Original Article

Clonidine as an adjunct to intravenous regional anesthesia: A randomized, double-blind, placebo-controlled dose ranging study

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Abstract

Background: The addition of clonidine to lidocaine intravenous regional anesthesia (IVRA) has been previously reported to improve postoperative analgesia in patients undergoing upper extremity surgery. Our objective was to perform a dose ranging study in order to determine the optimal dose of clonidine used with lidocaine in IVRA.
Design & Setting: We performed a double-blinded randomized placebo-controlled study with 60 patients scheduled for elective endoscopic carpal tunnel release under IVRA with 50 ml lidocaine 0.5%. University-affiliated outpatient surgery center. Data collected in operating rooms, recovery room, and by telephone after discharge from surgery center.
Materials & Methods: Sixty adult ASA I or II patients undergoing outpatient endoscopic carpal tunnel release under intravenous regional anesthesia.Patients were randomized into five study groups receiving different doses of clonidine in addition to 50 ml 0.5% lidocaine in their IVRA. Group A received 0 mcg/kg, group B 0.25 mcg/kg, group C 0.5 mcg/kg, group D 1.0 mcg/kg and group E 1.5 mcg/kg of clonidine.Intraoperative fentanyl, recovery room pain scores, time to first postsurgical analgesic, total number of acetaminophen/codeine tablets consumed postsurgery, incidence of sedation, hypotension and bradycardia.
Results & Conclusions: There was no benefit from any dose of clonidine compared to placebo. There were no clonidine-related side effects seen within the dose range studied. In short duration minor hand surgery, the addition of clonidine to lidocaine-based intravenous regional anesthesia provides no measurable benefit.

Key words: Analgesia and anesthesia, ambulatory surgical procedures, clonidine, intravenous regional anesthesia

Introduction

Lidocaine-based intravenous regional anesthesia (IVRA) is commonly utilized for superficial short duration upper extremity surgeries. However, when used as the sole IVRA anesthetic, lidocaine provides minimal postoperative analgesia,[1] and is limited by tourniquet pain. A number of

IVRA adjuncts, including opioids, tramadol, nonsteroidal anti-inflammatory drugs (NSAIDS), clonidine, steroids and sodium bicarbonate have been used along with lidocaine in order to improve onset time, intraoperative analgesia or to extend postoperative analgesia.[2] The anesthesiology literature had generally supported the use of clonidine for improving postoperative analgesia in IVRA,[2-6] as well as for a variety of other peripheral nerve blocks.[3] However, the withdrawal of sentinel work by Reuben, *et al*[4,6] has significantly diminished the strength of evidence supporting clonidine in IVRA. Clonidine may also cause undesirable side effects, such as sedation, hypotension and bradycardia. Our goal in this study was to determine the optimal dose of clonidine as an adjunct to standard lidocaine-based[7] IVRA, for the purpose of providing postoperative analgesia, while minimizing side effects and adverse reactions.

Materials and Methods

After obtaining approval from the Institutional Review Board

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serving the University of Vermont and Fletcher Allen Health Care (Burlington, Vermont, USA), 60 ASA physical status I-II patients between the ages of 18-65 years of age scheduled to undergo endoscopic carpal tunnel release (CTR) by the same surgeon were enrolled in this study. Written informed consent was obtained from each subject prior to entering the study. Patients were excluded if they reported allergies to codeine, acetaminophen, local anesthetics, or clonidine. We also excluded patients taking opiates or α-2 adrenergic antagonists and patients with certain medical conditions including cardiac conduction block, peripheral or central neurological disease, angina, cerebrovascular disease and valvular heart disease.

Study subjects were randomly allocated into five groups according to a computer-generated table of random numbers (Excel, Microsoft, Inc., Redmond, Washington, USA). Intraoperative physiologic monitoring was in accordance with the ASA standards. Each patient received midazolam 2 mg IV and 2 liters per minute of oxygen by nasal cannula on arrival to the operating room. A single cuff tourniquet was placed on the upper arm, which was then exsanguinated by elevation and the use of a tightly wrapped Esmarch bandage. The tourniquet was inflated to 250 mmHg and circulatory isolation was confirmed by skin pallor and absence of a radial artery pulse. IVRA was administered by intravenous injection of 50 ml of lidocaine 0.5% and the study drug into the isolated extremity over two minutes. Clonidine (Duraclon, Xanodyne Pharmaceuticals, Newport, KY, USA) doses were determined by each patient's randomized study group designation. Groups A, B, C, D and E receiving clonidine 0g, 0.25, 0.50, 1.0 or 1.5 mcg/kg, respectively. Group designations were blinded to the patient, the surgeon, the anesthesiologist performing the IVRA, the recovery room nurses, data collection personnel, and the investigator performing the study analysis. The syringe used to add clonidine to the lidocaine was prepared by a physician uninvolved in any aspect of the study. Each placebo or clonidine containing syringe was labeled "study drug" and diluted to a volume of 1 ml with 0.9% normal saline.

