Anesthesiology
1999; 91:654–8

Intravenous Regional Anesthesia Using Lidocaine and Clonidine

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Background: **Clonidine has been added to local anesthetic regimens for various peripheral nerve blocks, resulting in prolonged anesthesia and analgesia. The authors postulated that using clonidine as a component of intravenous regional anesthesia (IVRA) would enhance postoperative analgesia.**

Methods: **Forty-five patients undergoing ambulatory hand surgery received IVRA with lidocaine, 0.5%, and were assigned randomly and blindly to three groups. The control group received intravenous saline, the intravenous clonidine group received 1 μg/kg clonidine intravenously, and the IVRA clonidine group received 1 μg/kg clonidine as part of the IVRA solution. After their operations, the patients' pain and sedation scores and analgesic use were recorded.**

Results: **Patients in the IVRA clonidine group had a significantly longer period of subjective comfort when they required no analgesics (median [range]) for 460 min (215–1,440 min), compared with 115 min (14–390 min) for the control group and 125 min (17–295 min) for the intravenous clonidine group ($P < 0.0001$). The patients who received IVRA with clonidine reported significantly lower pain scores 1 and 2 h after tourniquet deflation compared with the other groups, and they required no fentanyl in the postanesthesia care unit. They also required fewer analgesic tablets (325 mg acetaminophen with 30 mg codeine) in the first 24 h (2 ± 1, mean ± SD) compared with the other two groups, 5 ± 1 tablets (control) and 4 ± 2 tablets (intravenous clonidine) ($P < 0.0001$). No significant postoperative sedation, hypotension, or bradycardia developed in any of the patients.**

Conclusion: **The addition of 1 μg/kg clonidine to lidocaine, 0.5%, for IVRA in patients undergoing ambulatory hand surgery improves postoperative analgesia without causing significant side effects during the first postoperative day. (Key words: α_2-Adrenergic agonists; local anesthetics; postoperative pain; surgical procedures to the hand.)**

INTRAVENOUS regional anesthesia (IVRA) is a safe and effective way to provide anesthesia for hand surgery expected to last less than 1 h, but it often does not provide effective postoperative analgesia. In an attempt to improve perioperative analgesia, various analgesics have been administered concomitantly with the local anesthetic in IVRA. Opioids including morphine,[1] fentanyl,[2] sufentanil,[3] and meperidine[4] have been added to the IVRA solution with contradictory results. Recently, we added ketorolac to IVRA with lidocaine, resulting in improved perioperative analgesia.[5,6] Although we observed no localized sequelae in these studies, other investigators have noted hematomas, which they attributed to ketorolac under similar conditions[7] (Paul F. White, personal communication, April 1996). The search continues for an ideal analgesic, devoid of side effects, that can be added to IVRA local anesthetics. The addition of clonidine to local anesthetics for regional anesthesia may prolong the analgesic effects of these techniques.[8] We reasoned that the addition of clonidine to lidocaine for use in IVRA might improve postoperative analgesia.

Materials and Methods

Forty-five patients scheduled for elective hand surgery by a single surgeon gave formal, written consent to participate in this double-blinded study approved by our institutional review board. They were scheduled to undergo carpal tunnel release or tenolysis. After routine monitors were applied, a double tourniquet was positioned on the upper operative arm. When necessary, patients received as much as 2 mg midazolam for sedation; no opiates or other analgesics were given before or during operation. A 1-ml volume of normal saline (NS) or 1 μg/kg clonidine, prepared by an assistant otherwise not involved with the study, was injected intravenously

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Received from the Department of Anesthesiology, Baystate Medical Center and the Tufts University School of Medicine, Springfield, Massachusetts. Submitted for publication December 16, 1998. Accepted for publication April 26, 1999. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, October 19, 1998.

