

## Ropivacaine 0.2% and Lidocaine 0.5% for Intravenous Regional Anesthesia in Outpatient Surgery

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**Background:** A longer-acting local anesthetic agent, such as ropivacaine, may offer advantages over lidocaine for intravenous regional anesthesia. The objectives of this study were to evaluate whether the findings of volunteer investigations with intravenous regional anesthesia with ropivacaine (which have shown prolonged analgesia after release of the tourniquet) translates into improved pain control after surgery.

**Methods:** With Human Investigation Committee approval and a double-blind study design, 20 healthy patients with American Society of Anesthesiologists physical status I or II classification who were scheduled to undergo forearm and hand surgery were randomly assigned to administration of 40 ml of either 0.2% ropivacaine or 0.5% lidocaine for intravenous regional anesthesia. Evidence of central nervous system side effects, such as lightheadedness, tinnitus, and metallic taste, as well as cardiac arrhythmias, were evaluated and treated (if necessary) after local anesthetic administration, before and during surgery, and after release of the tourniquet until discharge from the postanesthesia care unit. Regression of sensory anesthesia in the nerve distributions of the forearm and hand was recorded. Verbal numerical pain scores were monitored and quantified until the patients were discharged to home from the postanesthesia care unit. Patient pain scores, side effect profiles, time to first oral intake, and total amount of oral analgesics were recorded 24 h postoperatively.

**Results:** Intravenous regional anesthesia with 0.2% ropivacaine and 0.5% lidocaine provided equivalent levels of surgical anesthesia. After release of the tourniquet, the first evidence for return of sensation in the distribution of the five peripheral nerves occurred later in the ropivacaine group (median, 20 min; range, 15–40 min) than in the lidocaine group (median, 1 min; range, 1–25 min). Verbal numerical pain scores were significantly lower at the time of admission, whereas during the remainder of the postanesthesia care unit stay and later at home, the difference in verbal numerical pain scores between the two groups was no longer statistically significant.

**Conclusions:** Ropivacaine 0.2% may be an alternative to 0.5% lidocaine for intravenous regional anesthesia in the outpatient surgical setting. Longer-lasting analgesia in the immediate postoperative period may be due to a more profound and prolonged tissue binding effect of ropivacaine.

IN 1908, Karl August Gustav Bier<sup>1</sup> recorded 134 cases using procaine for intravenous regional anesthesia (IVRA) during upper limb surgery. In 1963, Holmes<sup>2</sup>

improved on the technique by using different drugs and modifying the site of drug injection. Further modifications have since occurred, and IVRA has proven to be successful for surgery of the extremities. It is a technically simple and reliable technique, with success rates of 94–98%.<sup>3,4</sup> In the United States, 0.5% lidocaine is the local anesthetic most frequently used for this technique, but it has a relatively short duration of action after tourniquet release.<sup>5</sup> A longer acting agent, such as bupivacaine, initially gained substantial popularity for use during IVRA but was laden with potentially serious side effects.<sup>6,7</sup> Several deaths have been reported from use of bupivacaine for IVRA when inadvertently administered intravenously and in obstetric patients during regional anesthesia with high concentrations of bupivacaine.<sup>7,8</sup> Bupivacaine has been identified as a “fast-in, slow-out” type of local anesthetic that maintains a high affinity and binds tightly to myocardial sodium receptors. Therefore, if high plasma concentrations of bupivacaine are achieved, prolonged cardiac arrest may occur, which frequently has proved to be irreversible.<sup>3,4</sup>

The amide local anesthetic ropivacaine is a pure S-enantiomer and is structurally related to bupivacaine. The duration of effect of ropivacaine is similar to that of bupivacaine,<sup>9,10</sup> and ropivacaine has been shown to result in less depression of the cardiac conduction system when compared with bupivacaine.<sup>11–15</sup> Intravenous ropivacaine, compared with bupivacaine and lidocaine in several volunteer studies, has yielded evidence of less cardiac and central nervous system (CNS) side effects but has achieved similar surgical anesthetic conditions.<sup>5,13,14,16</sup> Two studies<sup>5,16</sup> have shown fewer CNS side effects and prolonged sensory blockade after release of the distal tourniquet when using ropivacaine instead of lidocaine for IVRA. Therefore, ropivacaine may serve as a local anesthetic for IVRA that could provide prolonged and improved analgesia over lidocaine and have a lower toxicity profile when compared with bupivacaine.

