

The Efficacy of Ketorolac as an Adjunct to the Bier Block for Controlling Postoperative Pain Following Nontraumatic Hand and Wrist Surgery

LT Jesse J. Rivera, CRNA, MSN, NC, USN
LT Dante J. Villecco, CRNA, MSN, NC, USN
LT Bryan K. Dehner, CRNA, MSN, NC, USN
CDR(ret) Joseph F. Burkard, CRNA, DNSc, NC, USN
CDR Lisa A. Osborne, CRNA, PhD, NC, USN
CAPT Joseph E. Pellegrini, CRNA, PhD, NC, USN

Research indicates that using a combination of ketorolac and lidocaine in the administration of a Bier block results in significant postoperative analgesia and decreased inflammation; however, the optimal dose of ketorolac to coadminister with the local anesthetic has not been established. This study was performed to determine if a 20-mg dose of ketorolac is effective in providing prolonged postoperative analgesia without adverse effects.

A total of 55 patients (29 lidocaine-ketorolac, 26 lidocaine-placebo) were enrolled in this randomized, double-blind, placebo controlled study. Pain was measured using a 0 to 10 visual analogue scale and analysis of postoperative analgesic requirements. Incidence of bruising and postoperative analgesic satisfaction scores were determined 48 hours following discharge.

No difference in demographic variables, adverse effect profiles, or satisfaction scores was noted between groups. Visual analogue scale scores were increased in the placebo group in the hospital but not following discharge to home. There was also a prolonged time to postoperative analgesic requests in the ketorolac group compared with the placebo group following discharge to home, achieving statistical significance for the time to second analgesic request ($P = .012$). Based on the results of this study we recommend that 20 mg ketorolac be considered in intravenous regional anesthesia.

Keywords: Bier block, hand surgery, intravenous regional anesthesia, ketorolac, outpatient surgery.

Intravenous regional anesthesia (IVRA) has been commonly used for short-duration surgical procedures involving the hand and wrist. Although this technique avoids the potential complications of general anesthesia, it can result in significant acute postoperative pain.¹⁻⁵ The use of lidocaine for IVRA block or Bier block has been the mainstay for controlling perioperative pain, but it provides little to no benefit postoperatively.⁶ Increased opioid analgesic use, longer hospital stays, poor patient outcomes, and decreased patient satisfaction scores are associated with inadequate pain management modalities during the immediate postoperative period.^{7,8}

Postoperative pain as a result of Bier block and tourniquet use may stem from a combination of neuropathic and inflammatory pain, which might be attributed to transection of cutaneous nerves, disruption of tissue, and possible ischemia at the site of the tourniquet.^{5,6} As a result, nociceptive impulses lead to prolonged and widespread excitability in the spinal cord instigating central sensitization.^{7,9} Unfortunately, opioid and muscle relaxants have not demonstrated effective control of the

central sensitization, thus postoperative pain remains a significant complication in hand and wrist surgery patients.^{4,10-12}

Ketorolac is the only parenterally prepared nonsteroidal anti-inflammatory drug (NSAID) approved by the US Food and Drug Administration for use in treating the mediated inflammatory response.³ Inhibition of prostaglandin synthesis decreases the inflammatory response to surgical trauma and hence reduces peripheral nociception sensitization at the site of injury. Preoperative administration of NSAIDs inhibits cyclooxygenase and decreases tissue prostaglandin synthesis thereby reducing primary and secondary hyperalgesia. Ketorolac used as an additive to an IVRA has known properties that preemptively treat peripheral and central sensitization, and it is the postoperative drug of choice for treating patients experiencing a surgically induced inflammation.^{3,13}

Research has been conducted using ketorolac as an adjunct in an IVRA for preemptive pain management therapy.^{3-5,7-9} These studies have shown decreased post-

operative pain intervention requirements for patients undergoing hand and wrist surgery. Steinberg et al⁵ compared various doses of ketorolac (0 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, or 60 mg) combined with 200 mg of lidocaine in the administration of an IVRA. The results of this study suggest that 20 mg of ketorolac was as effective as 60 mg. Another study investigating this approach to the use of ketorolac, although successful, showed specific limitations. Johnson et al² concluded that 30 mg of ketorolac was not as effective for patients undergoing traumatic injury repair or invasive bone interventional surgery compared with nontraumatic hand surgery.⁴ The study included procedures that entailed significant tissue disruption as a result of traumatic injury, thus negating the preemptive benefits of ketorolac.