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Table 1. Patient Demographics and Surgical Data

Group	n	Age (yr)	Weight (kg)	Procedures		Duration of Surgery (min)	Tourniquet Time (min)
				Carpal Tunnel	Tenolysis		
Control	15	55 ± 13	71 ± 12	7	8	19 ± 4	35 ± 9
Intravenous clonidine	15	46 ± 11	74 ± 13	5	10	17 ± 5	32 ± 11
IVRA clonidine	15	50 ± 17	77 ± 11	6	9	20 ± 5	36 ± 10

Data are mean ± SD.

IVRA = intravenous regional anesthesia.

according to group assignment. The operative extremity was exsanguinated by elevating it and wrapping it with an Esmarch bandage. The proximal tourniquet was inflated to 250 mmHg and the Esmarch bandage was removed. A distal tourniquet was not used for any patient; it was included only as a safety feature. Circulatory isolation of the operative arm was confirmed by inspection of the hand and by absence of the radial pulse. IVRA was established in all patients using 40 ml of a solution containing 200 mg lidocaine and NS with or without clonidine. All patients receiving IVRA lidocaine had clonidine administered with the lidocaine, systemically, or they received no clonidine, according to group assignment. Patients were assigned at random to one of three groups: The control group (control) received 1 ml NS intravenously, and NS was added to the IVRA solution. The second group (intravenous clonidine) received 1 μg/kg clonidine intravenously and NS was added again to the IVRA solution. The third group (IVRA clonidine) received NS intravenously and 1 μg/kg clonidine was added to the IVRA solution. All solutions administered intravenously were given several minutes before the operative tourniquet was inflated, into an intravenous catheter established in the unaffected arm.

After surgery, a blinded observer assessed the patients' pain and sedation levels 1 and 2 h after tourniquet deflation. Pain was assessed using an integer verbal analog pain scale between 0 and 10, with 0 representing no pain and 10 representing the worst imaginable pain. Sedation was recorded on a numeric scale (1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, and 5 = asleep and not responsive to any stimulus). Intravenous boluses of 25 μg fentanyl were provided in the postanesthesia care unit whenever the verbal analog pain scale exceeded 3. The total number of fentanyl doses was noted.

Patients were instructed to take one tablet containing 325 mg acetaminophen with 30 mg codeine (Tylenol #3; McNeil Pharmaceuticals, Raritan, NJ) every 4 h as needed for pain at home. All the patients were contacted by telephone on the day after surgery. The time from tourniquet deflation until the patient first took an acetaminophen–codeine tablet was noted, as was the total number of acetaminophen–codeine tablets required during the first 24 h after operation.

Statistical Analyses

Demographic data and times (duration of the procedure, tourniquet time, time to discharge, and analgesic duration) were analyzed using analysis of variance. Pain scores, the amount of postoperative analgesics, and the level of sedation were analyzed using the Kruskal–Wallis test. If a significant result was obtained, the Wilcoxon signed rank test was performed to determine between which groups there was a significance difference; Bonferroni correction was used for multiple comparisons. The Mann–Whitney U test was used to compare the number of fentanyl doses. Significance was determined at the $P < 0.05$ level.

Results

There were no differences among the groups in demographic variables, the distribution of surgical procedures, durations of the operations, or tourniquet times (table 1). Discharge times (mean ± SD) were similar for the control (112 ± 11 min), intravenous clonidine (113 ± 14 min), and the IVRA clonidine groups (108 ± 16 min). Sedation scores (mean ± SD) were also similar among the three groups at 1 h, at 1.3 ± 0.5, 1.5 ± 0.4, and 1.8 ± 0.7 and at 2 h, at 1.1 ± 0.3, 1.4 ± 0.6, and 1.5 ± 0.6 for the control, intravenous clonidine, and IVRA clonidine groups, respectively. No patient experienced hypotension (mean arterial blood pressure < 80% of baseline), hypoxemia (pulse oximetry ≤ 90%), or bradycardia (heart rate ≤ 60 beats /min). Patients in the IVRA clonidine group had a signifi-

