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Intravenous Regional Clonidine in the Management of Sympathetically Maintained Pain

Scott S. Reuben, M.D., Robert B. Steinberg, Ph.D, M.D.,† Lakshmi Madabhushi, M.D.,‡ Erik Rosenthal, M.D.§*

INTRAVENOUS regional anesthesia (IVRA) can contribute to the management of sympathetically maintained pain. A variety of medications have been used in IVRA, including local anesthetics with guanethidine, reserpine, bretylium, steroids, and ketorolac.[1–4] Clonidine, an α_2-adrenergic agonist, has been used successfully in the management of refractory reflex sympathetic dystrophy when administered *via* the epidural[5] or the intrathecal[6] route. The current series of treatments was designed to test the efficacy and safety of intravenous regional clonidine (IVRC). This report presents the results of such treatment in 10 patients who were selected on the basis of having symptoms of sympathetically maintained pain for <3 months.

After approval by our committee on human research, written informed consent was obtained from all patients before procedural intervention. A 22-gauge catheter was inserted into a distal vein of the affected extremity. After application of an electrocardiogram monitor, a pulse oximeter, a noninvasive blood pressure cuff, and an occlusive double tourniquet, the affected extremity was exsanguinated by elevating the extremity and wrapping it with an Esmarch bandage. After inflation of the tourniquet, the intravenous regional solution was injected over 3 min. It included 1 μg/kg clonidine in a total volume of 40 ml for upper extremities and 50 ml for lower extremities. Normal saline or 0.5% lidocaine was used as the diluent. After 30 min, the cuff was deflated and all patients were monitored for an additional 60 min before discharge. Concentrations of clonidine in plasma were determined using a radioimmunoassay method[7] on blood sampled from the arm (contralateral to the IVRA site for patients with upper extremity pain) 30 min after deflation of the tourniquet. Pain was assessed using a verbal pain score (VPS) in which 0 = no pain and 10 = worst pain imaginable.

Case Reports

A typical case is that of a 37-yr-old woman who presented to the Pain Management Center 47 days after undergoing surgical repair for

* Associate Professor of Anesthesiology; Director, Acute Pain Service, Department of Anesthesiology.

† Assistant Professor of Anesthesiology; Chief, Pain Management Services, Department of Anesthesiology.

‡ Fellow, Pain Management, Department of Anesthesiology.

§ Clinical Professor of Orthopedic Surgery; Director of Hand Surgery Service, Department of Surgery.

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Address reprint requests to Dr. Reuben: Department of Anesthesiology, Baystate Medical Center, 759 Chestnut Street, Springfield, Massachusetts 01199. Address electronic mail to: Scott.reuben@bhs.org

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a lacerated tendon of her right arm (patient 1). Since her surgery, she had been experiencing diffuse burning pain (VPS = 6) throughout her arm. Her symptoms also included hyperesthesia, allodynia, edema, color changes, and increased skin temperature of the affected extremity. Previous treatment included physical therapy, amitryptiline, and ibuprofen. The patient experienced complete relief of pain after a right stellate ganglion block. Two days afterward, the pain recurred, and she was treated with IVRC diluted with saline. After 10 min, with the tourniquet inflated, the patient noticed complete resolution of her pain, allodynia, and hyperesthesia. This relief (VPS = 0) continued for an additional 3 days, after which the pain gradually returned at a lower intensity (VPS = 5). She also noticed a reduction in the edema and color changes of her affected extremity. A second IVRC procedure provided 5 days of complete relief of pain. The pain gradually returned at a still lower intensity (VPS = 4). Because of pain experienced from the tourniquet with the first two treatments, we elected to use 0.5% lidocaine as the diluent for her three successive procedures, which were performed in consecutive weeks. Six months after the last treatment, the patient remained painfree.

Ten patients with symptoms of sympathetically maintained pain (table 1) were treated with IVRC. The diagnoses were based on clinical symptoms of allodynia, hyperalgesia, edema, vasomotor changes, pain with a burning quality, sudomotor changes, or temperature differences between extremities. Although no patient presented with all of these features, we made a tentative diagnosis of sympathetically maintained pain if four or more were present. All patients had complete relief of pain after an appropriate sympathetic block. Intravenous regional clonidine was offered to each patient up to six times (maximum of once a week for 6 weeks). For every patient, the duration of pain relief increased with each subsequent procedure.

