Intravenous Regional Droperidol in the Management of Reflex Sympathetic Dystrophy: A Double-blind, Placebo-controlled, Crossover Study

ROBERT E. KETTLER, M.D.,* STEPHEN E. ABRAM, M.D.†

Although the mechanism of reflex sympathetic dystrophy (RSD) is unknown, sympathetic blockade is an important mode of diagnosis and therapy.1 Hannington-Kiff described the technique of iv regional guanethidine in the management of RSD2; however, an iv preparation of guanethidine is not commercially available in the United States. Other workers have substituted reserpine3,4; however, the design of these studies has been questioned,5 complications have been reported,6 and reserpine may not be as effective a sympatholytic as guanethidine.7 Furthermore, injectable reserpine is no longer commercially available. Recently, bretylium has been recommended as an iv regional agent8; however, this was based on four cases done in a nonrandomized, noncontrolled, nonblinded setting.

For the technique of iv regional sympathetic blockade to have widespread utility in the United States, a sympatholytic agent available in parenteral form is needed. Droperidol is readily available in parenteral form, is a commonly used anesthetic adjuvant with a relatively well-understood pharmacology,9 and is an alpha adrenergic antagonist.10 For these reasons we elected to study the efficacy of iv regional droperidol in the management of RSD.

In view of Brown's comments on the need for controlled studies in the area of pain management,5 we elected to utilize a double-blind, placebo-controlled methodology.

MATERIALS AND METHODS

The protocol was approved by the Institutional Research Committee and all subjects gave informed consent. The subjects were selected from patients whose history and physical findings were compatible with a diagnosis of RSD of the upper or lower extremity. Among the symptoms and signs elicited were continuous burning pain exacerbated by light touch, unilateral decreased skin temperature and increased sweating, glossy skin with atrophic nail and hair changes, and edema. All patients achieved relief with a local anesthetic sympathetic block; however, multiple sympathetic blocks did not provide long-lasting relief.

The study design was prospective, randomized, double-blinded, and placebo-controlled in a crossover manner. The study solutions were 2.5 mg of droperidol and 500 U of heparin in 30 ml of normal saline if the upper extremity was the affected one, or 2.5 mg of droperidol and 1,000 U of heparin in 50 ml of normal saline if the lower extremity was the affected one. The placebo solution was 500 U of heparin in 30 ml of saline for upper extremity blocks and 1,000 U of heparin in 50 ml of normal saline for lower extremity blocks.

Prior to the procedure each patient rated pain on a 10 cm visual analogue scale. A temperature probe was placed on the affected and contralateral extremities.

Initial skin temperatures, heart rate, and blood pressure were measured. A pneumatic tourniquet was applied to the affected extremity and exsanguination of the limb attempted with elevation and application of an Esmarch bandage. The tourniquet was inflated to a pressure of 50 mmHg above systolic arterial blood pressure on the arm and 100 mmHg above systolic pressure on the leg. The solutions were injected and the tourniquet left in place for 15 min. On tourniquet release skin temperatures of both extremities and systemic blood pressure were monitored for one hour. On discharge from the clinic each patient again rated their pain intensity on the visual analogue scale, and repeated this evaluation daily for two weeks. On their return to the clinic each patient was interviewed to determine his or her satisfaction with the procedure (overall pain relief, complications, medication use), and the procedure was repeated using the alternate solution.

RESULTS

Six patients (three with upper and three with lower extremity RSD) entered the study prior to its termination.
Table 1 lists the characteristics of the study patients. During the course of evaluating the patients, financial gain because of pain was identified in patients 5 and 6.

The results of each Bier block are listed in table 2. Because of the size of the sample, no statistical analysis was performed.

Patient 1 did not keep a visual analogue scale during the week subsequent to the droperidol injection because she was discouraged by the lack of relief compared to her first Bier block (placebo). Patient 2 misplaced his visual analogue scale after each injection; however, he denied any overall relief. Patient 6 refused to complete the study because he found the nausea, dysphoria, and akinesia too distressing after treatment with droperidol. He did record a pain intensity that corresponded to a delta VAS/VAS$_0$ of $-0.22$ for eight days. Patient 4 recorded no clinically important change in his pain intensity after either injection.

The placebo solution was associated with relief in three patients. Patient 1 had complete relief, which lasted almost two weeks and patient 3 had nearly complete relief (delta VAS/VAS$_0$ = $-0.95$) for two days. However, patient 1 had no relief after administration of the droperidol solution, and although patient 3 had moderate relief (delta VAS/VAS$_0$ = $-0.75$), it lasted less than 24 h. Patient 5 had mild relief with the placebo solution (delta VAS/VAS$_0$ = $-0.42$ for two days) and a longer lasting but less intense reduction in pain (delta VAS/VAS$_0$ = $-0.20$ for 10 days) with the droperidol solution.

With the exception of two incidents of thermometer malfunction, an increase in skin temperature was measured in the affected extremity after tourniquet release.