If additional analgesia was in needed intraoperatively, as indicated by a verbal pain score >3 (0=no pain to 10= worst pain possible), IV fentanyl 25 mcg was administered every 3 minutes until patient comfort was achieved. At the conclusion of surgery, the tourniquet was deflated, and patients were transported to the post-anesthesia care unit (PACU) where their pain level was assessed using the same integer (0-10) verbal analog pain scale. Pain scores were recorded every thirty minutes until discharge. The incidence of hypotension (systolic blood pressure < 90), bradycardia (HR<60), and oxygen desaturation (SaO$_2$ < 93%) observed in the PACU were recorded. Level of sedation was measured using a sedation scale (0=completely awake, 1=drowsy, 2=asleep but responsive to command, 3=asleep but responsive to glabellar tap, 4=unresponsive) and recorded every 15 minutes. During the recovery period, pain scores>3 were treated with two acetaminophen 325 mg/codeine 30 mg tablets. Upon discharge from the PACU, patients were instructed to take 1-2 acetaminophen 325 mg/codeine 30 mg tablets every 4 hours as needed only when their pain score exceeded a 3 on the previously described 10 point verbal score. Patients recorded the time of first analgesic and the total number of acetaminophen 325 mg/codeine 30 mg tablets required during the 24-hour period following surgery. All patients were contacted by telephone 24 hours following surgery to ascertain the analgesic consumption information.

Statistical analysis

Our primary outcome measure was "total postoperative analgesics consumed", defined as the number of acetaminophen 325 mg/codeine 30 mg tablets taken during the first 24 hours following surgery. Our secondary outcome measure was "duration of postoperative analgesia" which was defined as time from surgery end until time of first opioid requested. Continuous variables (age, weight, pain scores, sedation scores, time to discharge, operation duration, duration of analgesia and total analgesics consumed) were analyzed using one-way analysis of variance. Categorical variables (gender, treatment in PACU) were analyzed using α^2 for multiple groups. Group size determination was based on an estimated difference from control of the primary outcome variable of 1 tablet, a type 1 error of 0.05, a type 2 error of 0.2, a standard deviation of 50%, and a one-sided test for analgesic efficacy. Based on these assumptions, a group size of seven patients was required. If clonidine provided benefit in either the primary or secondary outcomes compared to the control group, then logistic regression analysis would be used to optimize a dose response curve. Primer of Biostatistics software (McGraw-Hill, 2002) was used for statistical analysis.

Results

Of the original 60 study participants enrolled, eight subjects were eliminated from analysis due to protocol violations, resulting in a final study population of 52 patients. The specific violations included four subjects who were given NSAIDS in the PACU, one subject withdrew without explanation, one case was converted to an open surgery, one subject who initially denied using opioids but was found to regularly use opioids and one subject violated the protocol by consuming ten acetaminophen 325 mg/codeine 30 mg tablets postoperatively despite having a pain score of 0 at all time points.

There were no differences between study groups for demographic variables (age, gender, weight), adverse reactions to clonidine (hypotension, bradycardia, sedation score), operation duration or time to discharge. There were no differences between study groups in intraoperative fentanyl administration, pain scores on arrival to PACU, pain scores during the recovery period, sedation scores in PACU, or analgesics required in PACU [Table 1]. Additionally, no statistically significant differences were observed between groups for duration of postoperative analgesia ($P=0.85$; Figure 1) or total number of acetaminophen 325 mg/codeine 30 mg tablets taken during the first 24 hours following surgery ($P=0.88$; Figure 2, Table 2). No dose response analysis was appropriate because patients receiving clonidine in the IVRA did not differ from placebo in any clonidine dose, or in aggregate versus placebo.

