Intravenous Regional Ketorolac and Lidocaine in the Treatment of Complex Regional Pain Syndrome of the Lower Extremity

A Randomized, Double-blinded, Crossover Study

Maxim Savillion Eckmann, MD, Somayaji Ramamurthy, MD, and James G. Griffin, PT

Background and Objectives: Intravenous regional blocks (IVRBs) with ketorolac and lidocaine have been reported to be useful in the treatment of complex regional pain syndrome (CRPS). This is the first controlled prospective study of IVRB with lidocaine and ketorolac for treatment of pain and edema in CRPS of the lower extremity in adults.

Methods: A prospective, randomized, double-blinded, crossover design was used. The primary outcome was overall pain numeric rating scale (NRS) at 1 week postinjection; secondary outcomes included pain with motion, allodynia, joint pain score, edema, range of ankle motion, skin temperature, and short-term pain relief. Ten of 12 adult patients diagnosed with unilateral lower extremity CRPS (type I) completed the study. Four IVRBs were performed 1 week apart in a random sequence with 50 mL lidocaine 0.5% and 0, 30, 60, and 120 mg ketorolac.

Results: Only 1 outcome achieved significant improvement; there was 1 day of significant pain reduction in the ketorolac groups (median NRS 6 to 4, $P = 0.002$). Overall pain NRS (10-point scale, mean ± SE) at 1 week was 6.2 ± 0.53, 6.5 ± 0.89, 6.0 ± 0.88, 5.9 ± 0.82, and 5.8 ± 0.9 at baseline, 0, 30, 60, and 120 mg, respectively ($P = 0.8$). Pain with movement was 7.15 ± 0.69, 5.7 ± 1.07, 6.1 ± 0.86, 5.0 ± 0.97, and 5.6 ± 0.86, ($P = 0.059$). Edema was not significantly reduced (2% reduction, $P = 0.6$).

Conclusions: IVRB with ketorolac and lidocaine produced only short-term pain reduction in patients with CRPS involving the lower extremity after 4 serial injections in our study group. Prospective study is warranted, particularly in the pediatric population.

Key Words: RSD, CRPS, ketorolac, regional, intravenous, bier

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Complex regional pain syndrome (CRPS) is a painful, often debilitating condition that occurs in some patients after injuries or immobility. Sensory symptoms are characterized by regional spontaneous or evoked pain that seems disproportionate in duration or intensity to any known trauma or lesion, often presenting as hyperalgesia or allodynia. In addition, vasomotor, sudomotor, motor, and trophic changes are present in the painful region, manifested as asymmetry in temperature, sweating, edema, muscle weakness, joint dysfunction, and osteopenia.

Intravenous regional blockade (IVRB) with a variety of sympatholytic, anesthetic, or anti-inflammatory medications has been used as a modality to treat CRPS-involving extremities.[1] As a nonsteroidal anti-inflammatory drug (NSAID) with demonstrated potent analgesic properties,[2–8] ketorolac may be particularly useful in treating the symptoms of hyperalgesia, joint pain, and edema in patients with CRPS. This clinical practice of IVRB has been reported to be beneficial in some patients when studied retrospectively in both adults and children.[9–11] We investigated the dose-related effect of IVRB with ketorolac and lidocaine in a prospective, randomized, crossover, double-blinded pilot study.

METHODS

A sample size of 25 was estimated to achieve a power of 0.9 for 50% reduction in pain; however, we elected to first perform a smaller pilot study because of uncertainty of the effect size in other important outcomes (edema and ankle motion) and the known side-effects of ketorolac. Twelve patients above the age of 18 years with unilateral CRPS I (International Association for the Study of Pain modified diagnostic criteria[12]) of the lower extremity, as confirmed by a pain medicine physician examination, were recruited for the study. Patients who had impaired renal function, impaired hepatic function, known sensitivity to ketorolac or other NSAIDs, peptic ulcer disease, or pregnancy were excluded. The study was approved by our Institutional Review Board, and written informed consent was obtained from each patient. A randomized, double-blinded, crossover design was used. Through computer algorithm, all patients were assigned a random treatment order of 4 IVRBs performed 1 week apart with 50 mL lidocaine 0.5% plus 0, 30, 60, and 120 mg ketorolac. Ketorolac of 120 mg was chosen in concordance with the maximum daily recommended dose of intramuscular/intravenous ketorolac in adults in the acute setting, whereas ketorolac of 60 mg has been used in prior studies.[9,10] The lidocaine dose of 250 mg reflected the upper limit of recommended dosing (3 to 5 mg/kg) for infiltration without epinephrine.