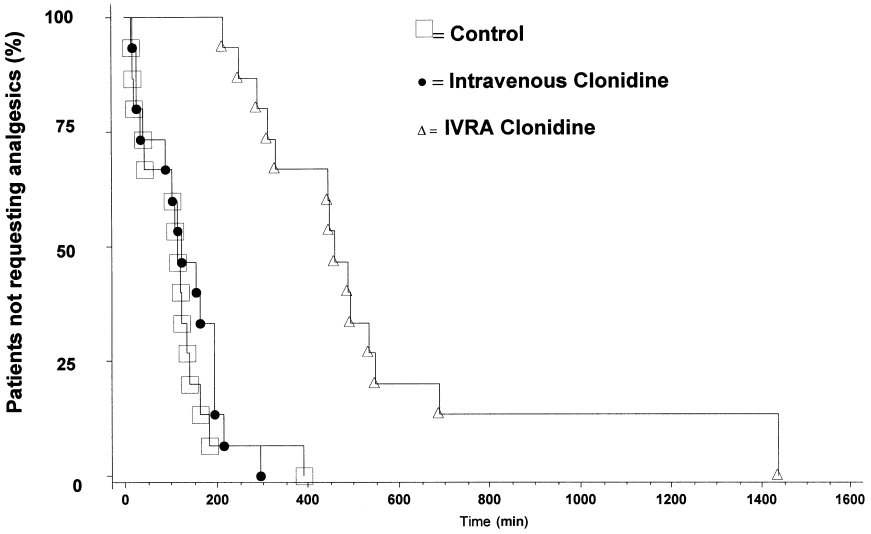

Fig. 1. The percentage of patients who did not request analgesia after tourniquet deflation is shown. Patients in the intravenous regional anesthesia clonidine group had a signigicantly longer period of subjective comfort when they required no analgesics compared with the control and intravenous clonidine groups ($P < 0.0001$). The control and intravenous clonidine groups were not significantly different.

cantly longer period of subjective comfort when they required no analgesics at a median of 460 min (range, 215–1,440 min) compared with 115 min (range, 14–390 min) for the control group, and 125 min (range, 17–295 min) for the intravenous clonidine group ($P < 0.0001$). Analgesic duration (fig. 1) was similar for the control and intravenous clonidine groups. In addition, patients in the IVRA clonidine group required no fentanyl for supplemental analgesia in the postanesthesia care unit, compared with 37.5 ± 47.5 μg (mean ± SD) for the control group and 27.5 ± 38.1 μg for the intravenous clonidine group ($P < 0.05$). Furthermore, 3 of the 15 patients in the IVRA clonidine group required no additional analgesics during the first 24 h after tourniquet release. All patients in the other two groups required acetaminophen–codeine tablets. The 24-h total acetaminophen–codeine tablet consumption (mean ± SD) was less in the IVRA clonidine group (2 ± 1 tablets) compared with the control group (4.8 ± 1.3 tablets) and the intravenous clonidine group (4.2 ± 1.6 tablets) ($P < 0.0001$; table 2). There was no difference in acetaminophen–codeine use between the control and intravenous clonidine groups.

Verbal analog pain scale scores 1 and 2 h after operation followed a similar pattern (table 2). The 1-h verbal analog pain scale (median [range]) was less ($P < 0.0001$) for the IVRA clonidine group (1 [0–2]) than for both the control (3 [1–6]) and intravenous clonidine (3 [2–5]) groups. Verbal analog pain scale values at 2 h were also less ($P < 0.0003$) for the IVRA clonidine group (2 [0–3]) than for both the control (4 [2–6]) and intravenous clonidine groups (3 [2–5]).

Discussion

Clonidine has been added to local anesthetics for various peripheral nerve blocks, resulting in improved an-

Table 2. Postoperative Pain Scores and Treatment

	VbAS*		Fentanyl in PACU		
Group	1 h	2 h	n (%)†	Dose (μg)	24-h Total T#3 Tablets‡
Control	3 (1–6)	4 (2–6)	5 (33)	37.5 ± 47.5	5 ± 1
Intravenous clonidine	3 (2–5)	3 (2–5)	4 (27)	27.5 ± 38.1	4 ± 2
IVRA clonidine	1 (0–2)§	2 (0–3)‖	0	0#	2 ± 1§

IVRA = intravenous regional anesthesia; VbAS = verbal analog score for postoperative pain; PACU = postanesthesia care unit.

