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Bilateral Intravenous Regional Anesthesia

A New Method to Test Additives to Local Anesthetic Solutions

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Background: **Ketorolac, when added to lidocaine, has been shown to reduce early tourniquet pain during intravenous regional anesthesia (IVRA) in patients. Although the effectiveness of ropivacaine 0.2% for IVRA is equal to that of lidocaine 0.5% but significantly reduces central nervous system side effects after release of the tourniquet, it provides no advantage with regard to tourniquet tolerance times. Simultaneous bilateral IVRA with ropivacaine 0.2% was used to test the hypothesis that ketorolac modifies tourniquet tolerance and to test whether drug combinations can be evaluated in one study session.**

Methods: **Ten healthy, unsedated volunteers received 30 ml of ropivacaine 0.2% in each upper arm with 2 ml of normal saline in one arm and 30 mg of ketorolac in the contralateral arm for IVRA. Both proximal tourniquets remained inflated for 30 min, followed by inflation of the distal tourniquets and release of the proximal ones. Verbal numeric scores for tourniquet pain were recorded for both extremities. Central nervous system side effects were graded after release of each distal tourniquet.**

Results: **There was no difference between the two upper extremities with regard to surgical anesthesia and tourniquet tolerance. Total tourniquet tolerance was a median of 58.5 min (range, 45–90 min) and 60.5 min (39–79 min) in the normal saline and ketorolac groups, respectively. After release of the distal tourniquets, 5 of 10 volunteers experienced mild dizziness.**

Conclusions: **The addition of ketorolac to ropivacaine does not improve tourniquet tolerance. Minimal central nervous system side effects after tourniquet release suggest that a total of 60 ml ropivacaine 0.2% for bilateral IVRA is a useful model for comparison of IVRA drug combinations.**

INTRAVENOUS regional anesthesia (IVRA) is a common procedure for brief surgical interventions on the upper and lower limbs. For procedures of longer duration, tourniquet pain is a limiting factor, and the addition of medication to local anesthetics has been advocated in an effort to improve tourniquet comfort and to reduce postoperative pain. A recent review[1] of adjuncts for IVRA reported 29 studies including more than 1200 study subjects. In most of these studies, either lidocaine or prilocaine was used as a local anesthetic. Adjuncts used were opioids (fentanyl, meperidine, morphine, sufentanil), tramadol, nonsteroidal antiinflammatory drugs (ketorolac, tenoxicam, aspirin), clonidine, or muscle relaxants (atracurium, pancuronium, mivacurium). Neither opioids nor muscle relaxants have been shown to affect tourniquet tolerance. Two studies involving the combinations of clonidine 1 μg/ml and lidocaine 0.5% yielded promising results in terms of tourniquet tolerance and postdeflation analgesia.[2,3] In another investigation,[4] ketorolac was shown to improve early tourniquet tolerance when used in combination with lidocaine for IVRA. Patients enrolled, however, were randomized to receive either lidocaine or lidocaine–ketorolac on separate occasions, *i.e.*, for different surgical interventions.

Comparisons of ropivacaine and lidocaine for IVRA in volunteers in two study sessions on the upper arm have shown equivalent surgical anesthesia with the two local anesthetic agents, but after tourniquet release, reduced central nervous system (CNS) side effects were seen with ropivacaine.[5] Because of the reduced CNS side effect profile, we speculated that ropivacaine would allow simultaneous bilateral IVRA of the arms in volunteers. This would permit the study of drug combinations in one session, thereby eliminating intersession variables. To address the hypothesis that the addition of ketorolac to a long-acting local anesthetic reduces tourniquet pain during IVRA at any time point, we used a new model of simultaneous bilateral IVRA with ropivacaine to allow bilateral IVRA of the upper arm.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

Approval for the study was obtained from the Yale Human Investigational Committee. After written informed consent had been obtained, tourniquet pain was evaluated in 10 healthy, unsedated volunteers (four female, six male; age, 25–48 yr) who participated in this randomized, double-blind investigation. Study drugs were provided by the hospital's pharmacy, and investigators remained blinded to the study solutions. One arm received 30 ml of ropivacaine 0.2% with 2 ml of normal saline; the other extremity was given 30 ml of ropivacaine 0.2% and 30 mg of ketorolac (15 mg/ml) after bilateral inflation of the proximal tourniquet cuffs. The drugs were injected into the dorsum of both hands. Measurements of pinprick sensation in the distribution of the easily accessible and pure sensory medial antebra-