The purpose of our study was to address the findings in the Johnson et al² study and to validate the findings of Steinberg et al.⁵ We limited our study population to patients undergoing carpal tunnel release, excision of ganglion cysts, and tenolysis, excluding traumatic hand and wrist operations that were included in the Johnson study. In addition, we limited our study to surgical procedures scheduled for less than 60 minutes, because patients typically experience discomfort when a tourniquet is required for greater than 60 minutes.¹

Methods

Following approval from the hospital institutional review board, a quasiexperimental, prospective, randomized, double-blind study was conducted at a large military training hospital. All nontraumatic hand and wrist surgery patients who requested IVRA during their preoperative visits were considered for inclusion in this study. Exclusion criteria included chronic use of NSAIDs, analgesics, antidepressants, and anxiolytics; neuropathological disease; allergies to study medications; previous post-traumatic hand injury; procedures greater than 1 hour; ASA physical status III or IV; inability to give consent for study; pregnancy; and renal disease. Signed informed consent was obtained from those meeting inclusionary criteria, and all patients were assigned a patient identification number and randomized into either an experimental or a control group using a computer-generated randomization process. Those patients randomized to the control group were scheduled to receive a Bier block using 50 mL of 0.5% lidocaine plus normal saline (placebo), and those assigned to the experimental group were scheduled to receive a Bier block using 50 mL of 0.5% lidocaine plus 20 mg of ketorolac. A total of 60 patients were randomized (30 patients per group) into the control and experimental groups.

Following group assignment, baseline data was recorded on a data collection sheet. Baseline data included demographic information (age, gender, height, and weight) and a baseline pain score using a 0 to 10 Verbal

Analogue Scale (VAS) in which a score of "0" indicated "no pain" and a score of "10" indicated the "worst pain imaginable."

All patients then had a peripheral 18-gauge or 20-gauge intravenous (IV) catheter inserted in the nonoperative extremity and an infusion of lactated Ringer's solution was initiated. All patients received preoperative IV sedation that consisted of 1 mg midazolam and 50 µg of fentanyl. Following sedation, a standardized technique for IVRA block was used on all patients (Table 1). If a patient experienced tourniquet pain, the distal tourniquet was inflated and the proximal tourniquet deflated. If an adequate IVRA block failed to be achieved at this time, an alternative anesthesia plan was implemented (general or local anesthesia) and the patient was dropped from the study. All medications and the success or failure of the IVRA block were recorded on a data collection sheet. Upon completion of the operation, all patients remained in the operating room 30 minutes for postoperative pain assessment, followed by 30 minutes of pain assessment in the holding area.

Pain assessments were performed using the 0 to 10 VAS scores and the amount of postoperative analgesia required was documented. The VAS scores were recorded on a data collection sheet immediately following the surgical procedure, and every 15 minutes thereafter for a 1-hour period. In addition, all patients were asked to record VAS scores for pain before self-administration of any analgesic medications using the 0 to 10 scale for the first 48 hours following discharge to home. After surgery all reports of pain were treated using the analgesic medication ordered by the orthopedic surgeon (hydrocodone and acetaminophen or oxycodone and acetaminophen) while the patient remained in the hospital setting and following discharge to home. All analgesic medications received preoperatively, perioperatively, and for the first 48 hours following discharge to home were converted to morphine equivalents before data analysis. Before being discharged to home all patients were instructed that they would be contacted by 1 of the investigators approximately 48 hours after surgery to obtain their postdischarge analgesic requirements and pain scores and to assess their overall level of satisfaction regarding their postoperative pain control. All patients were also asked to note the time they required any analgesic medications so that the investigators could determine the duration of analgesia provided by the IVRA technique. For the purposes of this study, duration of analgesia was defined as the time (in minutes) of block initiation until the patient's first analgesic requirement.

