Oral Clonidine Prolongs Lidocaine Spinal Anesthesia in Human Volunteers

Spencer Liu, M.D.,* Andrew A. Chiu, M.D.,† Joseph M. Neal, M.D.,‡ Randall L. Carpenter, M.D.,§ Bruce G. Bainton, M.D.,‖ J. C. Gerancher, M.D.‖

Background: Premedication with oral clonidine may improve the quality and duration of lidocaine spinal anesthesia, but this effect has not been examined in a quantitative fashion.

Methods: Eight volunteers received 50 mg lidocaine (1.5% dextrose free) both with and without 0.2 mg oral clonidine 1.5 h before spinal anesthesia in a randomized, double-blind, placebo-controlled, crossover fashion. Sensory block was assessed by pinprick, transcutaneous electric stimulation equivalent to surgical incision, and duration of tolerance to pneumatic thigh tourniquet. Motor block at the quadriceps and gastrocnemius muscles was assessed by isometric force dynamometry. Episodes of bradycardia, hypotension, and sedation were recorded.

Results: Regression of pinprick was unchanged with clonidine. However, duration of tolerance to electric stimulation was increased at the knee (28 ± 24 min) and ankle (31 ± 28 min) with clonidine (P < 0.05). The duration of tolerance to tourniquet-induced pain was increased with clonidine (14 ± 12 min; P < 0.05). The duration of motor block was increased at the quadriceps (20 ± 15 min) and gastrocnemius (33 ± 24 min) muscle groups with clonidine (P < 0.05). Although clonidine decreased systolic blood pressure (13 ± 4 mmHg, P < 0.005) and heart rate (15 ± 5 beats/min; P = 0.02), no subjects had hypotension or bradycardia. The incidence of sedation was greater with clonidine than with plain lidocaine (50% es. 0%, P = 0.04).

Discussion: Premedication with oral clonidine prolonged sensory and motor block from lidocaine spinal anesthesia. The exact mechanism whereby oral clonidine prolongs spinal anesthesia remains to be determined. (Key words: Anesthetics, local; lidocaine. Anesthetic techniques: spinal. Measurement techniques: tetanic stimulation. Pain: tourniquet. Prenesthesic medication. Sympathetic nervous system, α2-adrenergic agonists: clonidine.)

CLONIDINE is an α2-adrenergic agonist that produces analgesia in humans at spinal and supraspinal sites of action. Administration of oral clonidine results in dose-dependent analgesia,5,6 sedation,7 and hemodynamic depression.8 Previous studies have suggested that premedication with oral clonidine may prolong sensory and motor block from spinal anesthesia.9-12 However, these studies have primarily used pinprick and Bromage’s scale as measures of sensory and motor block.8,12 Although these measures may have clinical relevance, they are neither sensitive nor quantitative, and therefore the exact effects of oral clonidine on spinal anesthesia remain unknown. Recent studies have used more sensitive and quantitative measures of sensory and motor block such as transcutaneous electric stimulation (TES) and isometric force dynamometry to examine the effects of addition of intrathecal fentanyl and epinephrine on lidocaine spinal anesthesia.13,14

This study was designed to determine the effects of premedication with oral clonidine on sensory and motor block from lidocaine spinal anesthesia in a quantitative fashion.

Materials and Methods

After Institutional Review Board approval and informed consent were acquired, eight healthy volunteers (four men and four women) participated in the study. Each subject received two spinal anesthetics (50 mg 1.5% dextrose-free lidocaine, Abbott Laboratories,
North Chicago, IL) with 0.2 mg oral clonidine or oral placebo 1.5 h before spinal anesthesia in a double-blind, crossover fashion. The order of administration of clonidine and placebo was randomized and balanced. The two spinal anesthetics were separated by at least 48 h in each subject.

Subjects consumed nothing by mouth for 8 h and voided immediately before each study. Lactated Ringer’s solution was administered as a bolus of 6 ml·kg⁻¹·h⁻¹ over 15 min before subarachnoid block, followed by 8 ml·kg⁻¹·h⁻¹ for the first h, then maintenance infusion at a rate of 2 ml·kg⁻¹·h⁻¹. Lumbar puncture was performed (with the subject in the left lateral decubitus) at the L2-L3 interspace with a 25-G Whitacre spinal needle through a 20-G introducer with the orifice of the spinal needle turned cephalad. A volume of 0.2 ml cerebrospinal fluid was aspirated, and the study solution was injected at approximately 0.25 ml/s by hand. After injection, subjects were immediately placed supine and maintained level for the duration of the study. All subjects were monitored with blood pressure cuff, by electrocardiography, and by pulse oximetry every 5 min for the duration of the spinal anesthetic. Hypotension was defined as systolic blood pressure less than 90 mmHg with a greater than 20% decrease from baseline. Bradycardia was defined as heart rate less than 50 beats/min with a greater than 20% decrease from baseline. Respiratory depression was defined as pulse oximetry oxygen saturation less than 90% on room air. Sedation was assessed by a blinded observer on a four-point scale (1 = awake; 2 = drowsy but responsive to verbal stimulus; 3 = drowsy but arousable to physical stimulus; and 4 = unarousable).