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From the Department of Anesthesiology, University of Texas Health Science Center at San Antonio, San Antonio, TX.

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Reprints: Maxim Savillion Eckmann, MD, Department of Anesthesiology, The University of Texas Health Science Center at San Antonio, Mail Code 7838, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900 (e-mail: eckmann@uthscsa.edu).

The primary outcome was overall pain numeric rating scale (NRS; 0 = no pain and 10 = worst pain imaginable) at 1 week postinjection; secondary outcomes included short-term pain NRS (< 1 wk), limb volume difference, pain NRS with motion, pain NRS for allodynia, joint pain score (JPS), range of ankle motion, and skin temperature. We hypothesized that ketorolac would produce dose-related improvement in outcomes that were sustained at 1 week.

Patients presented to the University of Texas Health Science Center Pain Clinic for their procedures and follow-up. All clinical outcome measures were assessed by a blinded examiner at baseline and before each procedure; therefore, these measurements reflected the persistent effects, if any, of the treatment from the week prior. Patients also kept a daily log of overall pain NRS each between treatments, including baseline pain before treatment and postinjection days 1 through 7. For IVRB, a 22-gauge intravenous cannula was inserted into the distal vein of the affected extremity, which was then elevated and exanguinated using an Esmarch bandage. A pneumatic tourniquet was placed over the proximal portion of the extremity and inflated to 300 to 450 mm Hg. The solution was injected slowly over 4 minutes. Providers and patients were both blinded to the contents of the solution. After 20 minutes, the cuff was deflated intermittently. Vital signs and continuous electrocardiogram were monitored during and for 1 hour after the block.

Edema in the affected extremity was evaluated by difference in limb volume percent as calculated by water displacement volumetry.[13,14] Theoretically, this would negate the contribution of edema in the affected limb from systemic causes that would affect both limbs equally. The affected foot was immersed to a point 6 cm proximal to the distal edge of the lateral malleolus in a water-filled 5-gallon glass vessel. As the vessel had a known cross-sectional area, measurement of the height change allowed for calculation of the displaced volume. Three measurements were made for both the affected and unaffected limbs and averaged. The percent difference in limb volume was calculated by (affected–unaffected/affected) × 100%.

Patients were asked to report not only their overall pain NRS, but also maximal pain with active ankle movement to the extremes of range of motion (ROM), and pain with light touch over the affected area elicited by the examiner (allodynia). Measurement of ROM in ankle dorsiflexion, plantar flexion, eversion, and inversion was reported in degrees by a trained physical therapist in both the affected and unaffected extremity. Skin temperature was measured with an infrared thermometer. The joint pain score was quantified on a 4-point scale (0 = no pain, 1 = mild pain to deep palpation, 2 = severe pain to deep palpation, 3 = severe pain to mild palpation, and 4 = hyperesthesia) during evaluation by a trained physical therapist. The interphalangeal, metatarsophalangeal, and tibio-talar joints were palpated, and the score for the entire foot/ankle totalled. The possible range of total score was 0 to 44.

Statistical analysis was performed using the SigmaStat version 3.0 software package (SSPS, Inc, Chicago, IL). Limb volume difference and temperature were analyzed by a 1-way repeated measures analysis of variance. The remaining data were analyzed using the Friedman repeated measures analysis on ranks and the Wilcoxon signed ranks test (single tail). Residuals were checked for normal distribution. A P value of less than 0.05 was considered to be significant.