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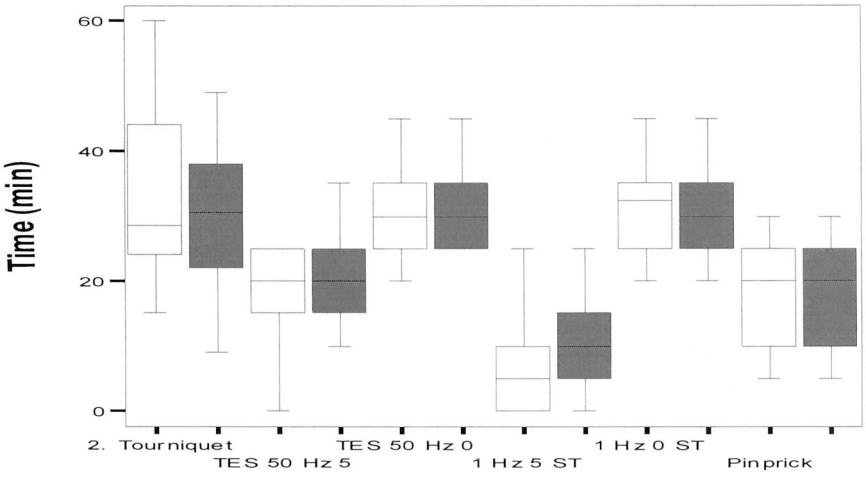

Fig. 1. Times to reach a VNS of: (1) 10 for distal tourniquet pain (*2. Tourniquet*), (2) 5 for pain after TES with 50 Hz (*TES 50 Hz 5*), (3) 0 for pain after tetanic TES with 50 Hz (TES; 50 Hz 0), (4) 5 for pain after 1-Hz single twitch stimuli (*1 Hz 5 ST*), and (5) 0 for pain after 1-Hz single twitch stimuli (*1 Hz 0 ST*). Also, times to complete loss of sensation to pinprick at the area innervated by the median antebrachial cutaneous nerve (*Pinprick*). Data are presented as box (25th–75th percentile) and whisker (10th–90th percentile) plot. *Open boxes* = ropivacaine 0.2% + ketoralac; *filled boxes* = ropivacaine 0.2% + saline.

chial cutaneous nerve and of pain to a 1-Hz single twitch stimulus and tetanic transcutaneous electrical stimulation (TES) were performed before and every 5 min during tourniquet inflation and 3, 10, 15, and 20 min after release of the distal tourniquet. Two cutaneous electrodes for 1-Hz single twitch and tetanic TES were placed over the ulnar nerves of both arms close to the wrist. Pain was evaluated on a verbal numeric score (VNS) scale, ranging from 0 = no pain to 10 = worst imaginable pain in response to a single twitch at 60 mA and to a 5-sec 50-Hz tetanic stimulus at 60 mA. This latter stimulus has been shown to be equivalent to a surgical incision.[6] Onset of surgical anesthesia was defined as a VNS of 5 or less to the tetanic stimulus, and surgical anesthesia was complete at a score of 0. Tourniquet pain was recorded every 5 min after inflation of the proximal tourniquets until deflation of the second distal tourniquet.

Volunteers had an additional venous access line on the lower extremity for emergency medication and were monitored by noninvasive blood pressure (lower extremity), a two-lead electrocardiogram (leads II and V_5), and pulse oximetry. After exsanguination by an Esmarch bandage, the proximal cuff of a double-cuff tourniquet placed on the subject's upper arm was inflated to a pressure of 250 mmHg. Limb occlusion pressure was verified by loss of pulse oximetry tracing; local anesthetic was then injected over a period of 1 min into both arms simultaneously. Beginning with the inflation of the proximal tourniquets and ending with the deflation of the second distal tourniquet, tourniquet pain was recorded for each extremity every 5 min using the VNS scale, ranging from 0 = no pain to 10 = worst imaginable pain. After 30 min, the distal cuff was inflated, followed by release of the proximal tourniquet. Both distal tourniquets remained inflated until a VNS of 10 was reported. After deflation of the tourniquets, the volunteers were questioned about CNS side effects and asked to rate them on a VNS scale between 0–10.

Data are expressed as median (range) and were analyzed by the Wilcoxon signed-rank test for nonparametric data; a value of $P < 0.05$ was considered statistically significant.

