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# Intravenous Regional Phenoxybenzamine in the Treatment of Reflex Sympathetic Dystrophy

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REFLEX sympathetic dystrophy (RSD) is a disabling pain disorder that may develop as a consequence of trauma or surgery affecting the limbs.[1] In the revised taxonomic system, the disorders RSD and causalgia are grouped under the umbrella term, complex regional pain syndrome (CRPS).[2] The syndrome of RSD includes manifestations such as severe burning pain, hyperpathia, allodynia, hyperhidrosis, edema, vasomotor instability, and characteristic demineralization of the bone.[3] The pathologic mechanism in RSD is not known, and various treatment modalities, including vasodilators, radiotherapy, acupuncture, steroids, and nerve stimulation techniques, have been used.[4]

Local anesthetic blockade of sympathetic ganglia or blocking the same fibers with other types of nerve blocks, including epidural block,[4,5] is commonly applied in the management of RSD. Sympatholytic drugs have been used to provide a sympathetic block that is more prolonged than that achieved by local anesthetic alone. Intravenous regional blockade with a local anesthetic combined with guanethidine, reserpine, or steroids[4,6-9] has been used in an attempt to provide prolonged sympathetic blockade. Oral $\alpha$-adrenergic blocking agents, including phenoxybenzamine, prazosin, and terazosin, have been used with varying degrees of success.[10,11]

The present series of treatments was designed to test the efficacy and safety of intravenous regional blockade with phenoxybenzamine in patients with RSD. The rationale for the use of phenoxybenzamine was related to its noncompetitive, irreversible blockade of $\alpha$-adrenergic receptors. It was considered that a long-lasting sympathetic blockade might decrease or eliminate the sensitization that characterizes the syndrome. The evaluation of treatment efficacy was made by assessment of pain relief, skin temperature changes, and hand grip strength. We present the results for the first five patients treated with a formulation consisting of a mixture of phenoxybenzamine and lidocaine.‖ The study population consisted of patients demonstrating allodynia, hyperalgesia or hyperesthesia, and vasomotor disturbances in the extremity consistent with the clinical picture of RSD. The study was approved by the New York Medical College Institutional Review Board, and informed written consent was obtained from all participants. Demographic and clinical histories of the patients are presented in table 1.

Patients were instructed before treatment on the use of a visual analogue scale (VAS, 0-10) for rating the intensity of pain. They were asked to consider the most intense degree of pain that they had experienced during their illness as a score of 10; and 0 represented absence of pain.

After establishing intravenous access in the unaffected limb, an intravenous cannula also was inserted and secured in the affected extremity. The affected extremity was elevated for 3 min and was further exsanguinated using an Esmarch bandage. A double-cuff tourniquet was placed proximally on the extremity. The tourniquet

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‖ This formulation is approved in a Food and Drug Administration Investigational New Drug (IND) application under the aegis of New York Medical College.

**Table 1. Demographic Data and Patient Histories**

| Patient No. | Age (yr) | Sex | Duration of Symptoms (mo) | History |
|---|---|---|---|---|
| 1 | 44 | F | 60 | Right upper limb injury in motor vehicle accident; burning pain in hand, edema, hyperalgesia with hand movement; stellate ganglion blocks, lidocaine intravenous regional blockade, trigger point injection, cervical epidural steroids, NSAIDs, antidepressants |
| 2 | 26 | M | 3 | Machine injury to right hand; severe burning pain, decreased mobility to wrist joint, decreased strength, diffuse edema, cold extremity; narcotics, NSAIDs, physical therapy |
| 3 | 56 | F | 2 | Surgery for carpal tunnel release in right limb; hyperesthesia, throbbing pain and diffuse edema of hand, restricted mobility; narcotics, NSAIDs, physical therapy |
| 4 | 56 | M | 18 | Injury to left hand and upper extremity, hand surgery; continuous pain, restricted mobility of metacarpophalangeal and interphalangeal joints, cold extremity; narcotics, NSAIDs, physical therapy |
| 5 | 60 | F | 3 | Fracture of left radius and ulna; diffuse edema, restricted mobility of fingers and wrist joint; narcotics, NSAIDs, physical therapy |

NSAIDs = nonsteroidal antiinflammatory drugs.

was inflated 100 mmHg above the systolic blood pressure of the arm, but did not exceed 300 mmHg. Thirty milliliters of solution was used for intravenous regional blockade of an upper extremity; this solution consisted of 15 ml of 0.5% lidocaine HCl, 5 mg of phenoxybenzamine HCl (SmithKline-Beecham Pharmaceuticals, King of Prussia, PA), 0.05 ml of absolute alcohol, 0.05 ml of propylene glycol, 0.0005 ml of hydrochloric acid, and isotonic saline to make up the final volume. Ultraviolet spectrophotometric analyses of the formulation demonstrated that there were no physical or chemical incompatibilities of the two drugs in the final solution; the mixture appears to be stable at room temperature indefinitely. The data for these analyses are part of our Food and Drug Administration IND application.