RESULTS

Of the 12 patients, 1 did not complete the study because of illness and 1 was invalidated because of pain medication changes during the series of blocks. Of the patients (5 male and 5 female) included in the analysis, mean age ± SE was 37.9 ± 12.6 years (range: 22 to 56 y). All but 1 patient (92%) had history of trauma or fracture. Duration of symptoms was 9.9 ± 5.4 months (range: 1 to 29 mo). Starting overall pain NRS was 6.2 ± 1.7. Only the secondary outcome of short-term overall pain improvement (1 d postinjection) achieved statistical significance in the ketorolac treatments, and there were no reported complications.

Overall pain NRS was neither statistically different at 1 week (6.2 ± 0.53, 6.5 ± 0.89, 6.0 ± 0.88, 5.9 ± 0.82, and 5.8 ± 0.9 at baseline, 0, 30, 60, and 120 mg respectively, $P = 0.8$), nor was pain with movement (7.15 ± 0.69, 5.7 ± 1.07, 6.1 ± 0.86, 5.0 ± 0.97, and 5.6 ± 0.86, $P = 0.059$). Figure 1 depicts the range, quartiles, and medians of these data. The joint pain score was also neither significantly different (16.5 ± 15.7, 16.8 ± 16.6, 17.4 ± 17.2, 18.0 ± 17.9, and 15.7± 16.3; $P = 0.9$; Fig. 2), nor were allodynia, skin temperature, or ankle ROM at 1 week. Conversely, when the patient pain logs were analyzed, the 30 and 120 mg ketorolac group showed a significant reduction in overall pain NRS 1 day after the injection (5.8 ± 1.0 vs. 4.4 ± 0.9, $P = 0.04$; 6.1 ± 0.8 vs. 3.6 ± 0.8, $P = 0.03$; Fig. 3), whereas the 0 and 60 mg group did not. Together as a group, all treatment with ketorolac reduced the median NRS from 6 to 4 ($P = 0.002$, Fig. 4) at 1 day after injection. Pain reduction was no longer significant beyond 1 day.

Limb volume was not significantly reduced in the treatments containing ketorolac (4.0 ± 6.4, 4.15 ± 3.3, 2.3 ± 5.1, 1.8 ± 3.2, and 2.4 ± 3.1; $P = 0.6$; Fig. 5). SD among the 3 individual measurements per session was 3.9% whereas standard error was 2.3%. On the basis of these results, post-hoc power analysis showed that to detect 3% difference in limb volume with a power of 0.8 and α of 0.05, 43 patients would have needed to be enrolled. We elected not to continue the study beyond the original 12 patients because of the apparent small ($\leq$2 points improvement in pain NRS and 2% reduction in limb volume difference) clinical effect size based on the pilot results.

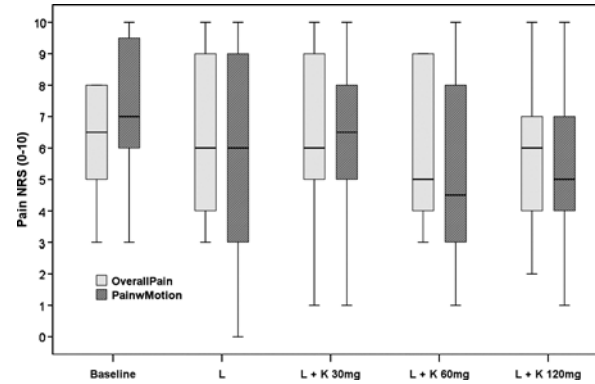

FIGURE 1. Overall pain NRS (P=0.8) and pain NRS with movement (P=0.059) were not significantly different at 1 week. K indicates ketorolac; L, lidocaine 0.5% × 50 mL; NRS, numeric rating scale.

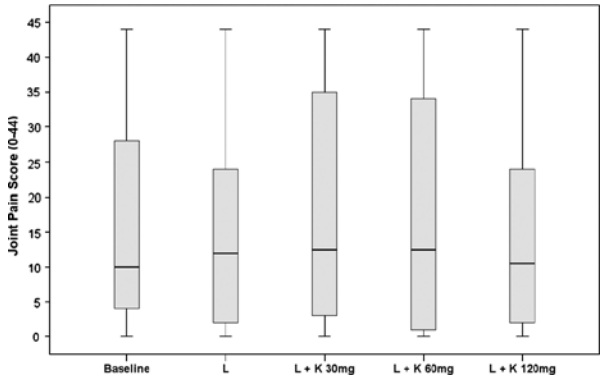

FIGURE 2. There were no significant differences in Joint Pain Score (P=0.9) at 1 week. K indicates ketorolac; L, lidocaine 0.5% × 50 mL.