Approximately 48 hours following discharge all patients were contacted by one of the investigators who recorded the analgesic requirements and VAS score data. In addition, a 1 to 5 Likert scale satisfaction score was obtained in which the patients were asked to document

1. Use a 20-gauge intravenous cannula to cannulate a dorsal hand vein on the operative arm.
2. Elevate the operative extremity for 3 minutes.
3. Exsanguinate the operative arm using an Esmarch bandage.
4. Place a double-cuffed pneumatic tourniquet on the upper arm, then inflate the distal cuff to 250 mm Hg and verify loss of pulse.
5. Inflate the proximal cuff and verify loss of pulse, then deflate the distal cuff.
6. Remove the Esmarch bandage and verify lack of pulse in the operative arm.
7. Place a simple forearm tourniquet (Penrose drain) on the mid-forearm of the operative arm.
8. Inject 25 mL of 0.5% lidocaine solution (with ketorolac) for 60 seconds.
9. Remove the forearm Penrose tourniquet and immediately inject an additional 25 mL of 0.5% lidocaine solution (with ketorolac) for 60 seconds.

Table 1. Standardized Intravenous Regional Anesthesia Technique

their overall level of satisfaction with the analgesic experience with a score of 1, very poor; 2, poor; 3, satisfactory; 4, good; and 5, very good. All patients were also asked to monitor their degree of postdischarge ecchymosis using the following verbal descriptor scale: none, minor (hardly at all), moderate (noticeable but only in one area of extremity), and severe (very noticeable over several areas on extremity or body).

Before initiation of this study a power analysis was performed using a Fisher exact test in which we estimated that those in the ketorolac group would have VAS scores approximately 50% lower than those in the placebo group. Using an α of .05 and a β of .20 it was determined that approximately 26 patients per group would be required to show significance. Factoring in an attrition rate of 15% the sample size was increased to 30 patients per group. Descriptive and inferential statistics were used to analyze data. Incidental data was analyzed using a χ^2 test. Ordinal data, satisfaction scores, and times to postoperative analgesic requests were analyzed using a Mann-Whitney *U* test. A Student *t* test was used to analyze VAS pain scores, anesthesia and surgical times, and overall analgesic requirements. Data were displayed as number, median, and mean \pm SD, and a *P* value of less than .05 was considered significant.

Results

A total of 60 patients were enrolled in this study, but 5 patients were dropped because of block failure or change or cancellation of surgery, leaving a total of 55 patients (29 ketorolac, 26 placebo) for analysis. No difference in demographic information was noted between the groups

Variable	Ketorolac	Placebo	<i>P</i> value
Age, mean (SD), y	39.5 (13.6)	37.58 (12.2)	.560
Height, mean (SD), cm	172.86 (11.2)	170.9 (10.5)	.418
Weight, mean (SD), kg	90.3 (19.2)	85.6 (19.2)	.365
Gender (no.)			
Male	19	16	
Female	10	10	.759
Race (no.)			
White	20	19	
Black	3	4	
Pacific Islander	2	2	.613
Asian	4	1	
ASA class (no.)			
I	7	9	
II	22	17	.393
Patient satisfaction, median (range)	5 (3-5)	5 (3-5)	.740

Table 2. Demographic and Independent Variables

(Table 2). All patients received the same amount of preoperative sedation (1 mg midazolam and 50 μ g fentanyl) before tourniquet pressures were applied. Following tourniquet inflation, there was no difference in analgesic or anxiolytic requirements between the groups. There were also no differences in anesthesia, surgical, or tourniquet times between the groups.

The analysis of the 0 to 10 VAS scores showed no difference in baseline scores between the groups, but the scores were higher in the placebo group at all postoperative time interval measurements, with the data achieving significance at 30 minutes, 45 minutes, and 60 minutes following surgery (Figure). There was no significant difference in 0 to 10 VAS scores between the groups following discharge to home. Postoperative analgesic requirements were also similar between the groups when morphine equivalent requirements were analyzed. A total of 7.83 mg plus or minus 6.6 mg was required in the ketorolac group compared with 6.9 mg plus or minus 4.4 mg requirement in the placebo group ($P = .573$). Patients in the ketorolac group had a longer time to analgesic requests at all time frames for the first 4 requests, but the data only achieved statistical significance for the time to second analgesic request ($P = .048$) (Table 3).