TES has been demonstrated to be as potent a stimulus as surgical incision, and thus tolerance to this model of surgical incision was assessed as previously described. TES leads were placed in the midline at the T10 and T12 dermatomes and bilaterally at L2-L3 (medial aspect above the knee) and L5-S1 (lateral aspect above the ankle). Five seconds of 50-Hz tetanus at 60 mA with a commercially available nerve stimulator (NS252, Fisher & Paykel, Auckland, New Zealand) was considered equivalent to surgical incision. This particular unit was tested by our bioengineering department to verify sustained delivery of displayed currents. Tolerance to TES was assessed 4 min after injection of spinal solution and measured every 10 min thereafter by initially testing with 10 mA and then increasing in 10 mA increments to a maximum of 60 mA for 5 s. Tolerance of the maximal stimulus without pain was considered equivalent to surgical anesthesia.

Each TES location was tested in a systematic order moving from distal to proximal sites. In addition, dermatomal levels to pinprick (18-G needle) were measured every 5 min after injection of spinal solution until 40 min postinjection, and then every 10 min until recovery of pinprick at S2.

Tourniquet pain was assessed using previously reported methods. Thirty minutes after injection of spinal solution, the left leg was exsanguinated by gravity, and a 7-cm orthopedic pneumatic tourniquet inflated around the left midcalf to 300 mmHg. At the first study, each subject was shown a visual analogue scale (VAS) marked from 0 to 100 mm with 0 representing no discomfort and 100 representing the worst discomfort imaginable. The subjects were instructed that the tourniquet would be deflated to relieve discomfort at any time. They were then asked to rate their discomfort on the visual analogue scale and to fix the degree of discomfort in their mind. During the subsequent study, subjects were shown their level of discomfort on the visual analogue scale and instructed to request tourniquet deflation at the same level of discomfort. Tourniquets were left inflated until subjects requested deflation or for a maximum of 2 h after inflation.

A commercially available isometric force dynamometer (Micro FET, Hoggan Health Industries, Draper, UT) was used to assess 5-s isometric maximal force contraction of the right quadriceps and gastrocnemius as previously reported.

Measurements were performed at baseline and every 10 min after injection of spinal solution until return to 90% of baseline. Measurements were performed in triplicate and then averaged at each measurement period. Isometric force dynamometry has been previously shown to be reliable, quantitative methods for evaluation of motor block during spinal and epidural anesthesia.

Ability to micturate was assessed as previously reported. All subjects received a standardized intravenous fluid infusion as outlined above. Subjects attempted to void when the pinprick reached dermatomal level S2. A commercially available bladder ultrasound (BladderScan BV12500, Diagnostic Ultrasound Corporation, Kirkland, WA) was used to quantify the volume of urine within the bladder before attempting to void. If subjects were unable to immediately void, then repeat attempts were made every 15 min, and time from injection of spinal solution was recorded.

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Results

The subjects were 22 males with a mean (± SD) age of 48 ± 7 y. Height was 175 ± 5 cm and weight was 87 ± 10 kg. Height and weight were similar in both groups (clonidine versus placebo). The body mass index was 27.2 ± 3.8. The systolic blood pressure and heart rate were 123 ± 4 mmHg and 74 ± 4 beats/min, respectively. The mean (± SD) dose of clonidine was 0.21 ± 0.05 mg.

Fig. 1. Repetitive pinprick at S2 and SD are shown. Differences between repeated measures were analyzed using repeated-measures analysis of variance.
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Differences in onset and duration of tolerance to TES, duration of tolerance of tourniquet, and time to micturition were assessed by paired t test with Bonferroni’s correction. Mean differences and 95% confidence intervals of differences between groups were calculated. Differences in regression of pinprick, regression of motor block, systolic blood pressure, and heart rate were analyzed with repeated measures analysis of variance followed by post hoc testing with Scheffé’s F test. The incidence of side effects was analyzed with Fisher’s exact test. Significance was $P < 0.05$. Results are reported as means ± SD.