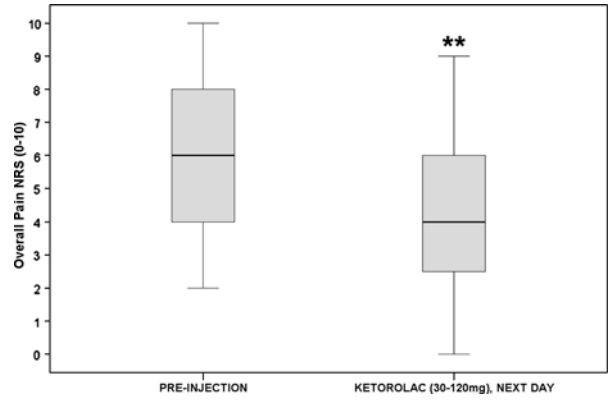

FIGURE 4. Overall treatment with ketorolac reduced median overall pain scores from 6 to 4 (P=0.002) 1 day after injection (**$P < 0.01$).

DISCUSSION

Many drugs have been used including guanethidine, reserpine, bretylium, phentolamine, prostaglandin E_1, prostaglandin E_2, calcium channel blockers, local anesthetics, and corticosteroids, in an effort to find effective ways to treat pain in CRPS.[1,9–11,15,16] Ketorolac is an injectable NSAID of the pyrrolo-pyrrole group of NSAIDs. As an exceptionally potent inhibitor of the cyclo-oxygenase pathway of arachidonic metabolism, ketorolac doses of 30 and 90 mg have been found to be comparable or better in analgesic efficacy to morphine 12 mg or meperidine 100 mg for moderate-to-severe postoperative pain. Ketorolac produces analgesia principally through reduction of sensitizing prostaglandins, and this is of particular relevance to CRPS as prostaglandin E_2 mediates bradykinin hyperalgesia whereas prostaglandin I_2 mediates norepinephine hyperalgesia.[17] Other mechanisms may be involved as well, such as reduction of tissue ischemia through vasodilation[9] and κ-opioid receptor action.[18] It is reasonable to consider ketorolac in IVRB of an extremity afflicted with CRPS, particularly as patients commonly have associated somatic joint pain, joint dysfunction, and edema underlying the neuropathic and sympathetically maintained aspects of their pain.

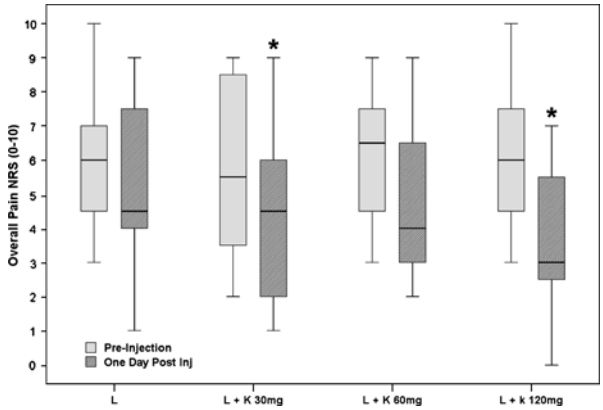

FIGURE 3. The 30 mg (P=0.04) and 120 mg ketorolac (P=0.03) group had significant reductions in overall pain numeric rating scale (NRS) 1 day after injection (Inj) (*$P < 0.05$). K indicates ketorolac; L, lidocaine 0.5% × 50 mL.

