

Can Ropivacaine and Levobupivacaine Be Used as Test Doses during Regional Anesthesia?

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Background: Lower systemic toxicity reported with ropivacaine and levobupivacaine may produce less reliable recognition of inadvertent intravenous injection during regional anesthesia. This study was undertaken to determine whether ropivacaine and levobupivacaine are suitable for use as intravenous test doses by evaluating central nervous system (CNS) symptoms after intravenous bolus injection.

Methods: Institutional approval and informed consent were granted for the study. One hundred twenty patients scheduled to undergo elective surgery were randomly assigned to receive 5 ml intravenous saline, 100 mg lidocaine, 25 mg ropivacaine, or 25 mg levobupivacaine before anesthesia. Patients reported CNS symptoms after injection and were monitored for hemodynamic change.

Results: Intravenous ropivacaine or levobupivacaine produced CNS symptoms in only 52% and 57% of patients, respectively, compared with 87% of patients after lidocaine ($P < 0.02$). Despite preparatory instruction, many patients receiving ropivacaine or levobupivacaine did not spontaneously volunteer symptoms because they were subtle and admitted symptoms only after in-depth questioning by the investigator.

Conclusions: Plain ropivacaine and levobupivacaine (25 mg) solutions are unsuitable for use as intravenous test doses during regional anesthesia because CNS symptoms are insufficient. When using ropivacaine or levobupivacaine for regional anesthesia, for test dose purposes, the authors recommend the addition of epinephrine to the local anesthetic solution or the use of a separate agent with more predictable CNS characteristics.

ROPIVACAINE and levobupivacaine are relatively new local anesthetics shown to be less toxic than bupivacaine in laboratory and human volunteer studies.¹⁻³ These agents are approved for use in epidural anesthesia and peripheral nerve block, where lower toxicity should be beneficial. A potential liability of lower toxicity, however, may be difficulty in recognizing central nervous system (CNS) symptoms during an inadvertent intravenous injection.

When performing regional anesthesia, it is customary to give a test dose of local anesthetic solution through a needle or catheter 3-5 min before administering larger volumes. This safety maneuver aids in detecting intravascular local anesthetic injection by the appearance of auditory or gustatory changes. Practitioners frequently

use the same local anesthetic solution for testing and therapeutic purposes. If a test dose yields false-negative results, large amounts of local anesthetic can be administered with potentially catastrophic results.

With the small local anesthetic dose customarily used for testing, ropivacaine and levobupivacaine may produce insufficient CNS symptoms to warrant use as test doses. Intravenous ropivacaine and levobupivacaine infusions are less likely than bupivacaine to elicit CNS symptoms in volunteers,^{2,3} and local anesthetic-induced seizure has been reported after therapeutic doses of ropivacaine or levobupivacaine because CNS symptoms were absent.⁴⁻⁷ When accidental intravenous injection occurs, ropivacaine and levobupivacaine should be less cardiotoxic, but it is equally important to initially recognize an intravenous injection to prevent the overdose altogether. Ropivacaine and levobupivacaine have not been evaluated for use as test doses, although both agents have been used for such purposes.^{5,8-13} This study was undertaken to determine whether ropivacaine or levobupivacaine (25 mg) is suitable for use as a test dose during regional anesthesia by evaluating the immediate CNS symptoms after intravenous bolus injection.

Materials and Methods

All study subjects were 18-50 yr old and were in good health (American Society of Anesthesiologists physical status class I or II), with normal airway anatomy as judged by an anesthesiologist. Subjects were excluded for weight greater than 90 kg, pregnancy, inability to communicate in the common language, or allergy to local anesthetics.

After institutional review board approval at Clinique Ste. Anne-St. Remi Hospital in Brussels, Belgium, 120 unpremedicated male and nonpregnant female patients were randomly assigned to receive intravenous saline, 2% lidocaine (100 mg), 0.5% ropivacaine (25 mg), or 0.5% levobupivacaine (25 mg) before general anesthesia. The group size ($n = 30$) was determined by power analysis based on the percent of predicted positive responses to drug injection. It was assumed that 10% of patients receiving saline, 90% receiving lidocaine, and 70% receiving ropivacaine or levobupivacaine would have a positive response. Considering these assumptions and using chi-square with 3 degrees of freedom ($P < 0.001$), a sample size of 29 (power = 0.80, $\alpha = 0.05$) was required. On the day of surgery, patients gave verbal informed consent to participate in a research study, and baseline blood pressure, heart rate, height, and weight were recorded.