### Methods

With Yale University Human Investigations Committee approval and after informed written consent, 20 healthy adult patients with American Society of Anesthesiologists I or II classification scheduled to undergo upper extremity surgery were enrolled in the study. Patients with reported allergies to local anesthetics or who were scheduled to undergo surgery that was anticipated to last

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Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Received for publication November 6, 2000. Accepted for publication March 30, 2001. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 14–18, 2000.

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more than 90 min were excluded from participation. The patients were randomly assigned to one of two groups for administration of either 0.2% ropivacaine or 0.5% lidocaine for IVRA. Syringes containing the local anesthetic solutions were provided by an investigator who did not participate in data collection. All patients were monitored continuously with noninvasive blood pressure, pulse oximetry, and a five-level electrocardiogram throughout the surgical procedure and until discharge from the postanesthesia care unit (PACU). An intravenous catheter (20 gauge) was inserted into a distal vein on the dorsum of the hand of the operative extremity for double-blind injection of local anesthetic solution. An additional intravenous catheter was placed in the contralateral upper extremity. A double-cuff tourniquet was placed on the upper arm of the operative extremity, and its proximal tourniquet was inflated subsequent to exsanguination of the limb with an Esmarch bandage. The proximal tourniquet was inflated to 100 mmHg above the patient's systolic blood pressure. Minimal tourniquet time was set at 20 min. An intravenous solution of 40 ml of either 0.5% lidocaine (200 mg) or 0.2% ropivacaine (80 mg) was injected over approximately 1 min by an anesthesiologist blinded to the local anesthetic, and patients were evaluated for any signs of cardiac arrhythmias or CNS side effects, such as dizziness, tinnitus, or metallic taste. During surgery, the proximal tourniquet remained inflated until the patient complained of severe discomfort (verbal numerical pain score [VNS] of 10). The distal tourniquet was then inflated, followed by deflation of the proximal tourniquet. Intraoperatively, patients remained awake or were sedated with propofol as needed. When the surgical procedure was completed, the distal tourniquet was deflated for initially 1 min, then reinflated for 1 min, and again deflated and removed from the patient's extremity. After tourniquet deflation, patients were continuously monitored for cardiac arrhythmias and asked about CNS side effects, such as dizziness, tinnitus, lightheadedness, or presence of metallic taste on a 0-10 verbal numeric scale. Assessments were made by a blinded observer at 1-min intervals for the first 10 min and then at 10-min intervals while in the PACU and until discharge to home.

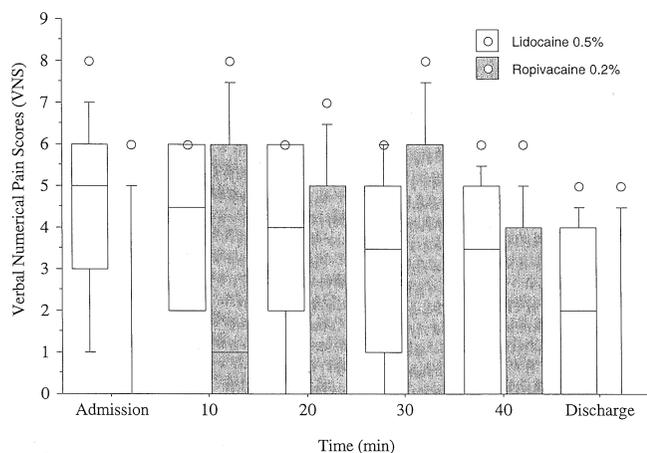
During these same time points, pain scores were recorded on a VNS scale of 0-10 (0 = no pain; 10 = worst imaginable pain). Regression of sensory anesthesia was assessed by pin prick (VNS 0-10) and evaluated in the dermatomal distribution of five peripheral nerves: the lateral and medial antebrachial cutaneous, median, radial, and ulnar nerves. Quantification of analgesic consumption was recorded and included time to first intake, as well as the total amount administered during the first 24 h after surgery. Analgesics administered in the PACU and used at home consisted of opioids, such as 25-50  $\mu$ g intravenous fentanyl (PACU only), oral hydrocodone-acetaminophen, oxycodone-acetaminophen, and co-