* Data are presented as median (range).

† Data are presented as number in group (% of group).

‡ Data are presented as mean ± SD.

§ $P < 0.0001$ for group IVRA clonidine *versus* other groups.

‖ $P < 0.0003$ for group IVRA clonidine *versus* other groups.

# $P < 0.05$ for group IVRA clonidine *versus* other groups.

esthesia and analgesia.[9] Our study also revealed that postoperative analgesia was improved significantly when clonidine was added to 0.5% lidocaine for IVRA. Patients who received clonidine in the IVRA group had lower pain scores and decreased analgesic use in the 24 h after surgery. Our results seem to differ from those of Kleinschmidt *et al.*,[10] who reported that the addition of 2 μg/kg clonidine to IVRA with 0.5% prilocaine provided no significant improvement in postoperative pain. However, that study defined the duration of analgesia as the time from tourniquet deflation until the first time patients reported "wound pain sensations." This was probably a more accurate reflection of the regression of sensory anesthesia rather than of analgesic duration. That study did not formally assess pain for more than 45 min after tourniquet deflation. In contrast, we defined analgesic duration as the time from tourniquet deflation until the patients' first opioid use, which coincided with a verbal analog pain scale score greater than 3.

The analgesic effect of clonidine appears to be mediated peripherally and not the result of central redistribution. Patients receiving IVRA lidocaine and intravenous clonidine failed to demonstrate any additional analgesia compared with lidocaine alone. Furthermore, our previous study using similar doses of IVRA clonidine revealed plasma concentrations of 0.12 ± 0.05 ng/ml obtained 30 min after tourniquet deflation.[11] This is significantly less than the reported plasma concentration of clonidine (1.5 to 2 ng/ml) that has been shown to be most efficacious when clonidine is administered parenterally as an analgesic adjuvant to manage postoperative pain.[12]

The precise mechanism by which clonidine exerts its analgesic effect remains unknown. Clonidine enhances peripheral nerve blocks of local anesthetics by selectively blocking conduction of A-δ and C fibers.[13] Clonidine also causes local vasoconstriction, thereby reducing the vascular uptake of local anesthetics.[14] Other investigators have suggested that clonidine may produce a peripheral analgesic effect by releasing enkephalin-like substances.[15]

The role of the sympathetic nervous system in nociceptive pathways is complex. Clonidine may possess peripheral analgesic effects in patients with sympathetically mediated pain.[11,16] Both animal[17,18] and human[19] studies suggest that sympathetic neural activity and noradrenaline have an excitatory effect on nociceptive discharge after cutaneous injury. Drummond[19] concluded that sympathetic neural activity might increase pain associated with skin damage. Because clonidine inhibits the release of norepinephrine from prejunctional α_2-adrenoceptors in the periphery,[20] it may potentially inhibit neural activity in nociceptive pathways.

When administered as part of a regional anesthetic technique, clonidine clearly prolongs anesthesia and analgesia in a dose-dependent manner.[9] Larger IVRA clonidine doses might have provided more prolonged analgesia than we observed. However, we elected to use a clonidine dose of 1 μg/kg, based on our previous experience using IVRA clonidine to manage sympathetically maintained pain.[11] Our previous experience using clonidine doses ≥2 μg/kg produced excessive sedation and hypotension that required a prolonged recovery time.

In conclusion, the addition of clonidine to lidocaine, 0.5%, for IVRA provided improved analgesia in the postanesthesia care unit during the first 2 h after operation and diminished the need for analgesic supplements during the first day after operation. The addition of 1 μg/kg clonidine seems to be well tolerated and causes no significant side effects.

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