Before treatment, these patients had pain symptoms for 49 ± 13 days. They required four to six IVRC procedures for complete resolution of their pain symptoms. All patients experienced complete relief of pain (VPS = 0) during and immediately after tourniquet deflation. Duration of complete relief of pain after the first intravenous regional procedure was 1.6 ± 0.7 days. The median duration of follow-up is currently 7 months (range, 5–9 months), and none have required further therapy.

No patient experienced hypotension (mean arterial pressure ≤ 20% at baseline), hypoxemia ($SpO_2 \leq 90\%$), bradycardia (heart rate ≤ 60 beats/min), or excessive sedation. In previous trials of IVRC with doses of clonidine ≥2 μg/kg, hypotension or sedation occurred frequently, requiring prolonged observation in the Pain Center. Concentrations of clonidine in plasma were 0.12 ± 0.05 ng/ml.

Only one patient (no. 3) was able to tolerate inflation of the tourniquet without lidocaine as the diluent. This patient underwent four successive IVRC and has remained painfree for 6 months.

Discussion

Clonidine is an α_2-adrenergic agonist that can affect both central and peripheral adrenergic receptors. Neuraxial clonidine, administered *via* the epidural[5] or the intrathecal[6] route, has been used previously to manage sympathetically maintained pain. Spinally administered clonidine may provide relief of pain in patients with sympathetically maintained pain by reducing sympathetic outflow from preganglionic sympathetic neurons in the spinal cord or by decreasing nociceptive transmission in the dorsal horn.[8] Recently, the peripheral administration of medetomidine, an α_2-adrenoreceptor agonist, was shown to attenuate allodynia produced by spinal nerve ligation in the rat.[9] The ability to alleviate allodynia was believed to be mediated by a central action on spinal α_2-adrenoreceptors, although the drug was administered peripherally.

Clonidine, however, possesses peripheral analgesic properties in patients with sympathetically maintained pain, possibly because it reduces release of norepinephrine from prejunctional α_2-adrenoreceptors in the periphery.[10] Data from several clinical investigations support the importance of peripheral adrenergic receptors in the maintenance of sympathetically maintained pain. First, adrenergic blockade with intravenously administered phentolamine,[11] phenoxybenzamine,[12] or prazosin[13] diminishes pain. Second, IVRA with guanethidine depletes peripheral catecholamines and can relieve sympathetically maintained pain.[1] Third, intradermal injection of norepinephrine rekindles sympathetically maintained pain in patients who have previously undergone a sympathectomy.[14] Fourth, topical application of clonidine has been shown to eliminate hyperalgesia only at the site of drug application. This hyperalgesia was later rekindled by the intradermal injection of norepinephrine or phenylephrine.[15]

All of our patients who received IVRC experienced a dramatic reduction in allodynia and hyperalgesia before and immediately after deflation of the tourniquet even without the concomitant use of lidocaine. Tourniquet-induced ischemia can decrease hyperalgesia in patients with neuropathic pain, beginning 4–20 min after inflation of the cuff, and may have contributed to the initial analgesia we observed during IVRC. This reduction is short-lived, however, and hyperalgesia returns several minutes after release of the cuff.[16] Because our patients experienced a significantly longer duration of analgesia after deflation of the tourniquet, clonidine probably contributes independently to the reduction of hyperalgesia and other symptoms in this patient population.

We considered whether the relief our patients obtained resulted from the lidocaine or the clonidine in our intravenous regional solution. We believe the therapeutic benefit derived from the use of clonidine. Patient 3 was painfree after undergoing four successive IVRC procedures, and other patients had relief after IVRC without lidocaine for some of their treatments. Further,

Table 1.