Results

The volunteers were comparable with respect to age, weight, and height (P = NS). All 10 volunteers had successful bilateral IVRA as determined by loss of sensation to single twitch stimuli, TES, and pinprick. The tourniquet was tolerated for a median time of 58.5 min (range, 45–90 min) and 60.5 min (range, 39–79 min) in arms receiving ropivacaine plus saline and ropivacaine plus ketorolac, respectively (fig. 1). There were no significant differences in tourniquet tolerance between ropivacaine plus saline and ropivacaine plus ketorolac at any time of measurement. Times to onset of sensory blockade (VNS $\leq$ 5) evaluated by the single twitch response took a median time of 5 min (range, 1–25 min) and a median time of 10 min (range, 1–25 min) in the ropivacaine plus saline and ropivacaine plus ketorolac groups, respectively (fig. 1). A VNS of 0 was reached after 33 min (range, 20–45 min) and 30 min (range, 20–40 min) (fig. 1). Loss of sensation to TES with a 50-Hz 60-mA tetanus (TES) took longer than after the 1-Hz single twitch stimulus, *i.e.*, median 20 min (range, 1–25 min) and 20 min (range, 10–35 min) in the ropivacaine plus saline and ropivacaine plus ketorolac groups, respectively (fig. 1). Complete loss of sensation to TES (VNS = 0) was achieved after 30 min (range, 20–45 min) and 30 min (range, 25–45 min) in these two groups (fig. 1). Loss to pinprick was complete after 20 min (range, 5–30 min) in both arms (fig. 1). In 6 of the 10 volunteers of both groups, 1-Hz single twitch and TES did not recover to baseline 20 min after release of the distal tourniquet.

Five of the 10 volunteers experienced no CNS side effects after distal tourniquet release. The other five

participants exhibited mild dizziness, rated 1–3 out of 10, for a maximum of 5 min predominantly after release of the second distal tourniquet. The median time difference was 2 min between releases of the two distal tourniquets. No cardiac events occurred.

Discussion

The findings of this investigation suggest that the addition of ketorolac to ropivacaine 0.2% does not improve tourniquet tolerance. This is the first investigation that studied the efficacy of nonsteroidal antiinflammatory drugs as adjuvants to IVRA by direct, simultaneous comparison of study drug with a control. Drug testing with ketorolac in this study served to validate the usefulness of the simultaneous bilateral IVRA model to eliminate intersession variability. The finding of minimal CNS side effects despite use of a volume of 60 ml of ropivacaine 0.2% suggests that ropivacaine in healthy experimental subjects and similar tourniquet times may be appropriate to test additives to local anesthetic solutions. This dose was 50% higher than the normal dose of a local anesthetic usually administered for IVRA (40 ml of either ropivacaine 0.2% or lidocaine 0.5%)[5,7] and deserves further investigation.

The Wilcoxon signed-rank test was used to determine whether the types of responses were statistically significantly greater than expected. This test was selected because of the nominal nature of the response measured and the small sample size. A power and sample-size analysis was performed with Query Advisor Version 4 (Statistical Solutions, Saugus, MA), and it was found that for the 10 pairs of volunteers, the power to detect a one-sided significance of a large effect size was 0.89, and the power to detect a medium effect size was 0.35, with a level of 0.05 and an expected difference in proportions of 0.9.

Tourniquet pain is a poorly understood entity that complicates the use of pneumatic tourniquets used to produce a bloodless operating field during surgical procedures involving the extremities or for IVRA. Several possible explanations have been proposed for the cause of the discomfort associated with prolonged tourniquet inflation. The mechanism presumably involves the sensitization or spontaneous activation of A-δ and C fibers.[8] A triggering stimulus may include ischemia of the peripheral neuron or receptor distal to the tourniquet or activation of the nerve fiber in the compressed area directly under or adjacent to the tourniquet. The pain during IVRA is frequently difficult to control and often requires supplemental intravenous sedatives, analgesics, or even a general anesthetic. Meperidine 100 mg added to a 25% prilocaine solution in volunteers[9] was shown to reduce forearm tourniquet pain significantly for a brief period of time (10 min), but at the expense of substantial postoperative nausea and vomiting. The α_2-agonist clonidine in a dose of 150 μg added to lidocaine was shown to increase tourniquet tolerance (median, 22 min; range, 10–50 min) *versus* control (median, 10 min; range, 5–10 min).[2] Similarly, clonidine 1 μg/kg delayed the onset of tourniquet pain by more than 7 min.[3] Ketorolac was shown previously to improve tourniquet tolerance when used in combination with lidocaine for IVRA, but only during the first 30 min of investigation.[4] The results of this study, however, might have been affected by the use of intraoperative sedation, which is known to improve tourniquet tolerance. Furthermore, these patients were randomized to receive either the local anesthetic alone or the anesthetic with the addition of ketorolac on separate occasions. Because the volume of injectate was held constant for different tissue masses of the arms and IVRA was also used for different surgical interventions, such as carpal tunnel release, ganglion cyst excision, or tenolysis, it is doubtful that the ketorolac effect can be held responsible for the improvement of tourniquet tolerance. In contrast, in the present study, volunteers were not sedated and were investigated in one session with identical cuffs and cuff pressures. This eliminates several variables that were part of the aforementioned study. Ketorolac, a nonsteroidal antiinflammatory drug approved for parenteral use in the United States, interferes with synthesis of inflammatory mediators and augments analgesia provided by systemic or epidural opiates. Nonsteroidal antiinflammatory drugs are thought to act at peripheral nociceptors, perhaps by interfering with the synthesis and activity of pain mediators derived from arachidonic acid.[4]