Discussion

Clonidine acts centrally by stimulating alpha2-adrenoreceptors in the dorsal horn of the spinal cord.[8,9] However, central mechanisms of analgesia may not be applicable when clonidine is added to IVRA. The mechanism by which clonidine may enhance peripheral analgesia are not completely understood; however, several hypotheses for this action have been proposed. Clgeonidine selectively depresses neuronal action potential conduction of peripheral nociceptive A-delta and C-fibers.[8,9] It also causes localized vasoconstriction, potentially resulting in prolonged action of local anesthetics by decreasing vascular uptake.[10] Additionally, there is convincing evidence that hyperpolarization of activated cation currents, as opposed to α-2-receptors, are important in the peripheral analgesia of clonidine.[11]

Clonidine has been described as an effective component in multimodal regional anesthesia when administered as an adjunct to lidocaine IVRA.[4-6] Enthusiasm for clonidine was based significantly on work submitted by Reuben *et al*. This group[4] reported a double-blind randomized clinical trial involving 45 patients undergoing elective hand surgery, and reported that adding clonidine 1 mcg/kg to lidocaine 0.5% IVRA improved postoperative pain control.[9] This paper has been withdrawn due to academic fraud. Likewise, work by Reuben and colleagues[6] suggested the addition of clonidine to lidocaine IVRA diminished tourniquet discomfort and intraoperative fentanyl requirements. This paper was also withdrawn for similar reasons. Further clouding the IVRA clonidine literature is that a systematic review[2] was published after Reuben's work appeared, but before it was withdrawn. The recommendations of this review may have differed without Reuben's (now withdrawn) papers.

In contrast to Reuben's work, Kleinschmidt, *et al*[12] conducted a placebo-controlled trial of clonidine 2 mcg/kg in a 0.5% prilocaine IVRA, which failed to demonstrate a significant difference in postoperative pain control between the control group and the treatment group.[12] Our study differs from Kleinschmidt's in their use of prilocaine (not available in the United States for IVRA), more complex and invasive surgical procedures, and the higher dose of clonidine. Our study attempted to establish the optimal dose of clonidine added to lidocaine in IVRA for the purpose of improving postoperative analgesia while minimizing side effects. Regional anesthesia doses of clonidine above 150 mcg have been shown to cause hemodynamic side effects; indeed, hypotension was noted in the Kleinschmidt's subjects. In our work, the inclusion of clonidine to lidocaine in IVRA did not appear to improve postoperative pain control. We found no difference in postoperative analgesia between our control group and any of the treatment groups. Because the addition of clonidine did not result in a measurable treatment effect, further dose ranging analyses were not appropriate.

Clonidine was tolerated throughout the study interval by all patients, as there were no side effects or adverse events
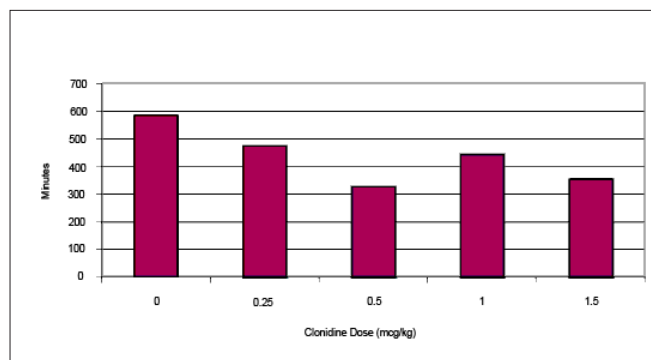

Figure 1: Duration of postoperative analgesia, defined as time from surgery end until the patient first required opioid postoperatively, plotted against dose of clonidine added to lidocaine IVRA. No significant difference was observed between groups
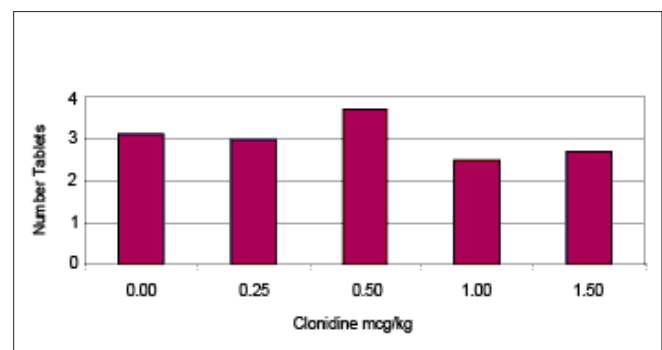