All complications occurred after the droperidol Bier blocks. Three patients noted complications of akinesia, dysphoria, or nausea, which they found moderately to severely distressing. These complications occurred several hours after discharge from the pain clinic. One patient was noted to be symptomatically hypotensive in the clinic and was given iv normal saline.

Because droperidol did not seem to give pain relief clearly better than placebo, and because of the number of patients complaining of side effects after droperidol, the study was terminated.

**Discussion**

The mechanism of reflex sympathetic dystrophy is unknown; however, local anesthetic sympathetic blocks are important diagnostic and therapeutic techniques. Intra-venous regional sympathetic blocks have been recommended for long-term management of RSD, which is refractory to repeated local anesthetic sympathetic blocks. Those patients who do not receive satisfactory relief with a local anesthetic technique would presumably be managed by the iv regional technique repeated as needed to provide long-standing relief.

Guanethidine was originally used by Hannington-Kiff.

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### Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Involved Extremity</th>
<th>Duration of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34</td>
<td>F</td>
<td>Lower</td>
<td>3 yr</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>M</td>
<td>Lower</td>
<td>6 yr</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>Upper</td>
<td>6 mo</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>Upper</td>
<td>1.5 yr</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>M</td>
<td>Upper</td>
<td>1.5 yr</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>Lower</td>
<td>6 yr</td>
</tr>
</tbody>
</table>

* 2nd Gain = secondary financial gain identified during evaluation.

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### Table 2. Bier Block Results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Soln</th>
<th>dT (°C)</th>
<th>(VAS)$_0$</th>
<th>(VAS)$_k$</th>
<th>dVAS/VAS$_0$</th>
<th>Duration</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D</td>
<td>+4.5</td>
<td>7.9</td>
<td>0.0</td>
<td>*</td>
<td>−1.00</td>
<td>No analgesia</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>+2.5</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>−0.75</td>
<td>−2 wk</td>
</tr>
<tr>
<td>3</td>
<td>P</td>
<td>+1.2</td>
<td>1.9</td>
<td>0.1</td>
<td>*</td>
<td>−0.95</td>
<td>−1 day</td>
</tr>
<tr>
<td>4</td>
<td>P</td>
<td>+2.6</td>
<td>8.0</td>
<td>8.2</td>
<td>*</td>
<td>+0.02</td>
<td>No analgesia</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>+5.0</td>
<td>8.5</td>
<td>8.4</td>
<td>−0.01</td>
<td>−0.20</td>
<td>−10 days</td>
</tr>
<tr>
<td>6</td>
<td>P</td>
<td>+1.5</td>
<td>7.4</td>
<td>1.4</td>
<td>*</td>
<td>−0.42</td>
<td>−2 days</td>
</tr>
</tbody>
</table>

D = droperidol; P = placebo; dT (°C) = change in skin temperature; (VAS)$_0$ = visual analogue scale rating prior to procedure; (VAS)$_k$ = visual analogue scale rating 20 min after tourniquet release; d(VAS) = (VAS)$_k$ − (VAS)$_0$; Duration = time until pain returned to preblock intensity as determined by visual analogue scale; *Patient did not return visual analogue scale. Denied change in pain.

† Thermistor malfunction.

‡ Refused further participation because of side effects.
however, a parenteral form of this agent is not available in the United States. There have been reports describing reserpine\textsuperscript{5,4} and bretyllium\textsuperscript{6} administered by Hannington-Kiff's technique. Droperidol is a butyrophenone anesthetic adjuvant with alpha adrenergic antagonist activity and was thought to have the potential for efficacy in the management of RSD. Some of the studies of iv regional sympathetic block have been criticized on methodologic grounds\textsuperscript{6}; thus, we evaluated droperidol in a prospective, randomized, double-blind, placebo-controlled manner.

Houde\textsuperscript{11} has discussed the importance of placebo controls in any study of pain management, emphasizing the variability among patients of the extent of placebo response. Houde\textsuperscript{11} also noted that placebo responders cannot be screened out of a study population due to their large number.

One option available to investigators is a parallel study wherein one group of patients receives a placebo and another group is given the study drug.\textsuperscript{12} Parallel studies allow for relatively uncomplicated data analysis; however, for several reasons a crossover methodology\textsuperscript{13} was considered more appropriate for this study. When interpatient variability of response is a significant factor, crossover studies reduce the importance of this variability because each patient acts as his or her own control. In a parallel study a patient could be matched to a control who had a placebo response that was considerably different in intensity. Because treatments are compared in the same patient, valid conclusions can be obtained with fewer patients in crossover studies. Based on previous experience in our clinic, we assumed that the number of patients eligible for the study would be small. A crossover design was presumed to allow more expeditious completion of the study than a parallel design.

