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## Effects of Local Anesthetic Concentration and Dose on Continuous Interscalene Nerve Blocks: A Dual-Center, Randomized, Observer-Masked, Controlled Study

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### Abstract

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**Conflict of Interest:** Sorenson Medical (West Jordan, UT, USA) provided funding and donated portable infusion pumps for this investigation. This company had no input into any aspect of study conceptualization, design, and implementation; data collection, analysis and interpretation; or manuscript preparation. None of the authors has a personal financial interest in this research.

**Background and Objectives:** It is currently unknown if the primary determinant of continuous peripheral nerve block effects is simply total drug dose, or whether local anesthetic concentration and/or volume have an influence. We therefore tested the null hypothesis that providing ropivacaine at different concentrations and rates—but at an equal total basal dose—produces similar effects when used in a continuous interscalene nerve block.

**Methods:** Preoperatively, an interscalene perineural catheter was inserted using the anteriolateral approach in patients undergoing moderately painful shoulder surgery. Subjects were randomly assigned to receive a postoperative perineural infusion of either 0.2% ropivacaine (basal 8 mL/h, bolus 4 mL) or 0.4% ropivacaine (basal 4 mL/h, bolus 2 mL) through the second postoperative day. Our primary end point was the incidence of an insensate hand/finger during the 24-hours beginning the morning following surgery.

**Results:** The incidence of an insensate hand/finger did not differ between the treatment groups (n=50) to a statistically significant degree (0.2% ropivacaine mean [SD] of 0.8 [1.3] times; 0.4% ropivacaine mean 0.3 [0.6] times; estimated difference=0.5 episodes, 95% confidence interval, -0.1 to 1.1 episodes; p=0.080). However, this is statistically inconclusive given the confidence interval. In contrast, pain (p=0.020) and dissatisfaction (p=0.011) were greater in patients given 0.4% ropivacaine.

**Conclusions:** For continuous interscalene nerve blocks, the 95% confidence interval (plausible differences in the incidence of an insensate hand/finger) contains values ranging from a clinically important disadvantage (1.1) to a clinically unimportant advantage (-0.1) for the lower concentration. Given the statistically inconclusive results and design limitations of the current study, further research on this issue is warranted. In contrast, providing a lower concentration of local anesthetic at a higher basal rate provided superior analgesia. These relationships are different than previously reported for continuous popliteal-sciatic nerve blocks. The interaction between local anesthetic concentration and volume is thus complex and varies among catheter locations.

## Keywords

anesthesia; continuous peripheral nerve block; continuous interscalene nerve block; patient-controlled regional analgesia; perineural local anesthetic infusion

## Introduction

While continuous peripheral nerve blocks provide potent analgesia and other benefits, one well-recognized and undesirable side effect is a transiently insensate limb.<sup>1,2</sup> Because insensate limbs may be prone to accidental injury, it is postulated that such incidences are best minimized.<sup>1-5</sup> It is currently unknown if the primary determinant of continuous peripheral nerve block effects is simply total drug dose, or whether local anesthetic concentration and/or volume exert an influence. As a result, many different concentration and basal-rate combinations have been utilized: for ropivacaine alone, concentrations have included 0.1%,<sup>6</sup> 0.15%,<sup>7</sup> 0.2%,<sup>8</sup> 0.25%,<sup>9</sup> 0.3%,<sup>10</sup> and 0.4%.<sup>11</sup> It was previously reported that for continuous popliteal-sciatic nerve blocks, insensate toes/feet were far more common with higher volumes of relatively dilute ropivacaine compared with lower volumes of relatively concentrated ropivacaine.<sup>12</sup> However, it is unclear if this relationship holds for all anatomic locations, or is rather specific to the sciatic nerve in the popliteal fossa.

This issue has additional implications for ambulatory perineural infusion. Providing patients with a ropivacaine (0.2%) continuous interscalene nerve block at 8 mL/h results in potent analgesia following moderate-to-severely painful shoulder surgery,<sup>13,14</sup> whereas lower infusion rates are often insufficient.<sup>8</sup> But, this relatively high basal rate—especially when patient-controlled bolus doses are provided—depletes the local anesthetic reservoir of most

disposable portable infusion pumps in less than 60 hours since pump reservoirs are generally restricted to a maximum of 400-500 mL.<sup>15;16</sup> Relatively rapid reservoir depletion is problematic because the moderate-to-severe pain from many shoulder procedures often extends beyond 60 hours.<sup>13;14</sup> It would thus be beneficial if a slower infusion of more concentrated local anesthetic were equally effective and safe. However, it remains unknown if patient benefits may be retained by increasing the ropivacaine concentration while decreasing the basal rate, and thus retaining the higher delivered dose of local anesthetic.