Figure 2: Acetaminophen 325mg/Codeine 30 mg tablets consumed, defined as the total number of tablets required for postoperative analgesia during the first 24 hours following the operation, plotted against clonidine dose added to lidocaine IVRA. No significant differences were observed between groups

Table 1: Patient demographics, surgical and post-anesthesia care unit data

Group	A (n=11)	B (n=9)	C (n=10)	D (n=10)	E (n=12)	
Age (years)	49.8 ± 10.9	49.22 ± 13.8	48.6 ± 13.9	45.7 ± 16.4	55.3 ± 9.7	P=0.54
Weight (kg)	87.4 ± 25.5	87.8 ± 13.1	91.4 ± 20.65	94.1 ± 25.8	88.4 ± 29.4	P=0.96
Intraoperative Fentanyl (mcg)	11.3 ± 30.3	11.11 ± 22.1	27.5 ± 24.9	20.0 ± 48.3	8.3 ± 19.5	P=0.59
Analgesics required in PACU (%)	64	33	80	30	50	P=0.14
Pain score (PACU admit)	0.9 ± 1.7	0.11 ± .3	1.9 ± 1.9	0.9 ± 1.8	0.3 ± .6	P=0.08
Pain score (30 min. postop)	2.7 ± 2.8	1.11 ± 1.7	2.8 ± 2.0	0.9 ± 1.1	1.9 ± 2.3	P=0.24
Pain score (1 hr. postop)	1.9 ± 1.7	1.5 ± 1.3	2.1 ± 1.8	1.8 ± 1.3	2.2 ± 1.5	P=0.95
Sedation score (PACU admit)	0.7 ± .8	0.4 ± .7	0.9 ± .6	0.5 ± .7	0.4 ± .7	P=0.55
Total time todischarge (min)	70.3 ± 22.5	56.7 ± 16.3	67.8 ± 16.2	61.2 ± 27.5	60.6 ± 17.8	P=0.56
Duration of surgery (min)	5.9 ± 1.13	7.2 ± 3.1	7.0 ± 2.4	6.0 ± 1.6	6.4 ± 1.0	P=0.45

Data presented as mean ± SD

Table 2: Postsurgical analgesia: Time from end of surgery to first analgesic request and total number of acetaminophen/codeine tablets in first 24 hours

Clonidine dose (mcg/kg)	Duration analgesia (min)	SD	Total analgesic tablet consumption	SD
0	584	682	3.1	3.7
0.25	473	584	3	2.3
0.5	325	587	3.7	2.9
1	440	544	2.5	2.3
1.5	353	521	2.7	2.1
		P=0.85		P=0.88

observed. Specifically, no episodes of hypotension, bradycardia or excessive sedation occurred during the study.

Overall, the results of this study suggest the use of clonidine as an adjunct in IVRA does not enhance postoperative analgesia following endoscopic carpal tunnel release. However, there are a number of limitations to our work. Our work examined only endoscopic carpal tunnel release. This population was chosen because the procedure is standardized and common. Characteristics of this surgical population include a short length of surgery (5-10 minutes) and tourniquet time (7-11 minutes). Pain after this procedure is likely less than many other upper extremity procedures. Despite our negative results, it remains possible that clonidine's analgesic benefit in IVRA would only be apparent during and following more extensive and longer duration surgeries. In addition, the clonidine dose range we studied was maximized at 1.5 mcg/kg. This was purposeful, as doses of clonidine >150 mcg are causative of sedation and hypotension. Larger doses of clonidine may have been beneficial in our study, although with increased risks.[5,12] Another issue is the use of acetaminophen 325 mg/codeine 30 mg tablets for analgesia. Both of these analgesic doses are relatively low, although they represent a common and institutional practice. Finally, our study should not be interpreted to minimize the potential of IVRA clonidine to lower intraoperative tourniquet pain. Gentili's[5] work found that in longer duration surgeries using a double pneumatic cuff IVRA technique that clonidine 150 mcg did decrease intraoperative tourniquet pain. Our study population was limited to very short duration procedures using a single pneumatic tourniquet; thus, tourniquet pain evaluation was not a primary study endpoint.

In conclusion, the addition of clonidine <1.5 mcg/kg as an adjunct to lidocaine in IVRA does not appear to improve postsurgical analgesia in patients undergoing outpatient short duration minor hand surgery.

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