There are several disadvantages to crossover studies. If an adequate amount of time does not pass between treatments, a carryover effect of the first treatment may confound the results of the second. In view of droperidol's 3–6 hour duration of effect as an iv agent,\textsuperscript{9} two weeks was assumed to be an adequate washout time after an iv regional technique. Because droperidol was found to be ineffective, there should have been no long-lasting carryover effect in this instance. Patient compliance with a crossover design can be worse than with a parallel design. In a parallel design the number of observations and treatments that each patient must undergo is less than with a crossover design. This may have been a factor in our study (e.g., patients 1 and 2 did not bring back their visual analogue scales and patient 6 refused to receive a second treatment); however, we had obtained adequate data to make the decision to terminate the study.

Three patients described either dysphoria (lethargy, anxiety) or akinesia (restlessness) occurring approximately six hours after droperidol administration. These side effects were so severe in patient 6 that he refused participation in the second limb of the study. Akinesia\textsuperscript{9} and dysphoria\textsuperscript{14} are recognized complications of droperidol administration.

Nausea was an unexpected complication of droperidol administration, as the drug has been shown to have antiemetic efficacy.\textsuperscript{9,15} One possible explanation for this complication would be if the patients were hypotensive and consequently nauseated.\textsuperscript{16}

As noted before,\textsuperscript{17} there was a certain amount of pain relief provided by the procedure of applying a tourniquet for a brief period and releasing it. This is a complicating factor of all iv regional pain management techniques and should probably be controlled for in any studies of this technique.

Because there was no quantitative (patients 3, 4, and 5) or anecdotal (patients 1 and 2) evidence of iv regional droperidol's superiority over placebo and because of the number and severity of side effects, we elected to terminate the study after only six patients. Because the drug seemed ineffective, we chose not to reduce the amount administered to reduce the chance of complications, and we thought increasing the amount to potentially achieve more pain relief was not warranted in view of the complications associated with the initial dose.

In summary, iv regional droperidol is not an effective technique in the management of reflex sympathetic dystrophy.

REFERENCES

Epidural Lidocaine for Cesarean Section: Effect of Varying Epinephrine Concentration

WILLIAM G. BROSE, M.D.,* SHEILA E. COHEN, M.B., CH.B., F.F.A.R.C.S.†

Epinephrine is commonly added to epidural lidocaine with the goal of decreasing serum lidocaine concentrations, and thus the risk of toxicity, 1-9 and improving the quality and duration of analgesic blockade. 10,11 In the obstetric patient there is also a desire to minimize fetal exposure to lidocaine, although earlier reports relating transient neonatal hypotonia to neonatal lidocaine levels 12 subsequently have not been substantiated. 13 The proposed mechanism for the above effects is that epinephrine causes vasoconstriction in the epidural space, retarding systemic absorption of lidocaine and allowing a higher concentration of the local anesthetic to persist at its site of action. An alternative but not dissimilar mechanism, recently suggested by Kozody et al. 14 for intrathecal administration, is that epinephrine acts by preventing the spinal cord vasodilatation caused by lidocaine. Whether this theory applies to epidural administration is not known.

Although there is general acceptance that epinephrine is beneficial in surgical patients, its use in obstetric patients remains controversial because of potential adverse effects on uterine blood flow 15-17 and maternal hemodynamics. 11,18 Despite these concerns, lidocaine with epinephrine has been used for cesarean section for many years. Although an epinephrine concentration of 1:200,000 (5 μg/ml) has been employed most commonly, the minimum effective concentration in this circumstance has not yet been determined. Several investigators 7-9 have claimed that maternal lidocaine levels were decreased by the addition of epinephrine (1:200,000-1:300,000) to epidural lidocaine for labor or cesarean section anesthesia. However, none of these studies measured serial lidocaine levels or systematically compared multiple epinephrine concentrations. The goal of the current study, therefore, was to determine the optimal concentration of epinephrine for use with epidural lidocaine for cesarean section, with respect to efficacy and potential toxicity. Serum lidocaine levels, analgesic efficacy, and neonatal status were evaluated following administration of a 400 mg dose of 2% lidocaine, either plain or with one of three concentrations of epinephrine.

MATERIALS AND METHODS

The study population consisted of 40 healthy term parturients scheduled for elective cesarean section under epidural anesthesia. All subjects gave written informed consent and the study was approved by the Stanford Committee for the Use of Human Subjects in Research. Patients were randomly assigned to receive 20 ml of 2% lidocaine (400 mg) either plain (group 1), or with epinephrine concentrations of 1:400,000 (group 2), 1:500,000 (group 3), or 1:200,000 (group 4). Each group consisted of ten patients. All lidocaine solutions were freshly prepared by the addition of the appropriate amount of 1:1000 epinephrine by a trained nurse not otherwise involved in the study or in the care of the patient.

Epidural anesthesia was performed using the loss of resistance technique at the L2-3 or L3-4 interspace with the patient in the sitting position. The study solution was administered in a double-blind fashion, via the needle, in several increments. A test dose of 3 ml was administered initially and the patient monitored for four minutes for signs of intravascular or intrathecal injection. The remaining 17 ml of local anesthetic was administered in two increments of 5 ml, and one of 7 ml, with two minutes