Levobupivacaine 0.125% and Lidocaine 0.5% for Intravenous Regional Anesthesia in Volunteers

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Background: Levobupivacaine, a long acting, amino-amide, local anesthetic, may offer advantages over lidocaine for intravenous regional anesthesia (IVRA). The objective of this investigation was to compare levobupivacaine to lidocaine for IVRA.

Methods: After institutional review board approval and informed consent, eight unpremedicated male American Society of Anesthesiologists (ASA) I–II volunteers received 40 ml of levobupivacaine 0.125% or lidocaine 0.5% for IVRA on separate days. Onset and regression of sensory anesthesia by pinprick, transcutaneous electrical stimulation (TES), and of motor function were tested before, during, and after release of the tourniquet. Central nervous system and cardiac side effects were evaluated after local anesthetic administration and tourniquet release. The tourniquet remained inflated for 30–45 min.

Results: Intravenous regional anesthesia with either agent provided surgical anesthesia. Sensory anesthesia to pinprick (lateral antebrachial cutaneous nerve) was faster with lidocaine at median 1.5 min, versus 12.5 min with levobupivacaine. Loss of sensation to TES occurred at median 22.5 and 27.5 min for lidocaine and levobupivacaine, respectively. Loss of motor function occurred earlier after lidocaine administration. After release of the tourniquet, return of sensation to TES, pinprick (ulnar nerve), and return of motor function occurred later with levobupivacaine at median 25, 15, and 21.25 versus 10, 4.5, and 10 min with lidocaine. Central nervous system side effects were absent in volunteers given levobupivacaine, but five of eight volunteers given lidocaine experienced mild side effects. No cardiac events were noted.

Conclusions: Levobupivacaine 0.125% may be an alternative to lidocaine 0.5% for IVRA. Longer lasting analgesia after release of the tourniquet may be caused by a more profound and prolonged tissue binding effect of levobupivacaine.

INTRAVENTOUS regional anesthesia (IVRA) is a widespread and well-established technique with high success rates.1,2 Local anesthetics such as prilocaine and lidocaine are commonly administered for IVRA on the upper or lower extremity. Both, however, have a brief duration of action, which may impact the duration of intraoperative analgesia and redistribution of the drug after tourniquet release. Theoretically, it would be beneficial to use a longer-acting agent, such as racemic bupivacaine. Its use, though highly successful and without serious side effects in IVRA initially,3,4 is now considered contraindicated because racemic bupivacaine binds tightly to myocardial sodium channels with the consequence that patients cannot be resuscitated.5,6

The latest additions to the group of amide local anesthetics are the pure S-enantiomers, ropivacaine and levobupivacaine. They are devoid of the potential toxic dextrorotatory version of racemic local anesthetic mixtures, though sufficient high dosages may still induce central nervous system and cardiac toxicity. While ropivacaine is structurally related to bupivacaine, levobupivacaine is a single enantiomer of the racemic mixture. Both have been shown to cause less depression of cardiac conduction and milder central nervous system (CNS) side effects in preclinical7 and clinical trials,8,9 when accidentally injected intravascularly.9 Intravenous infusions of up to 150 mg levobupivacaine administered to volunteers demonstrated a higher margin of safety when compared with bupivacaine.5 The potential benefit of a local anesthetic for IVRA that could provide anesthesia of greater duration than lidocaine after tourniquet release with less toxicity than racemic bupivacaine, as well as results obtained from previous investigations with ropivacaine for IVRA10,11 prompted the current comparison of levobupivacaine with lidocaine for IVRA in healthy volunteers. The potency of levobupivacaine is approximately four times greater than lidocaine.12,13 Therefore, a 0.125% solution of levobupivacaine was compared with lidocaine to most closely achieve equipotency with lidocaine 0.5%, which is generally used for IVRA.

Methods

With the approval of the Yale University Institutional Human Investigations Committee, and the written informed consent of the participants, eight unsedated healthy male volunteers participated in a randomized, double blind, cross-over comparison of lidocaine 0.5% (40 ml) and levobupivacaine 0.125% (40 ml). The study drugs were injected intravenously into the dorsal surface of the nondominant hand in two separate study sessions at least 7 days apart. A second intravenous catheter was placed into an antecubital vein of the dominant arm to provide a route for emergency drug administration. Throughout the investigation, volunteers were monitored continuously with noninvasive blood pressure measurements, a two-lead electrocardiogram (II and V5), and pulse oximetry.