The total volume of study drug and lidocaine (30 ml) was administered over 4 min. Distribution of the drug was hastened by brief periods of active or passive movements of the extremity. After a minimum period of 15 min, the tourniquet was deflated; it was then reinflated, and the patient was observed for possible drug side effects. It was then fully deflated. Monitoring of blood pressure, pulse oximetry, and electrocardiogram was performed continuously from 10 min before the procedure to 2 h after release of the tourniquet. The recordings 10 min before the procedure were considered as baseline values. The patients' intensities of pain using a VAS scale were recorded before and at 30, 60, 90, and 360 min after treatment; the 360-min record represented a score assigned by the patient at home approximately 6 h after the procedure. The patients were also asked to record VAS scores at home twice daily at approximately 12-h intervals for a period of at least 1 week. Daily follow-up calls were made to patients at home for 1 week. Skin surface temperature of the affected and unaffected extremity was measured before and at 30, 60, and 90 min after treatment; measurements were repeated at an early follow-up visit to the hospital, which ranged from 6 to 27 days after the procedure. The temperature measurements were made with skin tapes, graduated in 0.25°C, and applied to the dorsal surface of the hand. The measurements in the untreated hand served as a control for possible differences in environmental temperature at the various times of measurement, and for possible systemic effects of phenoxybenzamine after release of the tourniquet. Patients were evaluated for hand grip strength of the affected and unaffected extremity before and at 30, 60, and 90 min after treatment and at the early follow-up hospital