deine-acetaminophen, as well as nonsteroidal antiinflammatory drugs (ibuprofen, acetaminophen). To convert opioids into morphine equivalents, a factor of 10:1 (fentanyl:morphine) was used for fentanyl, a factor of 6:1 (oxycodone:morphine) was used for oxycodone hydrochloride plus acetaminophen, a factor of 6:1 (hydrocodone:morphine) was used for hydrocodone bitartrate plus acetaminophen, and a factor of 1:7 (codeine:morphine) was used for codeine phosphate plus acetaminophen.<sup>17</sup> Patients were instructed about how to complete a diary at home to record postoperative analgesic requirements, pain scores, and any side effects experienced during the subsequent 24 h after discharge from the PACU. Patient information recorded at home was obtained by a follow-up telephone call and confirmed on receipt of their written diary.

Data representing the patients' demographics, tourniquet times, injection-to-incision times, surgical times, and time the patients spent in the PACU were normally distributed as evaluated by the Shapiro-Wilkens test. They are expressed as mean  $\pm$  SD and were statistically evaluated by analysis of variance and the *t* test. Data representing the regression of sensory blockade, VNS, time to first analgesic intake, and total analgesic consumption in the PACU and at home were not normally distributed and are therefore expressed as median (range). They were analyzed using the Mann-Whitney U test for nonparametric data. The number of patients who took analgesic medication for their pain relief in the PACU and at home was compared by means of the chi-square test;  $P < 0.05$  was considered statistically significant.

## Results

All patients enrolled in the study completed the investigation. There were no differences with respect to age, weight, and height between the two patient groups. Type of surgical interventions were equally distributed between groups and included ganglion removal, finger amputations, tendon release, and carpal tunnel surgery. Surgeries lasted  $29 \pm 13$  and  $32 \pm 16$  min (mean  $\pm$  SD) for the ropivacaine and lidocaine groups, respectively ( $P =$  not significant [NS]). Intraoperatively, no medication other than propofol for sedation was administered to patients, and intraoperative analgesics did not become necessary. A median of 45 (range, 0-400) mg propofol was administered to patients in the ropivacaine group; 53 mg (0-400 mg,  $P =$  NS) was administered to patients in the lidocaine group. The times from injection of local anesthetic to surgical incision were  $15 \pm 4$  and  $12 \pm 4$  min for the ropivacaine and lidocaine groups, respectively ( $P =$  NS). Tourniquet times were  $46 \pm 13$  (range, 24-68) and  $44 \pm 8$  (range, 32-60) min for the ropivacaine and lidocaine groups, respectively ( $P =$  NS).



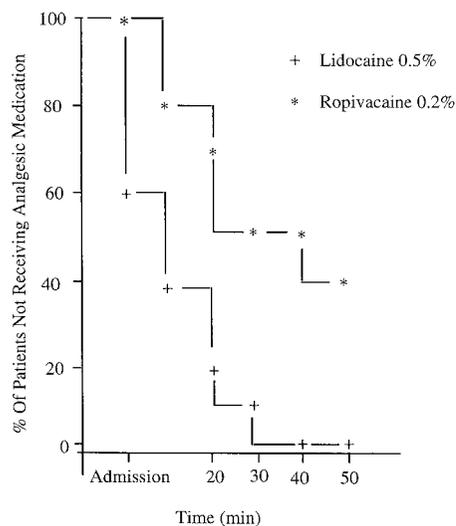
**Fig. 1.** Verbal numerical pain scores (VNS) during postanesthesia care unit stay. Data are presented as box (25th–75th percentile) and whisker (10th–90th percentile) plot. Open circles indicate maximum and minimum values (range). Admission = admission to the postanesthesia care unit; Discharge = release from the postanesthesia care unit to home.