Ecchymosis was analyzed, and bruising was reported by 35% of the placebo group compared with 21% of the ketorolac group, but the data did not achieve statistical significance ($P = .247$). No patient experienced bleeding abnormalities from the IV admixture, but when severity of bruising was analyzed, a higher percentage of the placebo group reported moderate bruising (15%) com-

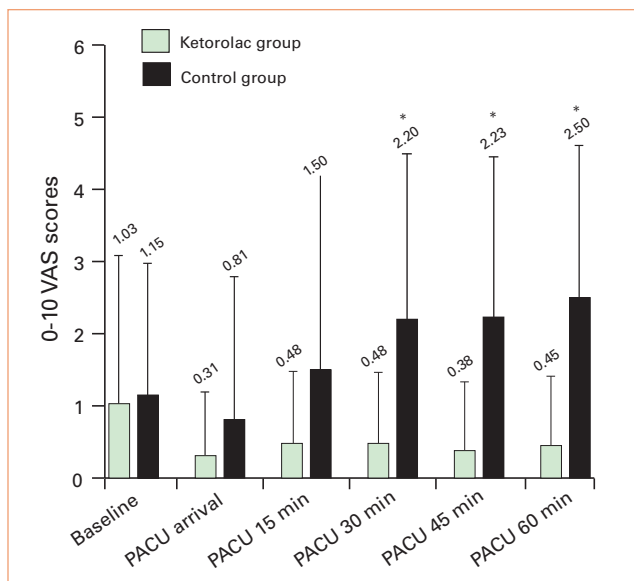


Figure. PACU VAS Scores for Pain

PACU indicates postanesthesia care unit; VAS, Visual Analogue Scale.

* Significance $P < .05$

pared with the ketorolac group (3%, $P = .264$) The area of ecchymosis was reported only on the operative extremity and no other areas of bruising were reported by any patient. No differences in overall analgesic satisfaction scores were noted between the groups; both groups reported a median score of 5, indicating very good postoperative analgesia.

Discussion

This study supports the Steinberg et al⁵ study results, which concluded that 20 mg of ketorolac is an effective dose for reducing postoperative analgesic requirements in those undergoing carpal tunnel release, excision of ganglion cysts, and tenolysis operations. Numerous studies have recommended preemptive treatment of postoperative pain as the modality of choice to decrease time to first opioid use, decrease hospital stays, improve patient outcomes, and increase patient satisfaction.^{2,4,9} Physiological inhibition of prostaglandin synthesis decreases the inflammatory response to surgical trauma and reduces peripheral nociception and sensitization at the injury site. Preoperative administration of NSAIDs inhibits cyclooxygenase and decreases tissue prostaglandin synthesis thereby reducing primary and secondary hyperalgesia.

This study concluded that use of ketorolac led to a decrease in postoperative analgesic requirements in the early postoperative period thus allowing patients to be discharged immediately. After discharge, neither group reported a significant difference in their VAS scores. However, the patients assigned to the ketorolac group had a significantly longer time from initiation of the block to postoperative analgesic requests (Table 3).

Request	Ketorolac median (range), min	Placebo median (range), min	P value
First request	285 (45-2,760)	203 (0-1,118)	.229
Second request	1,102 (289-2,004)	505 (0-1,418)	.048
Third request	1,525 (529-2,064)	928 (580-1,998)	.174
Fourth request	1,525 (1,120-2,271)	1,515 (820-1,920)	.341

Table 3. Time in Minutes From Initiation of Block to Postoperative Analgesic Requests

Although a statistical significance between groups was noted only for the time to second analgesic request (a 10-hour difference), the patients in the ketorolac group also had a clinically significant difference in periods of analgesia for the first (85-minute difference) and the third requests (10-hour difference). A normalization of times was noted for subsequent requests for analgesia; however, only a few patients in each group required more than 3 analgesic requests. This is important information because it is apparent from the duration of analgesia that ketorolac administered as an IVRA adjunct provides prolonged postoperative analgesia compared with a standard Bier block solution. Because the site of action for the analgesic and anti-inflammatory effects of ketorolac are in the periphery, its use in IVRA appears logical when preemptive analgesia is desired in the postsurgical patient.¹⁴

Another interesting finding was the incidence of ecchymosis or bruising between groups. Often ketorolac is not administered because surgeons are concerned about postoperative ecchymosis, bleeding, or bruising at the surgical site. The original research design included a plan for collecting a thromboelastograph on each patient to determine if ketorolac administration would have any impact on overall clot strength, but this element of the research design was abandoned because of logistical problems.