Earlier literature showed a strong correlation between pain visual analog scale, limb volume, objective joint pain measurement, and active ROM, and proposed a method for objectively evaluating pain in CRPS,[19] which we incorporated into our study. We felt that observations made 1 week from each injection would reduce the influence of placebo and of immediate relief of pain from ischemic interruption of sensory A-β fibers.[15,20] Over a series of 4 IVRBs, 3 of which contained ketorolac, no significant lasting improvement was seen at 1 week in terms of overall self-reported pain, pain with movement, allodynia, joint pain, ROM, or edema. Short-term pain relief was apparent on the first day after the IVRBs with ketorolac, in the 30 and 120 mg subgroups, according to patient pain logs. On the basis of these results, lower doses of ketorolac may be similarly effective to the 120-mg dose. IVRB with ketorolac could be used to assist patients in tolerating physical therapy in the 24-hour postinjection period, although the optimal use of physical therapy in the treatment of CRPS has not been determined.[1]

One potential weakness of our study was the chronicity of the pain, averaging 10 months in duration but with a maximum of 29 months; probably the upper outliers are more refractory to treatment. Edema may be modestly improved with IVRB ketorolac, although our study was underpowered to find this difference. One factor

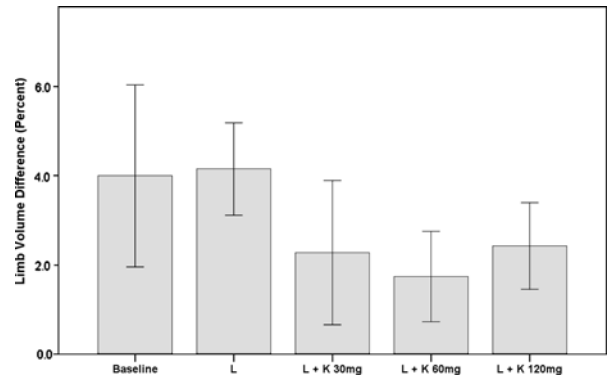

FIGURE 5. Limb volume difference (±SE) was not significantly reduced (P=0.6) at 1 week. K indicates ketorolac; L, lidocaine 0.5% × 50 mL.

may be that the vasodilation theoretically produced by ketorolac interference with thromboxanes could be offsetting reduction in edema. It is also possible that our patients did not have limb volume difference mediated by inflammation in their affected limbs, but rather other causes such as lymphedema related to trauma or dependent edema from disuse. The process of performing IVRB may contribute to the increased limb volume somewhat through occlusion of superficial veins from the tourniquet,[14] counteracting beneficial effects from ketorolac. Error in limb volumetry may have occurred because of variability in the time allowed for the limb to be at rest before measurement and in the time of day that the patient was evaluated (with edema possibly increasing throughout the day).[14] In addition, lidocaine interaction with the effects of ketorolac should be considered, although we have not found any evidence in the literature that would suggest this.

Although our study was possibly underpowered to find statistical significance, we did not proceed beyond the 12 patient pilot study population because of the apparent small effect size in light of the potential side-effects of ketorolac.[21] Taking into consideration that 4 IVRBs were performed on each patient in our study and yet no significant lasting benefits were achieved, the number of treatments performed by a clinician to even find a single responder may be impractical. Our results are in line with controlled studies of other medications besides ketorolac (eg, guanethidine, reserpine, and lidocaine-methylprednisolone) which have not shown lasting benefit of IVRB for the treatment of pain from CRPS.[1,16] Conversely, there are earlier case series[9,10] which report some success with systemic or IVRB ketorolac. These studies were retrospective, had differing numbers of treatments, used ketorolac with or without lidocaine, and apparently did not control for other changes in the patients' concurrent treatments (eg, oral medication changes). Successful treatment of IVRB ketorolac and lidocaine has been reported in children,[11] and it is possible that children respond differently to this intervention than adults.

Further controlled, prospective study is warranted as it is possible that certain patient populations are more responsive to this therapy, such as children or patients with more acute presentation. In addition, combinations of ketorolac and other medications (eg, guanethidine, reserpine, or bretylium[22]) may be more effective. For example, synergism may be possible by blocking both prostaglandin synthesis and norepinephrine release simultaneously. Intravenous ibuprofen should be compared against ketorolac as it may offer a better side-effect profile. More information on chemical or pharmacodynamic interactions of these medications in solution is required as well.

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