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Table 1. Demographic Data

	Saline (n = 28)	Lidocaine (n = 30)	Ropivacaine (n = 29)	Levobupivacaine (n = 30)
Male:Female*	13:12	9:19	8:20	14:15
Age, yr	40 ± 12	37 ± 12	36 ± 11	39 ± 11
Height, cm	171 ± 9	166 ± 13	170 ± 9	170 ± 8
Weight, kg	72 ± 12	69 ± 14	69 ± 15	74 ± 17

Data are expressed numerically for sex, otherwise as mean ± SD. There are no significant differences among groups.

* Gender data are missing for three patients in the saline group, two patients in the lidocaine group, one patient in the ropivacaine group, and one patient in the levobupivacaine group.

Assessments

Patients received a 5-ml intravenous bolus of study solution, with investigators and patients blinded to treatment. Before injection, patients were instructed as to the type of symptoms they might experience, including visual or hearing changes, perioral numbness, metallic taste, tingling in extremities, dizziness, slurred speech, shortness of breath, palpitations, and anxiety. They were also informed that other symptoms might occur and should be reported to the physician. After injection, the possible symptoms were repeated by the examiner so that when they occurred at approximately 45 s, the patients were acutely aware of them. Using a time-graduated data collection sheet, the onset and offset times of each symptom were noted, and patients graded the symptom severity as absent, mild, moderate, or severe on a scale of 0–3, respectively. For patients experiencing dysphoria from the CNS symptoms, midazolam (2 mg) was available.

Monitoring

Electrocardiography and oxygen saturation were continuously monitored during the 10-min study period before general anesthesia. In addition, noninvasive blood pressure measurements were recorded immediately and 5 min after study drug administration.

Follow-up

Patients had to be free of CNS symptoms, with vital signs at baseline, before the initiation of anesthesia. Other discharge criteria were as per the routine postoperative care.

Statistical Analysis

Numerical data were analyzed by one-way analysis of variance. Ordinal or nonparametric data were evaluated by Kruskal-Wallis one-way analysis of variance on ranks and the Dunn method of multiple comparisons (either pairwise or *vs.* control). Proportional data were analyzed by chi-square or Fisher exact test. Data are presented as mean ± SD or median (25th–75th percentile) as appropriate. Multiple comparison adjustments in significant *P* values were accounted for by the appropriate *post hoc* tests or Bonferroni-type modification of acceptable *P* values.

Results

One hundred twenty patients were enrolled, and 117 completed the study. Demographic data are shown in table 1. Two patients in the saline group and one patient in the ropivacaine group were excluded because the data sheet was misplaced.

CNS Symptoms

No patient experienced CNS symptoms after receiving intravenous saline. After 25 mg intravenous ropivacaine or levobupivacaine, only 52% or 57% of patients, respectively, reported one or more CNS symptoms (table 2). In contrast, lidocaine was significantly more reliable in producing recognizable CNS symptoms ($P < 0.02$, chi-square test) when compared with either ropivacaine or levobupivacaine (table 2). For lidocaine, ropivacaine, and levobupivacaine, the onset of CNS symptoms oc-

Table 2. Central Nervous System Symptoms

	CNS Symptoms*†	Symptom Severity§ Median (25th, 75th Percentiles)	Symptom Duration, s Mean ± SD
Lidocaine (n = 30)	87‡	2 (1, 3)	112 ± 61
Ropivacaine (n = 29)	52	2 (1, 2)	82 ± 39
Levobupivacaine (n = 30)	57	2 (1, 2)	95 ± 56
Saline (n = 28)	0	NA	NA

* Percentage of patients reporting one or more central nervous system (CNS) symptoms after intravenous injection of saline or local anesthetic solution. † $P < 0.001$ when compared with saline using one-way analysis of variance on ranks and Dunn *post hoc* analysis. ‡ Intravenous lidocaine was significantly ($P < 0.02$) more likely to produce CNS symptoms when compared with ropivacaine or levobupivacaine using chi-square analysis with adjustment for multiple comparisons. § Symptom severity was numerically graded as mild = 1, moderate = 2, and severe = 3.