The antiplatelet effects of ketorolac is well known, and it raised concerns regarding increased bleeding and bruising among the patients receiving this NSAID. The risks of gastrointestinal bleeding and operative site bleeding are clinically important when ketorolac is used in high doses, in older patients, and for more than 5 days.¹⁵ The potential for postoperative bleeding is associated with cyclooxygenase pathway interference and thromboxane synthesis inhibition.^{10,14,15} Coagulopathies and hematoma formation are known reactions from NSAID administration. However, recent ketorolac studies have shown no significant effect on bleeding times and hematoma formation.^{2,15-17} Thwaites et al¹⁶ concluded that platelet formation evaluated by platelet aggregometry and thromboelastography was not inhibited after intravenous ketorolac use despite nearly complete abolition of thromboxane β_2 production.

Our study did not find the antiplatelet effects of ketorolac to be clinically evident, which likely is related to the fact that ketorolac use with IVRA is a 1-time, low-dose injection. In addition to these anecdotal observations we also asked the patients to report any ecchymosis or bruising at the surgical site or systemically in the first 48 hours after discharge from the hospital. We were surprised that a higher incidence of ecchymosis was reported in our placebo group compared with our ketorolac group; however, it did support the Thwaites studies and others that reported no problems with bleeding or clot formation caused by concomitant ketorolac administration.¹⁶ Perhaps the finding in our study was a result of the small dose of ketorolac that was administered (20 mg), and different results may have been found if a larger dose of ketorolac was given or if ketorolac was administered systemically as opposed to as an adjunct to the IVRA regimen.

Conclusion

Intravenous administration of ketorolac is used routinely to reduce postoperative opioid requirements. An equianalgesic dose of ketorolac, 30 mg, IV, is comparable to morphine, 10 mg, IV.¹⁸ Ketorolac is 99.2% bound to serum albumin; concentrating ketorolac distal to the tourniquet in an upper extremity potentially permits higher ketorolac free-fraction concentrations above systemic free-fraction concentrations. This increased free fraction of ketorolac may maximize the benefits of preemptive analgesic and anti-inflammatory actions. Thus, further studies are necessary to determine if a lower IVRA dose of ketorolac is more effective than a standard IV dose in decreasing postoperative pain related to surgical tissue disruption of the upper extremity. A study evaluating the effectiveness of ketorolac IVRA vs a systemic dose of ketorolac is planned as follow-up research to this study; however, a 20-mg dose of ketorolac used for preemptive analgesia in an IVRA is recommended.

REFERENCES

- Hartmannsgruber MW, Plessmann S, Atanassoff PG. Bilateral intravenous regional anesthesia: a new method to test additives to local anesthetic solutions. *Anesthesiology*. 2003;98(6):1427-1430.
- Johnson CN, Heindel LJ, Shin AY, Olsen RL, Vacchiano CA. The addition of ketorolac to lidocaine intravenous regional block of the upper extremity. Poster presented at: 64th AANA Annual Meeting; August 9-14, 1997; San Francisco, California.
- Reuben SS, Steinburg RB, Kreitzer JM, Duprat KM. Intravenous regional anesthesia using lidocaine and ketorolac. *Anesth Analg*. 1995;81(1):110-113.
- Reuben SS, Steinburg RB, Maciolek H, Manikantan P. An evaluation of the analgesic efficacy of intravenous regional anesthesia with lidocaine and ketorolac using a forearm versus upper arm tourniquet. *Anesth Analg*. 2002;95(2):457-460.
- Steinberg RB, Reuben SS, Gardner G. The dose-response relationship of ketorolac as a component of intravenous regional anesthesia with lidocaine. *Anesth Analg*. 1998;86(4):791-793.