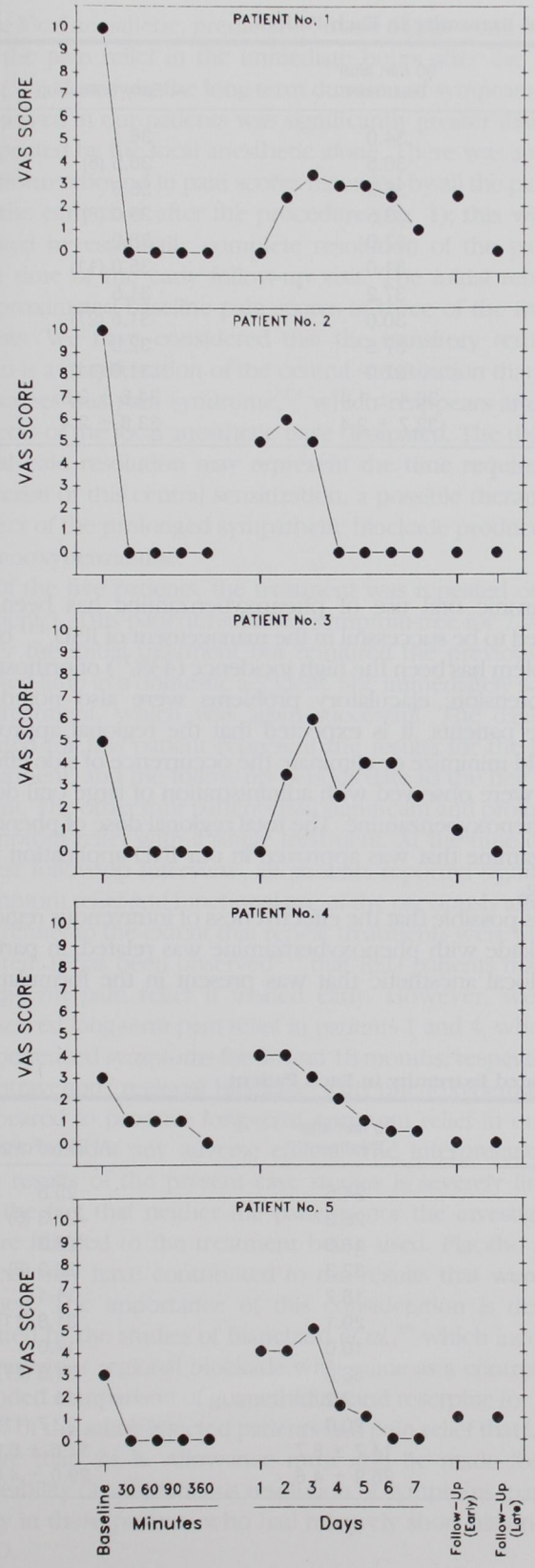


**Fig. 1. Baseline and post-procedure VAS scores for patients treated by intravenous regional blockade with phenoxybenzamine. Early follow-up evaluation times were at 6, 8, 11, 27, and 11 days after the procedure for patients 1, 2, 3, 4, and 5, respectively. The latest follow-up evaluations were at 17, 7, 5, 9, and 7 months for patients 1, 2, 3, 4, and 5, respectively.**

visit; a hand dynamometer was used for these measurements. Long-term follow-up evaluation of VAS score was obtained either by personal or telephone interview, ranging from 7 to 17 months after the procedure.

Baseline and post-procedure VAS scores for each patient are presented in figure 1. There were similar profiles in the pain scores among the subjects in the days after the treatment, with complete or nearly complete termination of pain after 1 week. Pain was still absent at short-term and long-term follow-up evaluations. All subjects showed an increase in skin surface temperature of the treated extremity at 90 min after procedure (table 2), but the differences were not statistically significant at early follow-up evaluation. Skin temperature showed no pattern of change in the untreated extremity (table 2).

Hand grip strength of the treated extremity showed a progressive trend toward improvement after intravenous regional blockade that continued to the early follow-up evaluation (table 3); the untreated extremity did not show any changes in strength.

There were no hemodynamic changes after removal of the tourniquet, in any patient, that required intervention.

## Discussion

The regional intravenous administration of phenoxybenzamine for the treatment of RSD does not appear to have been evaluated previously. A search of the literature revealed only one reference to the regional administration of phenoxybenzamine.[12] No data were provided, and the evaluation of its efficacy was confounded by the special circumstances of its use; the author used phenoxybenzamine, among other $\alpha$-adrenergic antagonists, to blunt the transiently increased vasoconstriction that is associated with the release of norepinephrine by guanethidine, an effect that exacerbates the pain in RSD.

We hypothesized that intravenous regional administration of the noncompetitive $\alpha$-adrenergic antagonist, phenoxybenzamine, combined with a local anesthetic, would prolong the period of effective sympathetic blockade after the treatment. The local anesthetic, lidocaine, was included

**Table 2. Changes in Skin Temperature (°C) of the Treated and Untreated Extremity in Each Patient**

| Patient No. | Limb | Baseline | 90 min after Treatment | At Early Follow-up |
|---|---|---|---|---|
| 1 | Treated | 31.0 | 34.0 | 36.4 |
| | Untreated | 32.0 | 36.5 | 36.5 (6) |
| 2 | Treated | 31.0 | 36.5 | 35.0 |
| | Untreated | 35.0 | 33.5 | 35.0 (8) |
| 3 | Treated | 35.0 | 37.0 | 38.0 |
| | Untreated | 34.0 | 31.0 | 35.0 (11) |
| 4 | Treated | 28.9 | 37.2 | 31.5 |
| | Untreated | 30.6 | 30.6 | 31.5 (27) |
| 5 | Treated | 34.0 | 37.5 | 32.0 |
| | Untreated | 31.5 | 32.0 | 31.0 (11) |
| Mean ± SD | Treated | 32.0 ± 2.5 | 36.4 ± 1.4* | 34.6 ± 2.8 |
| | Untreated | 32.6 ± 1.8 | 32.7 ± 2.4 | 33.8 ± 2.4 |

Values in parentheses are number of days at early follow-up.

* $P < 0.05$ *versus* baseline data by paired *t* test.

to optimize patient comfort during the period that the limb was ischemic. The noncompetitive nature of the blockade by phenoxybenzamine results from an irreversible (covalent) binding of the agent to $\alpha$-adrenergic receptors.[13] Because of the covalent bonding of the drug to the receptors, the block persists long after free drug has been cleared because the return of normal function depends on the synthesis of new receptors, a process that may require days. Because the drug would be expected to also bind irreversibly to nonspecific macromolecules in the treated limb, such binding would decrease the amount of drug available for systemic distribution when the tourniquet is released.

