if "yes," record associated factors)

Manufacturers donated the portable infusion pumps (Smiths Medical) and catheters (Arrow International) used for this investigation.

References

1. Ilfeld BM, Morey TE, Wright TW, et al. Continuous interscalene brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2003;96:1089-95.
2. Ilfeld BM, Morey TE, Wang RD, Enneking FK. Continuous popliteal sciatic nerve block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* 2002;97:959-65.
3. Klein SM, Grant SA, Greengrass RA, et al. Interscalene brachial plexus block with a continuous catheter insertion system and a disposable infusion pump. *Anesth Analg* 2000;91:1473-8.
4. Ilfeld BM, Morey TE, Enneking FK. Continuous infraclavicular brachial plexus block for postoperative pain control at home: a randomized, double-blinded, placebo-controlled study. *Anesthesiology* 2002;96:1297-304.
5. Ilfeld BM, Morey TE, Wright TW, et al. Interscalene perineural ropivacaine infusion: a comparison of two dosing regimens for postoperative analgesia. *Reg Anesth Pain Med* 2004;29:9-16.
6. Capdevila X, Barthelet Y, Biboulet P, et al. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; 91:8-15.
7. Singelyn FJ, Gouverneur JM. Extended "three-in-one" block after total knee arthroplasty: continuous versus patient-controlled techniques. *Anesth Analg* 2000;91:176-80.
8. Singelyn FJ, Deyaert M, Joris D, et al. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* 1998;87:88-92.
9. Singelyn FJ, Vanderelst PE, Gouverneur JM. Extended femoral nerve sheath block after total hip arthroplasty: continuous versus patient-controlled techniques. *Anesth Analg* 2001;92:455-9.
10. Singelyn FJ, Seguy S, Gouverneur JM. Interscalene brachial plexus analgesia after open shoulder surgery: continuous versus patient-controlled infusion. *Anesth Analg* 1999;89:1216-20.

11. Singelyn FJ, Aye F, Gouverneur JM. Continuous popliteal sciatic nerve block: an original technique to provide postoperative analgesia after foot surgery. *Anesth Analg* 1997;84:383-6.
12. Iskandar H, Guillaume E, Dixmieras F, et al. The enhancement of sensory blockade by clonidine selectively added to mepivacaine after midhumeral block. *Anesth Analg* 2001;93:771-5.
13. Ilfeld BM, Morey TE, Enneking FK. Continuous infraclavicular perineural infusion with clonidine and ropivacaine compared with ropivacaine alone: a randomized, double-blinded, controlled study. *Anesth Analg* 2003;97:706-12.
14. Ilfeld BM, Enneking FK. A portable mechanical pump providing over four days of patient-controlled analgesia by perineural infusion at home. *Reg Anesth Pain Med* 2002;27:100-4.
15. Boezaart AP, de Beer JF, du TC, van Rooyen K. A new technique of continuous interscalene nerve block. *Can J Anaesth* 1999;46:275-81.
16. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984-1995). *Anesthesiology* 1996;85:655-74.
17. Culebras X, Van Gessel E, Hoffmeyer P, Gamulin Z. Clonidine combined with a long acting local anesthetic does not prolong postoperative analgesia after brachial plexus block but does induce hemodynamic changes. *Anesth Analg* 2001;92:199-204.
18. De Kock M, Crochet B, Morimont C, Scholtes JL. Intravenous or epidural clonidine for intra- and postoperative analgesia. *Anesthesiology* 1993;79:525-31.