We therefore conducted a dual-center study to test the null hypothesis that providing ropivacaine at different concentrations and rates (0.2% at 8 mL/h vs. 0.4% at 4 mL/h)—but at an equal total basal dose of 16 mg/h—produces similar effects when used in a continuous interscalene brachial plexus block. Our primary end point was the incidence of an insensate limb (e.g. inability to perceive touch on any aspect of the hand) during the 24-hour period beginning the morning after surgery. Secondary endpoints included baseline (average) and breakthrough (worst) pain scores, opioid requirements, sleep disturbances, and patient satisfaction.

## Materials and Methods

### Enrollment

The Institutional Review Board at each participating clinical center approved all study procedures (University of Florida, Gainesville, Florida; University of California San Diego, San Diego, California). All subjects provided written, informed consent; and because this was a multi-center trial, a Data Safety Monitoring Board (University of Florida, Gainesville, Florida) reviewed combined data and adverse events.

Patients offered enrollment included adults (18-75 years) scheduled for moderately painful, ambulatory, unilateral, orthopedic surgery of the shoulder who desired a continuous interscalene nerve block for postoperative analgesia. Exclusion criteria included weight less than 40 kg; a history of opioid dependence or current chronic opioid use (defined as frequent use for more than one week prior to surgery); chronic obstructive pulmonary disease; known contraindication to any study medication; known hepatic or renal insufficiency/disease; insulin-dependent diabetes mellitus; known neuropathy of any etiology in the surgical extremity; pregnancy; incarceration; difficulty understanding the study protocol or caring for the infusion pump/catheter system; American Society of Anesthesiologists Physical Status 4-6;<sup>17</sup> and any major incision outside of the brachial plexus sensory distribution (e.g., an iliac crest bone graft) or at/distal to the elbow.

### Protocol

A stimulating catheter (StimuCath, Arrow International, Reading, Pennsylvania) was inserted adjacent to the brachial plexus *via* the anterolateral approach using a previously-described technique.<sup>8;18</sup> The catheter was inserted through the needle only after stimulated motion occurred in the ipsilateral biceps and/or deltoid muscles with a current between 0.30 and 0.70 mA after the catheter was inserted 3-5 cm past the needle tip. Forty milliliters of 1.5% mepivacaine, with epinephrine, 5 µg/mL, was injected *via* the catheter with gentle aspiration every 3 mL. The interscalene nerve block was evaluated 15 minutes later and considered successful when patients demonstrated muscle weakness upon shoulder abduction and a decreased sensation to cold over the distal ipsilateral deltoid muscle. Subject demographic and catheter placement data were uploaded *via* the Internet to a secure,<sup>19</sup> password-protected, encrypted central server (www.PAINfRE.com, General Clinical Research Center, Gainesville, Florida).<sup>20</sup>

Patients with a successful catheter placement and nerve block onset per protocol were retained in the study. Patients were randomized to one of two groups—ropivacaine 0.2% or 0.4%—stratified by institution using computer-generated tables and provided to study centers *via* the PAINfRE.com Web site.

Following surgery, the ropivacaine infusion was initiated using a portable, programmable, disposable, electronic infusion pump (ambIT PCA, Sorenson Medical, West Jordan, Utah). The pumps were programmed by investigators and the infusion basal rate and patient-controlled bolus dose volume depended upon the designated treatment group (Table 1). Although patients were not specifically informed of their ropivacaine concentration, the infusion pump and local anesthetic reservoir which were accessible to subjects revealed enough information that subjects should not be considered masked to treatment group. At the discretion of investigators, a 20 mL bolus of 1.5% mepivacaine (with epinephrine, 5 µg/mL) could be injected *via* the interscalene catheter to prolong the initial surgical block in the case of an unexpected delay in the surgical start (perineural catheters were placed in preoperative holding areas—or “block rooms”—prior to entering the operating room).