NA = not applicable.

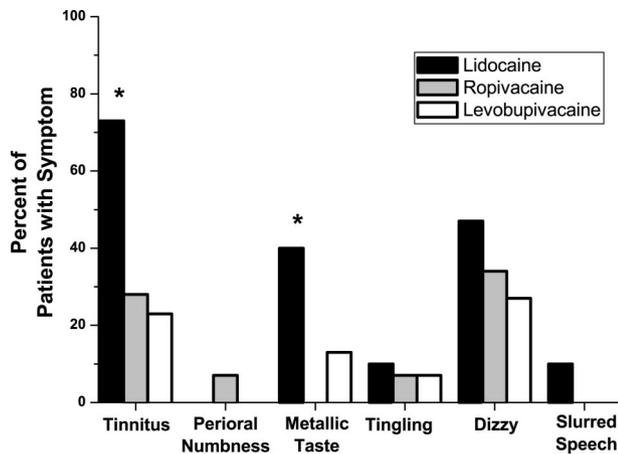


Fig. 1. Percentage of patients with central nervous system symptoms after administration of intravenous lidocaine, ropivacaine, or levobupivacaine. Lidocaine differed from ropivacaine and levobupivacaine using the exact chi-square test (* $P < 0.05$).

curred at averages of 43 ± 14 , 44 ± 14 , and 40 ± 12 s ($P =$ not significant) after injection, respectively, and persisted 112 ± 61 , 82 ± 39 , and 95 ± 56 s ($P =$ not significant) (table 2).

With regard to symptomatology, for lidocaine, tinnitus was reported in 73% of patients, followed by dizziness in 47% and metallic taste in 40% (fig. 1). In addition, one patient experienced severe anxiety, and three patients had mild slurring of speech after receiving intravenous lidocaine.

In contrast, for ropivacaine, dizziness was the most commonly reported symptom in 34% of patients, followed by tinnitus in 28% (fig. 1). There were no reports of metallic taste, anxiety, or slurred speech after ropivacaine injection. Levobupivacaine injection produced similar results, with dizziness occurring in 27%, tinnitus in 23%, and metallic taste in 13%, without reports of slurred speech or anxiety. Of interest, two patients in the ropivacaine group and one patient in the levobupivacaine group experienced subtle tingling isolated in a digit or one extremity as the only manifestation of intravenous local anesthetic injection. The overall symptom frequency and severity are summarized in table 2. For ropivacaine and levobupivacaine, many of the symptoms were discrete and were recalled retrospectively by the patient after repeated questioning by the examiner.

Side Effects

Blood pressure and heart rate were stable before and after intravenous injection in all but one patient (data not shown). One patient given levobupivacaine reported severe palpitations, and heart rate increased from 96 to 123 beats/min, accompanied by a blood pressure change from 151/80 mmHg to 121/83 mmHg. No therapy was rendered. In addition, no patient required midazolam for CNS-related symptoms.

Discussion

During regional anesthesia, a local anesthetic intravenous test dose should produce a fast onset of reliable symptoms that resolve quickly with low probability for harm. In the current study, a 25-mg intravenous bolus of ropivacaine or levobupivacaine produced CNS symptoms in only 52% or 57% of patients, respectively. This observation is concerning because 15- to 22.5-mg ropivacaine or levobupivacaine test doses have been used during epidural anesthesia and peripheral nerve block.^{5,8-13}

Accordingly, there are 19 reports of seizure after accidental intravenous injection of ropivacaine or levobupivacaine, and in only 8 cases, toxicity was preceded by warning symptoms. When CNS symptoms were present, agitation¹⁴⁻¹⁷ has been more commonly reported than dysarthria,^{18,19} facial numbness,²⁰ or the "prodrome" of toxicity.²¹ Interestingly, agitation, uninhibited vocalization, and bizarre behavior have been described after large unintended intravenous injections of ropivacaine¹⁵ and levobupivacaine,¹² without seizure. These reports highlight the relative absence of prodromal CNS toxicity symptoms after large intravenous injections of ropivacaine or levobupivacaine.