After exsanguination of the nondominant arm with an Esmarch bandage, the proximal cuff of a double-cuff tourniquet placed on the volunteer’s upper arm was

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Anesthesiology. V 97, No 2, Aug 2002 325
inflated to a pressure of 250 mmHg. Limb occlusion pressure was verified by loss of pulse oximetry tracing of the ipsilateral index finger. Then, the local anesthetic was injected over 1 min. When the proximal tourniquet pressure became unbearably painful (rated as 10 on a verbal numeric scale [VNS]), the distal cuff was inflated, and after inflation the proximal tourniquet was released. The distal tourniquet remained inflated minimally for 30 min and maximally for 45 min, or was deflated in between these two time points once the pain became unbearable (VNS = 10).

Assessments during cuff inflation were obtained at baseline, at 1-min intervals for the first 5 min, then at 2.5 min intervals for the remainder of the session until tourniquet release. Response to pinprick was evaluated on a 0–10 scale (0 = no sensation and 10 = normal sensation) in the dermatomal distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. Pain in response to tetanic stimulation (5-s, 50 hertz [Hz] at 60 milliamperes) delivered at the surface electrodes placed within one inch of each other over the ulnar nerve at the wrist, was evaluated on a VNS scale, ranging from 0 (no pain) to 10 (worst imaginable pain). This stimulus has been shown to be equivalent to a surgical incision, initially in studies assessing mean alveolar concentrations of volatile anesthetics and subsequently in assessments of regional anesthesia. Onset of pinprick and TES analgesia was defined as decrease from baseline (VNS = 10). A VNS less than 5 was chosen to represent acceptable surgical conditions after this stimulus. Motor function was evaluated by asking the volunteer to squeeze a blood pressure cuff, which was preinflated to 40 mmHg. Onset of motor blockade was defined as decrease from baseline; complete motor blockade was achieved when the volunteer was no longer able to squeeze the preinflated blood pressure cuff above 40 mmHg.

The previously described assessments were repeated at the same time intervals (baseline, at 1-min intervals for the first 5 min, then at 2.5 min intervals) after deflation of the distal tourniquet until the volunteer reported baseline values. In addition, the volunteers were asked to rate CNS side effects such as dizziness, tinnitus, light-headedness, and the presence of metallic taste on a 0–10 VNS scale at these same times.

Data are expressed as median and range and were analyzed using Wilcoxon signed test for nonparametric data; to detect the frequency of CNS side-effects a chi-square test was administered. Actual P values were presented for all P < 0.05 determinations to permit “corrections” for repetitive testing at multiple time-points.

Results

All participating volunteers completed the investigation successfully. Significant differences were found in the loss of sensation to pinprick in the distribution of the five peripheral nerves of the forearm and hand and in the loss of motor function (fig. 1). The lateral antebrachial cutaneous nerve was the first to lose sensation at median 1.5 (range 1–12.5) min and 12.5 (5–17.5) min, whereas the median nerve was the last at 8.75 (range 2–17.5) min and 17.5 (12.5–30) min for lidocaine and levobupivacaine, respectively (fig. 1). There was no significant difference between the two local anesthetics with respect to loss of sensation after transcutaneous electrical stimulation. Loss of sensation to TES (VNS < 5) occurred at median 22.5 (17.5–30) min and 27.5 (5–40) min for lidocaine and levobupivacaine, respectively.

After the distal tourniquet was released, decreased sensation to pinprick and TES persisted longer, and recovery to full motor function took longer after IVRA with levobupivacaine (fig. 2). Full regression to baseline TES

![Fig. 1. Onset times (median, range) of sensory and motor blockade measured by transcutaneous electrical stimulation (TES) and pinprick (sensory) as well as grip strength (motor). Box plots represent median (50th), range (25th–75th), and whisker (10th–90th) percentiles. *P < 0.05 versus levobupivacaine 0.125%. TES = transcutaneous electrical stimulation, Lat anterbr = lateral antebrachial cutaneous nerve, Med anterbr = medial antebrachial cutaneous nerve.](image1)

![Fig. 2. Recovery times (median, range) of sensory and motor blockade measured by transcutaneous electrical stimulation (TES) and pinprick (sensory) as well as grip strength (motor). Box plots represent median (50th), range (25th–75th), and whisker (10th–90th) percentiles. *P < 0.05 versus levobupivacaine 0.125%. TES = transcutaneous electrical stimulation, Lat anterbr = lateral antebrachial cutaneous nerve, Med anterbr = medial antebrachial cutaneous nerve.](image2)
occurred at median 10 (4–25) min and 25 (3–55) min in the lidocaine and levobupivacaine groups, respectively. The ulnar nerve was the first and the median nerve the last to recover in both sessions (fig. 2). In the lidocaine session, the ulnar and median nerves recovered at 4.5 (1–15) min and 13.75 (4–17.5) min, respectively. After levobupivacaine injection, these two peripheral nerves resumed full sensory function after 15 (30–60) min and 20 (12–50) min, respectively. Motor blockade also persisted markedly longer in the levobupivacaine session. Full strength was resumed after 10 (7.5–17.5) min following lidocaine injection, and after 21.25 (12.5–50) min following levobupivacaine injection. After release of the distal tourniquet, the volunteers, when receiving levobupivacaine, reported no CNS side effects. In contrast, five of the eight volunteers receiving lidocaine reported dizziness, tinnitus, or metallic taste within the first 10 min after release of the tourniquet ($P = 0.138$). On a VNS scale ranging from 0–10 (0 = no side effect and 10 = maximum possible side effect), three volunteers reported an intensity between 3 and 7 for dizziness, four rated their tinnitus between 3 and 9, and four rated metallic taste between 2 and 7. Cardiovascular side effects such as arrhythmias or hypotension were not observed with either local anesthetic agent.