### Patient education

Patients were discharged home with their infusion pump and perineural catheter *in situ*. Patients were instructed on care of the perineural catheter, the infusion pump, and signs and symptoms of local anesthetic toxicity; they were also given contact details for a continuously-available local physician. For breakthrough pain, patients were instructed to depress the bolus button on their infusion pump, wait 15 min, and then take 5-10 mg of the oral opioid oxycodone if necessary.

Patients were also informed that an insensate extremity is expected following surgery because of the dense surgical block (reinforced with the ropivacaine infusion). However, if any part of their ipsilateral hand and/or fingers was completely insensate after 09:00 the morning following surgery, patients were to pause their infusion until they regained feeling in their extremity, and then restart the infusion. “Completely insensate” was defined as being unable to determine with eyes closed that another individual was touching various parts of the hand/fingers. Patients were instructed to perform this exam during telephone calls in both the morning and afternoon of postoperative day (POD) 1-3. They were also encouraged to perform the exam throughout the infusion period, beginning the morning of POD 1.

Patients were contacted by healthcare providers beginning the night of surgery, and each afternoon thereafter through POD 3. Patients were questioned about symptoms of local anesthetic toxicity, catheter migration, and infection; gross sensory and motor function; and the appearance of the catheter site. In the afternoon of POD 2 patients' caretakers removed the catheters with a physician in telephone-contact. The presence of a metallic catheter tip confirmed complete removal.

### Measurements

Subjects were contacted by telephone in the mornings of postoperative day (POD) 1-3 by a clinical research nurse at the University of Florida General Clinical Research Center. Nurses were masked to treatment group. Pain severity and oral oxycodone use for the previous 12 h (POD 1) or 24 h (PODs 2 and 3) were recorded. Pain severity was evaluated using a Numeric Rating Scale (NRS) of 0-10, with 0 equal to no pain and 10 being the worst imaginable pain.<sup>21</sup> The number of awakenings resulting from pain the previous night was also recorded, as were the number of times the infusion pump was paused because of an insensate extremity. Patient satisfaction with postoperative analgesia was recorded on POD 2 using a 0-10 scale, 0 equal to “very unsatisfied” and 10 equal to “very satisfied.” All data were recorded on case

report forms and then uploaded to the secure PAINfRE.com Web site. The case report forms data were subsequently entered into a separate database which was, upon study completion, compared with the Web site data to identify and correct any data entry errors. Of note, the number of patient-administered bolus doses and total infusion volume was not available to investigators.

### Statistical Analysis

The study was powered for null hypothesis that altering the concentration of ropivacaine while providing an equal total dose does not change the incidence of numbness in the 24-hour period beginning at 09:00 on POD 1. Based on previously-published data,<sup>8;14</sup> the planning distribution for the number of events for the two groups (0.2% vs. 0.4%) was: 0 (60% vs. 24%), 1 (30% vs. 48%), 2 (10% vs. 22%), and 3 (0% vs. 6%). Based on a two-sample, two-sided t-test, to obtain 80% power at  $P=0.05$ , a sample size of 25 patients per group was required. The calculation used large sample methods, but simulation results agreed well for both type I error (0.05) and power (79.0%).

Since the number of events is a quantitative end point, we utilized the two-sample two-sided t-test which is virtually identical to the two-sided Z-test when sample sizes are approximately equal.<sup>22</sup> All other outcome variables (secondary, ordinal) were analyzed by the Two-sided Wilcoxon Test, which provides distribution-free P-values and is highly robust against outliers. A two-sided  $P<0.05$  was considered statistically significant for the primary end point. Because each comparison dilutes all other P-values, we restricted our analysis to 4 comparisons among secondary end points, including the average daily pain scores and satisfaction with postoperative analgesia.<sup>23</sup>  $P<0.05$  was again considered significant. Significant findings in secondary outcomes should be viewed as suggestive, requiring confirmation in a future trial before considering them as definitive.

### Results

Sixty-two patients enrolled and 50 had a perineural catheter successfully placed per protocol, all of whom developed a successful surgical block following local anesthetic injection. These 50 subjects were randomized to one of the two treatment groups. The demographic, morphometric, and surgical characteristics were similar in each group (Tables 2 and 3). Applying statistics to pre-intervention variables for subjects randomized to treatment groups is inappropriate and no statistical comparisons were applied to this data.