There was no difference in the incidence and intensity of tourniquet pain during surgery. After release of the tourniquet, the first evidence for return of sensation in the distribution of the median, ulnar, radial, antebrachial medial and lateral cutaneous nerves occurred at a median of 20 (range, 15–40) min in the ropivacaine group and at 1 (range, 1–25) min in the lidocaine group ( $P < 0.05$ ). Patients randomized to the ropivacaine group spent  $55 \pm 26$  min in the PACU, in contrast to  $73 \pm 32$  min for the patients of the lidocaine group ( $P = NS$ ). At the time of admission to the PACU (fig. 1), VNSs were markedly lower in patients to whom ropivacaine was administered for IVRA when compared with those to whom lidocaine was administered ( $P < 0.05$ ). At the time of discharge from the PACU and at home, the difference in pain scores between the two groups became less prominent ( $P = NS$ ). Time until first intake of pain medication after local anesthetic injection was longer for the ropivacaine group (median, 47 min; range, 27–340 min) compared with the lidocaine group (median, 34 min; range, 2–140 min;  $P < 0.05$ ). During the patients' PACU stay, between 25 and 100  $\mu\text{g}$  fentanyl was administered intravenously to three patients in the ropivacaine group; 5 mg oral hydrocodone-acetaminophen was administered to one patient. Patients in the ropivacaine group consumed between 0 and 30 (median, 0) mg of morphine equivalents in the PACU. Six of 10 patients in this group did not receive any analgesic medication during their PACU stay. The number of patients to whom analgesics were administered in the PACU was lower in the ropivacaine group than in the lidocaine group, but the difference in number did not reach statistical significance (fig. 2). At home, seven patients in the ropivacaine group consumed 70 mg hydrocodone-acetaminophen, 5 mg oxycodone-acetaminophen, and 1,600 mg codeine-acetaminophen.

This corresponded to a median of 45 mg of morphine equivalents (range, 0–230 mg). Three patients in this group did not need any analgesics for pain relief. Four patients in the lidocaine group consumed between 25 and 125  $\mu\text{g}$  fentanyl in the PACU; further, four received hydrocodone-acetaminophen orally, and one patient received 5 mg oral oxycodone-acetaminophen. Nine patients in the lidocaine group consumed between 0 and 30 (median, 21.25) mg of morphine equivalents in the PACU. At home, six patients in the lidocaine group consumed 45 mg hydrocodone-acetaminophen, 60 mg oxycodone-acetaminophen, and 600 mg codeine-acetaminophen. This represents 120 (range, 85–150) mg morphine equivalents. Four patients took only nonsteroidal antiinflammatory drugs, such as acetaminophen and ibuprofen. There was a borderline statistical difference between the two groups in the amount of pain medication consumed in the PACU ( $P = 0.07$ ), with no such difference in the amount taken at home. At the time when patients took their first analgesic medication in the PACU, pain scores were 7.5 (range, 6–8) and 6 (range, 4–6) in the ropivacaine and lidocaine groups, respectively ( $P = NS$ ). The time of the first analgesic dose at home identified lower VNSs of 5.5 (range, 3–8) and 6.5 (range, 4–8) in the ropivacaine and lidocaine groups, respectively ( $P = NS$ ). No patient in the ropivacaine group had cardiac arrhythmias or reported CNS side effects, whereas one patient in the lidocaine group reported mild tinnitus after tourniquet release.

**Discussion**

This investigation in outpatient procedures shows that IVRA with 0.2% ropivacaine provides anesthesia of slightly slower, clinically irrelevant onset but of the same



**Fig. 2.** Kaplan-Meier plot for percent of patients to whom analgesic medication was not administered during their postanesthesia care unit stay.