Chronic oral use of phenoxybenzamine has been reported to be successful in the management of RSD,[4,11] but a problem has been the high incidence (43%[11]) of orthostatic hypotension; ejaculatory problems were also noted by some patients. It is expected that the regional approach would minimize or eliminate the occurrence of side effects that were observed with administration of large oral doses of phenoxybenzamine. The total regional dose of phenoxybenzamine that was approved in our IND application was 5 mg.

It is possible that the effectiveness of intravenous regional blockade with phenoxybenzamine was related, in part, to the local anesthetic that was present in the formulation.

**Table 3. Changes in Hand Grip Strength (kg) of the Treated and Untreated Extremity in Each Patient**

| Patient No. | Limb | Baseline | 90 min after Treatment | At Early Follow-up |
|---|---|---|---|---|
| 1 | Treated | 10.0 | 24.5 | 25.5 |
| | Untreated | 23.6 | 25.0 | 27.3 (6) |
| 2 | Treated | 5.9 | 18.6 | 22.3 |
| | Untreated | 35.5 | 32.3 | 32.3 (8) |
| 3 | Treated | 9.1 | 18.2 | 11.4 |
| | Untreated | 28.2 | 29.1 | 31.8 (11) |
| 4 | Treated | 10.0 | 10.0 | 14.0 |
| | Untreated | 29.0 | 28.0 | 31.0 (27) |
| 5 | Treated | 3.6 | 2.2 | 14.7 |
| | Untreated | 23.6 | 20.0 | 22.7 (11) |
| Mean ± SD | Treated | 7.7 ± 2.9 | 14.7 ± 8.7 | 17.6 ± 6.0* |
| | Untreated | 28.0 ± 4.9 | 26.9 ± 4.6 | 29.0 ± 4.0 |

Values in parentheses are number of days at early follow-up.

* $P < 0.05$ *versus* baseline data by paired *t* test.

The local anesthetic, predictably, made a large contribution to the pain relief in the immediate hours after the block (fig. 1). However, the long-term duration of symptom relief observed in our patients was significantly greater than that expected by the local anesthetic alone. There was a rather uniform rebound in pain scores recorded by all the patients in the early days after the procedure (fig. 1); this was followed by essentially complete resolution of the pain by the time of the early follow-up visit. The initial rebound approximated baseline pain scores in three of the five patients. We have considered that the transitory return of pain is a manifestation of the central sensitization that characterizes this pain syndrome,[2,4] which reappears after the effects of the local anesthetic have dissipated. The delay to final pain resolution may represent the time required for reversal of this central sensitization, a possible therapeutic effect of the prolonged sympathetic blockade produced by phenoxybenzamine.

Of the five patients, the treatment was repeated only in patient 1. This patient had been symptom-free for 7 weeks after the initial treatment but reinjured the previously affected limb in a domestic accident. She immediately sought re-treatment, which was again successful. The data presented for this patient represent the results for the initial treatment, and the follow-up periods date to the first treatment. The other four patients had significant and prolonged symptom relief with a single treatment. At the time of the latest follow-up interview, all patients reported significant symptom relief and functional use of the previously affected extremity to the extent that repeat treatments were unwarranted. It has been observed[3,14] that RSD patients may get long-term pain relief if treated early. However, we also observed long-term pain relief in patients 1 and 4, who had experienced symptoms for 60 and 18 months, respectively.

Intravenous regional blockade with phenoxybenzamine appeared to produce long-term symptom relief in our patients without any adverse effects. The interpretation of the results of the present case studies is severely limited by the fact that neither the patients nor the investigators were blinded to the treatment being used. Placebo influences may have contributed to the results that were obtained. The importance of this consideration is demonstrated by the studies of Blanchard *et al.*,[15] which included intravenous regional blockade with saline as a control in a blinded comparison of guanethidine and reserpine for RSD; 83% of the saline-injected patients had pain relief that lasted more than 24 h. Allowance must also be made for the possibility of spontaneous resolution of symptoms, particularly in those patients who had relatively short histories of RSD.

A controlled study, in which lidocaine alone is administered in a randomized, double-blind comparison with phenoxybenzamine plus lidocaine, is essential to evaluate the potential of this therapy for RSD and related disorders.

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