- Morgan GE Jr, Mikhail MS, Murray MJ, Larson CP Jr. *Clinical Anesthesiology*. 3rd ed. New York, NY: Lange Medical Books/McGraw-Hill Medical Publishing Division; 2002.
- Bridenbaugh PO. Preemptive analgesia—is it clinically relevant? *Anesth Analg*. 1994;78(2):203-204.
- Joshi GP. Pain management after ambulatory surgery. *Amb Surg*. 1999;7(1):3-12.
- Woolf CJ, Chong M. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*. 1993;77(2):362-379.
- Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidal anti-inflammatory drugs. *Anesth Analg*. 1994;79(6):1178-1190.
- Reuben SS, Steinberg RB, Klatt JL, Klatt ML. Intravenous regional anesthesia using lidocaine and clonidine. *Anesthesiology*. 1999;91(3):654-658.
- Reuben SS, Steinberg RB, Lurie SD, Gibson CS. A dose-response study of intravenous regional anesthesia with meperidine. *Anesth Analg*. 1999;88(4):831-835.
- Gibbs NM, Sear JW. Effect of ketorolac, bupivacaine and low-dose heparin on thrombelastographic variables in vitro. *Br J Anaesth*. 1995;75(1):27-30.
- Norman PH, Daley MD, Lindsey RW. Preemptive analgesic effects of ketorolac in ankle fracture surgery. *Anesthesiology*. 2001;94(4):590-603.
- Strom BL, Berlin JA, Kinman JL, et al. Parenteral ketorolac and risks of gastrointestinal and operative site bleeding. A postmarketing surveillance study. *JAMA*. 1996;275(5):376-382.
- Thwaites BK, Nigus DB, Bouska GW, et al. Intravenous ketorolac tromethamine worsens platelet function during knee arthroscopy under spinal anesthesia. *Anesth Analg*. 1996;82(6):1176-1181.
- Thwaites BK, Nigus DB, Gregory W, Paul D, Ayala EF, Merrill GA. Intravenous ketorolac tromethamine does not worsen platelet function during knee arthroscopy under general anesthesia. *Anesth Analg*. 1995;81(1):119-124.
- Tai-Shion L. Intensive care anesthesia & analgesia. In: Bongard FS and Sue DY, eds. *Critical Care Diagnosis & Treatment*. 2nd ed. New York, NY: McGraw-Hill; 2002:104-125.

AUTHORS

LT Jesse J. Rivera, CRNA, MSN, NC, USN, is a graduate of the Navy Nurse Corps Anesthesia Program, San Diego, California.

LT Dante J. Vilecco, CRNA, MSN, NC, USN, is a graduate of the Navy Nurse Corps Anesthesia Program, San Diego, California.

LT Bryan K. Dehner, CRNA, MSN, NC, USN, is a graduate of the Navy Nurse Corps Anesthesia Program, San Diego, California.

CDR(ret) Joseph F. Burkard, CRNA, DNSc, NC, USN, was the clinical coordinator at the Navy Nurse Corps Anesthesia Program, San Diego, California.

CDR Lisa A. Osborne, CRNA, PhD, NC, USN, is the research coordinator at the Navy Nurse Corps Anesthesia Program, San Diego, California. Email: lisa.osborne@med.navy.mil.

CAPT Joseph E. Pellegrini, CRNA, PhD, NC, USN, is the research director at the Navy Nurse Corps Anesthesia Program, Bethesda, Maryland.

ACKNOWLEDGMENTS

Thank you to Eric Hoffmeister, MD, and Brian Fitzgerald, MD, from the Orthopedics Department at the Naval Medical Center, San Diego, for your support of this project. We would also like to thank the Navy Nurse Corps Anesthesia Program, Naval School of Health Sciences, San Diego, California. The chief of the Bureau of Medicine and Surgery at the Navy Department in Washington, DC, Clinical Investigation Program sponsored this report, #S-05-098, as required by NSHSBETHINST 6000.41A.

DISCLAIMER

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.