#### Primary end point

Patients given 0.2% ropivacaine ( $n=24$ ) experienced an insensate limb a mean (SD) of 0.8 (1.3) times, compared with 0.3 (0.6) times for subjects receiving 0.4% ropivacaine ( $n=26$ ; estimated difference=0.5 episodes, 95% confidence interval, -0.1 to 1.1 episodes;  $p=0.080$ ). Among patients assigned to 0.2% ropivacaine, 33% experienced at least one instance of an insensate extremity compared with 19% of the patients receiving 0.4% ropivacaine.

#### Secondary end points

Compared with patients given 0.4% ropivacaine, patients given 0.2% ropivacaine experienced a lower level of baseline (average) and breakthrough (worst) pain while using only half the supplemental opioids during the 24-hour period beginning the morning after surgery (Figure 1 and Table 4). There were minimal differences between the two treatment groups in sleep disturbances due to pain (Table 4). Satisfaction with postoperative analgesia (scale 0-10, 10=highest) was scored a median (25th-75<sup>th</sup> percentiles) of 10 (9-10) in Group 0.2% and 9 (8-10) in Group 0.4% ( $p=0.011$ ). There were no infusion pump malfunctions during the infusions.

## Protocol deviations and adverse events

One subject from Group 0.2% experienced difficulty speaking (but no dyspnea) the evening of POD 0, paused her pump for two hours, and then restarted it at a decreased basal rate of 5 mL/h. The problem did not recur.

## Discussion

For continuous interscalene nerve blocks, the 95% confidence interval (plausible differences in the incidence of an insensate hand/finger) contains values ranging from a clinically important disadvantage (1.1) to a clinically unimportant advantage ( $-0.1$ ) for the lower concentration of ropivacaine (0.2%). Curiously, this contrasts with perineural ropivacaine infusion during continuous popliteal-sciatic nerve blocks, in which insensate toes/feet were far more common with 0.2% ropivacaine delivered at 8 mL/h compared with 0.4% ropivacaine delivered at 4 mL/h (mean [SD] of 1.8 [1.8] times for 0.2% ropivacaine compared with 0.6 [1.1] times for 0.4% ropivacaine;  $p=0.009$ ).<sup>12</sup>

For continuous peripheral nerve blocks, it now appears that the relative importance of local anesthetic concentration and/or volume versus dose varies with anatomic catheter location.<sup>12</sup> We can only speculate on why the relationship between ropivacaine concentration and effect varies for continuous popliteal-sciatic and interscalene nerve blocks. Anatomic relationships of the perineural space and target nerve/plexus may play a significant role in determining the relative effects of volume and concentration for perineural infusions. For a continuous popliteal nerve block *via* a catheter placed using the inter-tendonous approach, the sciatic nerve is relatively compact at the level of infusion and a small volume of local anesthetic may more easily spread to the entire target nerve.<sup>24</sup> In contrast, for a continuous interscalene brachial plexus block, local anesthetic must spread to five roots or three trunks of the brachial plexus if it is to affect all of the major nerves of the upper extremity.

Our catheter insertion protocol specified that only biceps and deltoid muscle contractions would be accepted, suggesting that the tips of the stimulating catheters used in this trial were closest to the superior trunk of the brachial plexus. It is possible that during the subsequent ropivacaine infusion, local anesthetic remained concentrated in this location and did not spread to the middle or inferior trunks of the brachial plexus. Even with a large bolus of local anesthetic, the inferior trunk often remains unanesthetized, as evidenced by a frequent sparing of the ulnar nerve following a single-injection interscalene nerve block.<sup>25</sup> It is thus possible—even probable—that local anesthetic did not reach the middle or inferior trunks with the relatively low-volume perineural infusion. If so, then the local anesthetic concentration/volume might have influenced the incidence of an insensate target nerve; but the nerves emanating from the superior trunk provide sensory input mostly proximal on the arm than the hand/fingers—the endpoint of our study—and thus would not be noted by the patients of this study. Alternatively, if the primary concern is to limit the incidence of an insensate hand/finger, it should be of great comfort to know that, absent contradicting future research, little may be lost by choosing the better performing higher-volume (and lower concentration) local anesthetic.