**Discussion**

The study demonstrated that IVRA with levobupivacaine 0.125% provided equivalent surgical anesthesia when compared with the more frequently used local anesthetic lidocaine 0.5%. Though there was a significant difference in the loss of sensation to pinprick in the distribution of the five peripheral nerves, no such difference was found in the onset of surgical anesthesia when tested by transcutaneous electrical stimulation. As the stimulus to TES (60 mA at 50 Hz) is by far more painful, being equivalent in intensity to a surgical skin incision, it is presumably more closely related to an acceptable depth of surgical anesthesia than evaluation by pinprick. After tourniquet release, levobupivacaine had a prolonged residual effect. The interdrug difference was significant for sensation to TES as well as pinprick in the distribution of all five peripheral nerves and for grip strength at each of the postdeflation test times. The longer duration of posttourniquet sensory and motor block after IVRA with levobupivacaine 0.125% may be attributable to more complete and more persistent tissue protein binding, and hence slower release into the systemic circulation. Similarly to ropivacaine, when given for IVRA to volunteers or patients undergoing outpatient surgery, this will presumably translate into superior pain control in patients in the postoperative period.

Accidental intravenous administration of racemic bupivacaine frequently proved to be fatal because patients could not be resuscitated. In contrast, case reports involving the accidental intravascular injection of levobupivacaine showed signs of light (lightheadedness, blurred vision) to severe (seizures) CNS side effects with the absence of cardiac dysrhythmias. One article dealing with an intravascular injection of 140 mg of levobupivacaine 0.75% administered epidurally reported only lightheadedness and blurred vision, however, the patient had been premedicated with midazolam and received a barbiturate prophylactically. Plasma levels not determined until 14 min after injection displayed a value of 2.7 µg/ml. A second case (Dr. Puri, personal communication, November 2001) involved the administration of a combination of lidocaine 2% (20 ml) and levobupivacaine 0.75% (20 ml) for axillary plexus blockade. After injection using a transarterial approach, a major amount entered the systemic circulation. Though premedicated with midazolam, the patient developed seizures, which were successfully treated with benzodiazepine and propofol. No cardiac events were noted. In healthy volunteers who received an intravenous infusion (10 mg/min to a maximum of 150 mg) of either racemic bupivacaine or levobupivacaine in a double-blind, crossover manner, the $S$-enantiomer had less effect on myocardial contractility and stroke index than its racemic counterpart. Levobupivacaine and racemic bupivacaine reduced the myocardial contractility index by 4.5 and 13%, and the stroke index by 6% and 20%, respectively.

In the current study, even mild CNS side effects such as tinnitus, lightheadedness, or metallic taste were absent in volunteers treated with levobupivacaine, in contrast to five of eight participants who received lidocaine. Similar results were obtained in a recent investigation when lidocaine was compared with ropivacaine. In this study, all participating volunteers given lidocaine (10/10) developed CNS side effects after release of the tourniquet, in contrast to only 4 of 10 subjects who received ropivacaine. The intensity of these CNS side effects was also higher after lidocaine administration, as evaluated by a visual numeric scale. In volunteers who experienced CNS symptoms such as tinnitus, dry mouth, and numbness of the tongue and lips with racemic bupivacaine, an equivalent intravenous dose of levobupivacaine was associated with fewer central nervous system disorders. Thirty-six percent of levobupivacaine recipients reported no CNS events at all.

In conclusion, based on the findings of equivalent surgical anesthesia, prolonged analgesia after tourniquet release, and absent CNS and cardiac side effects, it seems reasonable to consider levobupivacaine as a potential alternative to lidocaine for IVRA. The advantages of levobupivacaine 0.125% in context with intravenous regional anesthesia warrant further investigation, particularly in patients under surgical conditions. Similar to ropivacaine, presumably a prolonged decrease in postoperative pain scores and overall analgesic consumption may then be seen.
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Anesthesiology, V 97, No 2, Aug 2002