Addition of ketorolac to ropivacaine 0.2%, however, did not produce any improvement in tourniquet tolerance in unsedated volunteers at any time point. Furthermore, ketorolac in this study did not alter sensation to pinprick stimulation, which activates predominantly A-δ fibers, or to electrical stimulation, which activates all pain nerve fiber populations.[10] The possibility exists that ketorolac might be effective when added to lidocaine, as shown during the first 30 min of one investigation,[4] but may not be effective with ropivacaine. Only a bilateral IVRA study with a ketorolac–lidocaine combination *versus* lidocaine alone could rule out this possibility. Most likely, however, a bilateral model with such a ketorolac–lidocaine combination would not show a significant difference at any time point, and lidocaine blood levels would most likely reach toxic levels. Also, such a study would be of doubtful clinical relevance, because tourniquet pain during the first 30 minutes is usually low. A double-blind study comparing ropivacaine 0.2% and lidocaine 0.5% could not demonstrate significant differences in tourniquet pain scores at any time points or significant differences in tourniquet tolerance times.[5]

Currently, the local anesthetics of choice for IVRA are lidocaine 0.5% in the United States and prilocaine 0.5%

in Europe. In a previous volunteer study,[5] ropivacaine was shown to generate substantially fewer side effects than lidocaine 0.5%. In that study,[5] a total volume of 40 ml of either local anesthetic was injected into one arm on separate days. In sedated patients,[7] ropivacaine 0.2% used for IVRA on the upper limb generated surgical anesthesia equivalent to lidocaine 0.5%, with the additional advantage of longer-lasting postoperative pain relief. No CNS and particularly no cardiac side effects were seen after tourniquet release in these two investigations. To exclude intersession variables, the volunteers in the present investigation received ropivacaine 0.2% (30 ml into each arm), which constitutes 50% more ropivacaine than would be used in clinical practice and was used in the two previous investigations.[2,7] The two distal tourniquets were released once intolerability set in, but the median time difference of 2 min between release of the two distal tourniquets was short enough to potentially cause toxic symptoms. Only minor CNS side effects (mild dizziness) were seen in 5 of 10 volunteers after release of the second distal tourniquet. This may be because of the high protein-binding capability of ropivacaine causing slow release from tissue. Several case reports,[11–13] however, have shown that even high concentrated solutions of ropivacaine, inadvertently injected intravascularly, did not produce as serious side effects as were seen after racemic bupivacaine.[14,15] Abouleish *et al.*[11] reported on the occurrence of a single seizure and sinus tachycardia after intravenous administration of ropivacaine 120 mg intended for extradural block. Korman and Riley[12] described tonic–clonic movements without detection of arrhythmias on the electrocardiogram in a patient after a presumed intravascular injection of 135 mg ropivacaine, and Ruetsch *et al.*[13] described an incident with seizure and severe cardiac arrhythmia after accidental injection of 225 mg ropivacaine intended for sciatic block. Side effects from ropivacaine were easy to treat, and none had long-term clinical consequences.

In conclusion, this investigation in volunteers could not confirm previous results[4] of improvement of tourniquet tolerance in patients by addition of ketorolac to a local anesthetic for IVRA. No differences in tourniquet pain scores were seen in the two upper extremities investigated simultaneously. Ropivacaine 0.2% in this study model, even at higher volumes than used clinically, did not lead to severe CNS side effects. This simultaneous bilateral IVRA model may allow clarification if additives to local anesthetic solutions improve tourniquet tolerance.

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