Evidence from previous studies suggests that for continuous interscalene nerve blocks, a basal local anesthetic infusion is required to maximize patient benefits,<sup>26</sup> adding patient-controlled bolus doses does not compensate for a decreased basal rate,<sup>8</sup> and the addition of clonidine does not improve analgesia.<sup>27</sup> Results from the present study are disappointing from a clinical standpoint since it now appears that even increasing the local anesthetic concentration to counter lowering the basal infusion rate and provide the same relatively high anesthetic dose does not retain analgesic potency. While the requirement for a high basal rate may not particularly affect hospitalized patients, it does limit the duration of ambulatory perineural infusion when using portable infusion pumps with a limited reservoir.<sup>15;16</sup>



### Catheter placement success rate

We were unable to position catheters per protocol in 12 of 62 patients (81% success rate). Failures occurred when the stimulating current could not be reduced below 0.7 mA *via* the insulated needle or when muscle contractions decreased during stimulating catheter insertion. Using an identical catheter-insertion technique and protocol, previous studies have reported success rates of 95% and 97% when placement was not limited by time,<sup>8;14</sup> and 71% when insertion attempts were aborted after 30 min.<sup>27</sup> For these previous investigations, an attending anesthesiologist experienced with the insertion technique placed all perineural catheters.

However, for the current investigation, trainees placed nearly all catheters with oversight from an experienced attending, which may—along with limited time for catheter insertion—help explain the relatively low success rate of the current study. Although not specifically investigated, our experience suggests that the anterolateral approach using a stimulating catheter is a highly challenging, and often time-consuming, technique. It may be of interest to readers that most of the authors of the current study now use an ultrasound-guided posterior approach when placing an interscalene perineural catheter,<sup>28</sup> because we perceive the insertion is easier and faster than with the anterolateral technique. Of course, this assertion requires prospective study to objectively differentiate between these two methods as well as others.<sup>29</sup>

### Study limitations

A limitation of our study is that subjects and investigators were not masked to treatment group. However, it is improbable that patients had a bias towards one concentration or the other, and data collection was performed by clinical research nurses masked to treatment-group assignments. While the postoperative questionnaire included validated measures such as the Numeric Rating Scale for pain assessment,<sup>21</sup> the instruments used to assess sleep quality and analgesia satisfaction have not been previously validated. There are two additional significant limitations of this study. First, the primary endpoint used in this study was somewhat subjective in that patients and their caretakers evaluated extremity sensation and reported the results without a clinical exam by an investigator. Given these were ambulatory patients, there was no way to evaluate or control for the thoroughness of patient self-exams, and therefore the accuracy of this measurement remains unknown. However, given that all subjects were randomized to their respective treatment group, we presume that the quality and quantity of patient self-exams was relatively similar between the two groups; and thus internal validity remains high for the study.

Second, although each patient-controlled bolus dose delivered the same ropivacaine dose for both treatment groups (8 mg available every 30 min), the actual delivered doses for each group are unavailable. Therefore, it is possible that patients assigned to one of the treatment groups self-administered a greater number of bolus doses resulting in a higher total dose of delivered ropivacaine. This methodological weakness decreases confidence in our results. Future investigation is required that corrects for both the limitations on the primary endpoint external validity (incidence of an insensate limb) and the lack of total local anesthetic delivered in each treatment group (including patient-controlled bolus doses). It is noteworthy that, even given the weaknesses of this study, the results are of clinical use: if practitioners desire maximizing analgesia and patient satisfaction during continuous interscalene nerve blocks, this study provides valid information to help achieve these goals. In other words, regardless of the total amount of local anesthetic delivered to each treatment group, providing a 0.2% ropivacaine infusion at a basal rate of 8 mL/h resulted in improved analgesia and patient satisfaction relative to a 0.4% ropivacaine infusion at a basal rate of 4 mL/h.