Case Number	Age (yr), Gender	Injury	Symptoms	Duration of Symptoms (days)	Prior Treatment	Diluent*	IVRA Treatment Number	Pain before IVRA†	Duration of Relief‡ (days)
1	37, Female	Lacerated tendon, arm	Al, BP, E, Hy, TD, Va	47	NSAID TCA	S	1	6	3
						S	2	5	5
						L	3	4	8
						L	4	3	7
						L	5	3	Complete
2	38, Male	Carpal tunnel syndrome	Al, BP, E, TD, Va	29	None	S	1	9	2
						L	2	7	4
						L	3	4	6
						L	4	3	Complete
3	34, Male	Fracture, wrist	Al, BP, E, Hy, TD	43	NSAID	S	1	7	2
						S	2	5	4
						S	3	3	6
						S	4	3	Complete
4	43, Female	Sprain, knee	Al, BP, Hy, TD, Va	46	NSAID TCA	S	1	8	1
						L	2	7	2
						L	3	7	4
						L	4	5	4
						L	5	3	5
						L	6	3	Complete
5	42, Female	Sprain, wrist	Al, BP, E, Hy, TD	50	NSAID TCA	S	1	9	1
						L	2	8	2
						L	3	6	2
						L	4	5	4
						L	5	5	5
						L	6	4	Complete
6	38, Female	Crush, hand	Al, BP, Hy, Su, TD	45	NSAID	L	1	8	1
						L	2	7	2
						S	3	5	4
						L	4	4	4
						L	5	4	Complete
7	28, Male	Fracture, thumb	BP, E, Hy, TD	43	None	L	1	9	2
						L	2	7	5
						L	3	4	6
						S	4	4	Complete
8	48, Female	Carpal tunnel syndrome	Al, BP, E, Hy, Su	44	NSAID TCA	L	1	10	1
						L	2	8	2
						S	3	8	4
						L	4	6	4
						L	5	4	Complete
9	42, Male	Fracture, elbow	Al, BP, E, Hy, TD	71	NSAID	L	1	9	1
						L	2	7	2
						L	3	6	4
						L	4	4	4
						L	5	3	6
						L	6	3	Complete
10	34, Female	Fracture, toe	Al, BP, Su, TD, Va	74	NSAID TCA	L	1	10	2
						L	2	8	2
						L	3	5	4
						L	4	3	7
						L	5	3	Complete

Al = allodynia; BP = burning pain; E = edema; Hy = hyperalgesia; Su = sudomotor changes; TD = temperature difference compared with opposite extremity; Va = vasomotor changes; NSAID = nonsteroidal anti-inflammatory agent; TCA = tricyclic antidepressant; L = lidocaine; S = saline.

* Diluent in intravenous regional clonidine solution.

† Pain assessed on a Verbal Analog Scale from 0–10, with 0 being no pain and 10 the worst pain imaginable.

‡ Defined as the number of days with pain assessed as 0 on the Verbal Analog Scale.

McKain *et al.*[1] found that lidocaine IVRA failed to provide relief of pain in patients with sympathetically maintained pain beyond the duration of the block. The use of lidocaine in our patients allowed them to tolerate inflation of the tourniquet for 30 min and successfully complete a subsequent physical therapy session more comfortably than with clonidine alone.

Although the current study cannot exclude an analgesic action of clonidine by central redistribution, our patients experienced significant relief of allodynia and hyperalgesia in the isolated extremity before deflation of the tourniquet. Further, concentrations of clonidine in plasma (0.12 ± 0.05 ng/ml) obtained 30 min after deflation of the tourniquet were significantly lower than those required for a central sympatholytic effect. Maximum hypotensive and sedative effects usually occur with concentrations of clonidine in plasma between 1.5 and 2.0 ng/ml.[17] This range of concentrations of clonidine in plasma also has been shown to be most efficacious when used as an analgesic adjuvant in the management of postoperative pain.[18]

Additional studies are needed to establish the effectiveness of IVRC. In particular, patients whose pain has been present for >6 months may not respond to IVRC as well as the group reported here. Double-blind studies of IVRA using lidocaine with and without clonidine should be performed. Intravenous regional clonidine also should be compared to regional sympathetic blocks as the initial treatment for sympathetically maintained pain. All such studies should include the parenteral administration of clonidine as an active control group.

We report the successful use of IVRC in 10 patients with sympathetically maintained pain of <3 months' duration. Clonidine doses of 1 μg/kg appear to be well tolerated without significant side effects.

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