For ropivacaine, the mean \pm SD dose resulting in convulsion was 181.5 ± 86 mg (range, 20-300 mg) in patients weighing 65 ± 15 kg (range, 44-90 kg). For levobupivacaine, seizure has been reported after patients received 125 mg²² or 150 mg^{7,23} during brachial plexus anesthesia. In all but one case,¹⁷ emergency control of the airway was required, and in nearly half of the cases, surgery was postponed or canceled. Fortunately, there are few accounts of cardiac instability^{4,24} after accidental intravenous ropivacaine injection, and in all other reports, the only cardiac manifestation of toxicity was self-limited sinus tachycardia.^{7,14-17,20,23}

In most cases of ropivacaine- and levobupivacaine-induced toxicity, "safe" administration methods were used; attempts were made to aspirate blood through the needle or catheter,^{4,6,14,16,18,21-23} and a test dose was given.^{5,13,17,20} Ropivacaine and levobupivacaine as test doses, however, have not been evaluated. Only one editorial has questioned the suitability of ropivacaine as a test dose²⁵ after Morton *et al.*¹³ reported two unrecognized intravenous catheters in 31 patients undergoing cesarean delivery with epidural anesthesia (representing 6% of the patients studied). Not only did the 3-ml ropivacaine test dose (22.5 mg) fail to identify the intravenous catheter placement, symptoms were not elicited until one patient received 75 mg and the other received 150 mg (the total dose). Fortunately, there were no adverse maternal or fetal effects. This study is alarming, however, because in pregnancy, a 5-10% incidence of intravascular catheter insertion occurs during epidural anesthesia and must be recognized.

One might argue that a larger test dose may produce

more reliable CNS symptoms. In reviewing the literature, however, it is doubtful that a larger dose would be more useful, and it could be potentially harmful. In one report, a 2-ml test dose of 1.0% ropivacaine (20 mg) produced seizure in a 44-kg patient receiving epidural anesthesia.²⁰ Furthermore, during epidural anesthesia, one combination dose is frequently used for both intravenous and subarachnoid testing, and larger doses could result in total spinal anesthesia with subarachnoid injection. For example, 15 mg ropivacaine has been used as a combined test dose⁹⁻¹¹ during epidural anesthesia where 3 ml ropivacaine (0.5%) was administered and a 4-min¹⁰ or 5-min^{9,11} waiting period preceded the 10- to 20-ml total dose administered over 4 min⁹ or 5 min.^{10,11} This dosing pattern is common in clinical practice, and although it is possibly suitable for some local anesthetics (*i.e.*, lidocaine), it is not for ropivacaine and levobupivacaine. Seizures have been reported after a "negative" combined 15-mg test dose because CNS symptoms were not elicited.^{5,17} Furthermore, titrating the total dose over 5 min may be problematic because seizure onset can be delayed.^{14,17,21,24} Using a larger combined test dose of plain ropivacaine or levobupivacaine solution is not recommended because CNS symptoms would not be guaranteed and might risk possible seizure or total spinal anesthesia in the event of subarachnoid injection.

The recognition of intravenous symptoms reported by patients in this study probably overestimates what would occur in clinical practice. The study patients were carefully instructed and repetitively questioned during the observation period. Despite preparatory instruction, many patients did not spontaneously volunteer symptoms because they were so subtle. Only with persistent questioning by the investigator did some patients retrospectively report and grade symptoms. This methodology of persistent questioning was probably more rigorous than commonly practiced clinically.

In summary, the 25-mg intravenous bolus of ropivacaine or levobupivacaine failed to produce sufficient CNS symptoms to warrant routine use as a test dose. The literature does not support using larger doses. When ropivacaine or levobupivacaine are used for regional anesthesia, for test dose purposes, we recommend the use of separate agents with more predictable characteristics, such as lidocaine,²⁶ or the addition of epinephrine to the test dose. It is important to know, however, that convulsions from intravenous ropivacaine and levobupivacaine injection have been reported after a negative combined lidocaine-epinephrine test dose,²⁷ when epinephrine was added to the local anesthetic solution^{12,15,23} and when lidocaine was concurrently administered.²⁸ Systemic toxicity resulting from accidental intravascular local anesthetic injection is possible during every regional anesthetic; therefore, appropriate test doses, fractionated injections, adequate monitoring, and immediate availability of emergency

airway and resuscitation equipment remain essential to safe patient care. No preventive technique is infallible, and above all, vigilance must prevail.

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