Clinicians must be cognizant of the fact that our results hold only for the concentration/rate combination examined in this investigation. Only additional dose-response studies can provide

practitioners with the optimal local anesthetic type,<sup>30-33</sup> concentration,<sup>32;34</sup> infusion rate,<sup>8;26</sup> and bolus-dose volume combinations.<sup>26</sup>

In summary, for continuous interscalene nerve blocks, the 95% confidence interval (plausible differences in the incidence of an insensate hand/finger) contains values ranging from a clinically important disadvantage (1.1) to a clinically unimportant advantage (−0.1) for the lower concentration of ropivacaine (0.2%). Given the statistically inconclusive results and design limitations of the current study, further research on this issue is warranted. In contrast, providing a lower concentration of local anesthetic at a higher basal rate provided superior analgesia. These relationships are different than previously reported for continuous popliteal-sciatic nerve blocks. The interaction between local anesthetic concentration and volume is thus complex and varies among catheter locations.

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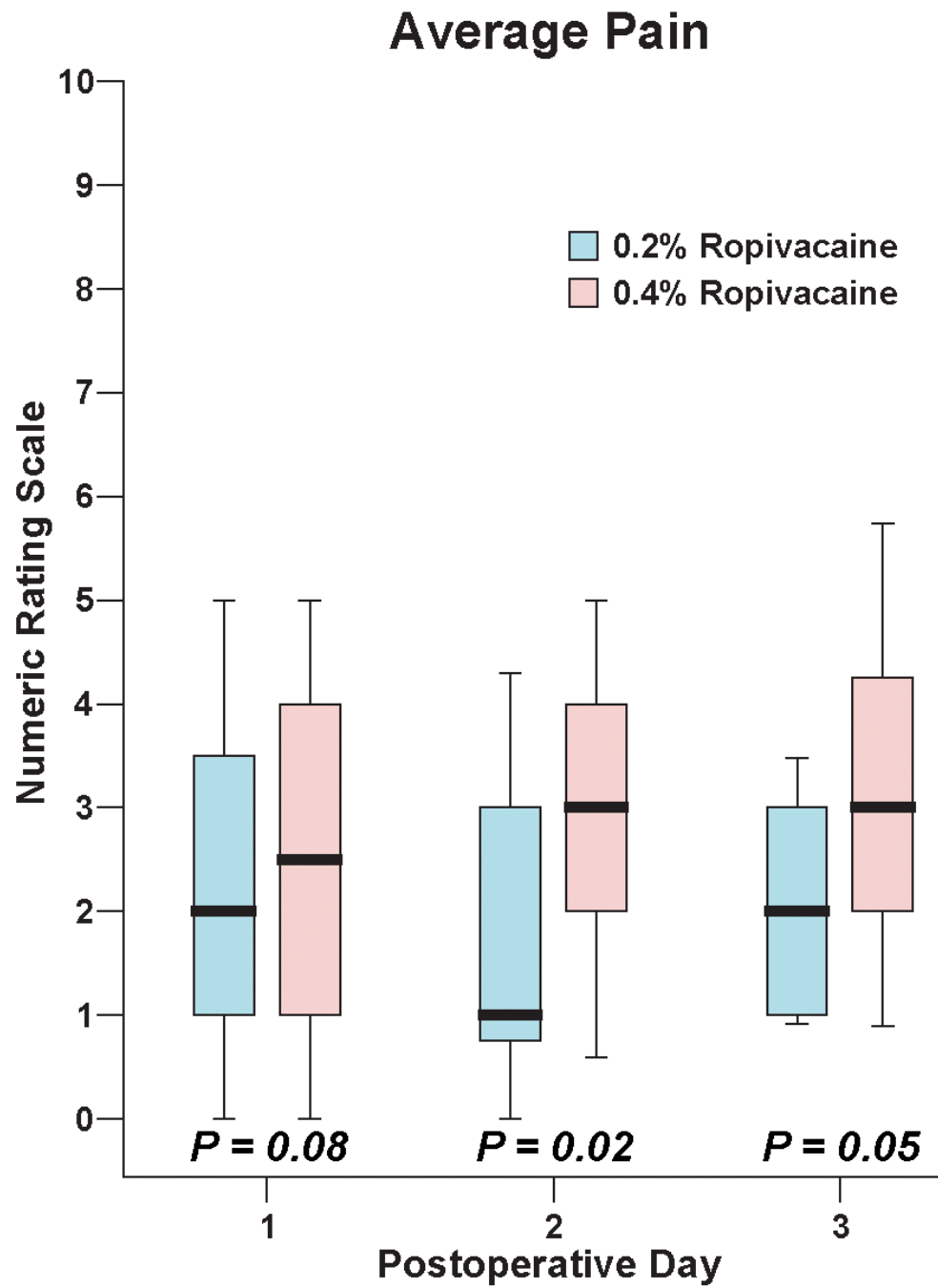
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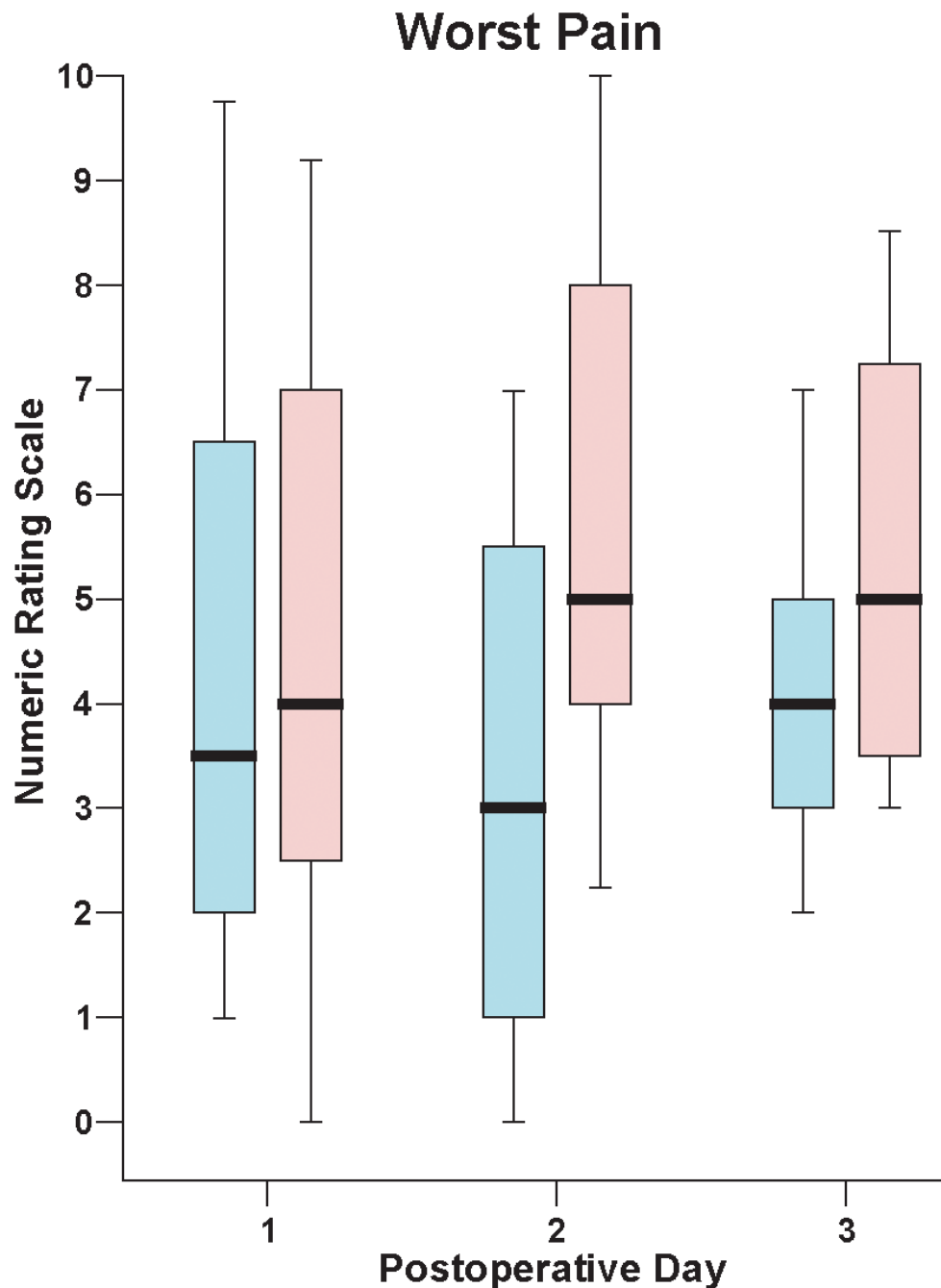
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**Figure 1.**