surgical quality when compared with 0.5% lidocaine. Based on a previous investigation in volunteers, a dose of 80 mg ropivacaine 0.25% was considered appropriate for comparison to 200 mg lidocaine 0.5%.<sup>16</sup> In contrast to this previous investigation, CNS side effects experienced from both local anesthetic groups were virtually absent in the current study, presumably because of the use of propofol for sedation. After completion of the surgical procedure and subsequent to tourniquet release, ropivacaine provided an extended analgesic effect, and patients took their first analgesic medication significantly later than those patients from the lidocaine group. Though not statistically different, in this study population, fewer patients from the ropivacaine group required less analgesic medications and reported lower overall scores during the first 24 h after surgery than the patients of the lidocaine group. Because of extended analgesic effects in the ropivacaine group, VNSs recorded were comparably low from admission to the PACU and throughout the PACU stay when compared with patients of the lidocaine group. The higher pain scores at the time of admission to the PACU in patients of the lidocaine group resulted in comparatively earlier requests for pain medication in this group, leading eventually to lower pain scores and thereby decreasing the difference between the two groups.

Reports of long-lasting postoperative analgesia subsequent to IVRA date back to the 1970s and 1980s when long-lasting local anesthetics, such as etidocaine and bupivacaine, were used.<sup>6,18</sup> Ware<sup>6</sup> reported 2,500 surgical procedures performed under IVRA using 0.2% bupivacaine and cited one patient experiencing drowsiness after tourniquet release. Similar CNS side effects have been reported in recent volunteer studies using 0.5% lidocaine for IVRA.<sup>5,16,19</sup> A study investigating "washout" of lidocaine from the upper extremity showed a biphasic release of the drug into the systemic circulation.<sup>20</sup> An initial fast release of 30% of the drug was followed by a gradual washout of the remainder. An investigation using a radiolabeled compound similar to lidocaine has shown that during the first 3 min after tourniquet deflation, 58% of the substance was washed out; further, 11% of the compound was released during the subsequent 17 min after tourniquet release.<sup>21</sup> The remaining radiolabeled compound still present at 20 min after tourniquet deflation was 15.6%.

In contrast to 0.5% lidocaine, 0.2% ropivacaine in volunteer studies did not show the intensity or frequency of CNS side effects.<sup>5,16</sup> The lower incidence, reduced intensity, and short duration of CNS side effects when using long-lasting local anesthetics, such as ropivacaine<sup>16</sup> and bupivacaine,<sup>22</sup> presumably results from slow absorption of drug from the extremity after tourniquet release, which in turn is a function of the high tissue protein binding properties of these two agents. In two studies, venous plasma concentrations of 0.2% ropiva-

caine (80 mg<sup>19</sup> and 120–170 mg<sup>5</sup>) were measured during 30 and 90 min after tourniquet release. After tourniquet deflation, measured venous plasma concentrations of  $1.2 \pm 0.3 \mu\text{g/ml}$ <sup>19</sup> and  $1.7 \pm 0.5 \mu\text{g/ml}$ ,<sup>5</sup> respectively, were highest at 10 min, whereas CNS symptoms peaked at 3 min.<sup>19</sup> A better correlation was found between arterial plasma concentrations of ropivacaine and CNS symptoms after tourniquet release.<sup>5</sup>

The longer acting local anesthetics may be the drugs of choice for IVRA due to slow release from tissue binding sites with subsequent slow increase in plasma concentrations. Reports of cardiac arrest after intravascular absorption of larger volumes of bupivacaine, however, have resulted in reconsideration and the eventual discontinuation of bupivacaine for IVRA.<sup>7</sup> In contrast, ropivacaine has been reported to be accidentally administered intravascularly at doses of 120 and 150 mg, respectively, resulting in seizures.<sup>23,24</sup> These seizures were successfully treated without sequelae, and the reports did not indicate the deleterious cardiovascular side effects as can sometimes be seen with bupivacaine. Therefore, ropivacaine may be an alternative to lidocaine for IVRA, providing a longer duration of analgesia after surgery.

The study has shown a small but significant difference in the duration of postoperative analgesia, time to first analgesic request, and the overall analgesic requirement in the immediate postoperative time period in those patients to whom 0.2% ropivacaine was administered, when compared with those to whom 0.5% lidocaine was administered for IVRA. Based on the results of previous volunteer studies<sup>5,16</sup> and this investigation in patients undergoing upper extremity surgery, ropivacaine may be considered an alternative to lidocaine for IVRA.

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