Effects of interscalene perineural ropivacaine concentration on *postoperative pain* following moderately-painful surgery of the shoulder. Pain severity indicated using a Numeric Rating Scale (NRS) of 0-10, with 0 equal to no pain and 10 being the worst imaginable pain. Data are expressed as median (horizontal bar) with 25<sup>th</sup>-75<sup>th</sup> (box) and 10<sup>th</sup>-90<sup>th</sup> (whiskers) percentiles for patients randomly assigned to group 0.2% (0.2% ropivacaine, 8 mL/h basal, 4 mL bolus) or group 0.4% (0.4% ropivacaine, 4 mL/h basal, 2 mL bolus). Because each comparison dilutes all other P-values, we restricted our analysis to 4 comparisons among secondary end points. P-values are provided where statistical comparisons were applied.

**Table 1**  
Perineural ropivacaine infusion profile by treatment group.

Ropivacaine Concentration	Basal Rate (mL/h)	Basal Dose (mg/h)	Bolus Volume (mL)	Bolus Dose (mg)	Lockout Duration (min)	Maximum Dose (mg/h)
0.2% (2 mg/mL)	8	16	4	8	30	24
0.4% (4 mg/mL)	4	16	2	8	30	24

**Table 2**

## Population data and surgical information

	Group 0.2% (n=24)	Group 0.4% (n=26)
Age (yr)	53 ± 15	45 ± 13
Sex (female / male)	12 / 12	18 / 8
Height (cm)	171 ± 11	175 ± 11
Weight (kg)	78 ± 19	91 ± 17
Minimum current <i>via</i> needle (mA)	0.54 ± 0.25	0.53 ± 0.19
Minimum current <i>via</i> catheter (mA)	0.55 ± 0.23	0.56 ± 0.22
Subjects receiving an additional perioperative mepivacaine bolus (#)	18	22
Intraoperative midazolam (mg)	2 (0 - 4)	2 (1 - 4)
Intraoperative fentanyl (µg)	100 (0 - 200)	150 (0 - 200)
Intraoperative morphine (mg)	0 (0 - 0)	0 (0 - 0)
Surgery duration (min)	65 ± 30	79 ± 34
Subjects from site A / B (#)	18 / 6	18 / 8

Values are reported as mean (SD), median (25<sup>th</sup>-75<sup>th</sup> percentiles), or number of subjects, as indicated.

Applying statistics to pre-intervention variables for subjects randomized to treatment groups is inappropriate. For this reason, no statistical comparisons were applied to the data of this table.



**Table 3**

## Primary surgical procedures

	Group 0.2% (n=24)	Group 0.4% (n=26)
Open rotator cuff repair	1	1
Arthroscopic rotator cuff repair	13	12
Arthroscopic Mumford and/or SAD	5	5
Arthroscopic capsulectomy	1	1
Arthroscopic labral repair	2	3
Acromioclavicular joint reconstruction	1	2
ORIF of the proximal humerus	1	2

SAD: subacromial decompression

ORIF: open reduction internal fixation

Applying statistics to pre-intervention variables for subjects randomized to treatment groups is inappropriate. For this reason, no statistical comparisons were applied to the data of this table.

**Table 4**

## Secondary endpoints

	Group 0.2% (n=24)	Group 0.4% (n=26)
Home oral opioid consumption (mg) *		
Postoperative day 1	5 (0-10)	5 (0-10)
Postoperative day 2	5 (0-15)	15 (5-30)
Postoperative day 3	10 (5-20)	10 (5-30)
Awakenings because of pain (#)		
Postoperative day/night 0	0 (0-1)	0 (0-2)
Postoperative day/night 1	0 (0-1)	0 (0-2)
Postoperative day/night 2	0 (0-2)	0 (0-3)

Values are reported as median (25<sup>th</sup>-75<sup>th</sup> percentiles)

Because each comparison dilutes all other P-values, we restricted our analysis to 4 comparisons among secondary end points. For this reason, no statistical comparisons were applied to the data of this table.

\* Oral opioid provided as 5 mg oxycodone tablets. Values include home opioid consumption in the 24-hours previous to the daily data-collection phone calls.