Results

The subjects’ ages ranged from 24 to 42 yr, their heights from 144 to 162 cm, and their weights from 55 to 85 kg. Regression of sensory block to pinprick was unaffected by clonidine (fig. 1). Onset of tolerance to TES was also unaffected by premedication with clonidine (onset at T10 was 7 ± 6 min vs. 7 ± 6 for lidocaine and clonidine vs. plain lidocaine; onset at T12 was 4 ± 0 min vs. 8 ± 11, onset at L2 was 7 ± 7 vs. 8 ± 5; and onset at L5 was 7 ± 5 vs. 9 ± 5).

In contrast, duration of tolerance to TES at the knee and ankle was prolonged by clonidine (table 1). The duration of tolerance to pneumatic thigh tourniquet time was also increased with clonidine (table 1). All subjects experienced pain before 2 h of tourniquet inflation. There was no difference in duration between the left and right sides, thus average values are displayed.

Premedication with clonidine prolonged the duration of motor block at both the quadriceps (20 ± 13 min; $P < 0.05$) and gastrocnemius (55 ± 24 min; $P < 0.05$) muscle groups (fig. 2).

Although clonidine decreased systolic blood pressure (15 ± 4 mmHg; $P < 0.003$) (fig. 3) and heart rate (13 ± 5 beats/min; $P = 0.02$) (fig. 5), no subjects experienced hypotension, bradycardia, or respiratory depression. Incidence of sedation was greater in the clonidine group (50% vs. 0%; $P < 0.04$). The degree of sedation in all of these subjects was mild (2 on the four-point scale), and sedation resolved by the end of the study period.

All subjects had significant amounts (256–838 ml) of urine in their bladders before attempting to void. The time until voiding was unaffected by clonidine (149 ± 27 min for clonidine vs. 131 ± 23 min for plain lidocaine).

Discussion

Our results demonstrate that premedication with 0.2 mg oral clonidine prolongs sensory and motor block

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Fig. 1. Regression of sensory block to pinprick after spinal anesthesia. Means and SD are displayed. There were no differences between groups as assessed by repeated-measures analysis of variance.

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from lidocaine spinal anesthesia. The mechanisms whereby oral clonidine affects sensory block remain speculative. Oral administration of clonidine results in virtually complete absorption,\textsuperscript{20} and peak plasma concentrations occur 1–3 h after administration.\textsuperscript{21} Clonidine is highly lipid soluble,\textsuperscript{22} easily crosses the blood–brain barrier,\textsuperscript{23} and therefore may interact with \( \alpha \)-adrenergic receptors at spinal and supraspinal sites within the central nervous system. In addition, previous studies suggest that clonidine may inhibit neurogenic inflammatory pain thresholds.\textsuperscript{24} Oral clonidine has been demonstrated to reduce the efficacy of local anesthetics in the rat model.\textsuperscript{25} It has been suggested that clonidine reduces spinal activity in the rat model.\textsuperscript{26} The reduction of efficacy of local anesthetics may provide a stimulus to block local anesthetic action. As the spinal cord is the source of noxious sensory input, a reduction of efficacy may reduce the intensity of pain sensation. The present study investigated the effect of oral clonidine on local anesthetic efficacy in the rat model.

Table 1. Duration of Tolerance to Electrical Stimulation and of Pneumatic Thigh Tourniquet

<table>
<thead>
<tr>
<th>Dermatomal Site</th>
<th>Lidocaine with Clonidine (min)</th>
<th>Plain Lidocaine (min)</th>
<th>Difference (clonidine – plain) Mean (95% confidence interval) (min)</th>
</tr>
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<tbody>
<tr>
<td>T10</td>
<td>31 ± 31</td>
<td>20 ± 34</td>
<td>11 (–2, 24)</td>
</tr>
<tr>
<td>T12</td>
<td>43 ± 38</td>
<td>29 ± 43</td>
<td>14 (–2, 29)</td>
</tr>
<tr>
<td>L2–L3</td>
<td>100 ± 22*</td>
<td>71 ± 38</td>
<td>28 (8, 47)</td>
</tr>
<tr>
<td>L5–S1</td>
<td>119 ± 30*</td>
<td>88 ± 26</td>
<td>31 (8, 55)</td>
</tr>
<tr>
<td>Tourniquet</td>
<td>65 ± 19*</td>
<td>51 ± 10</td>
<td>14 (4, 24)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* Different from plain lidocaine, \( P < 0.05 \).

Fig. 2. Regression of motor block in the quadriceps and gastrocnemius muscles after spinal anesthesia as assessed by isometric force dynamometry. Means and SD are displayed. *Different from plain lidocaine: \( P < 0.05 \).
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ities suggest that clonidine also may affect peripheral sensory nerves as a sole agent or in combination with local anesthetics. Clonidine has been demonstrated to inhibit neurotransmission in both Aδ and C nerve fibers, which are theorized to mediate pinprick, surgical pain, and tourniquet pain. Finally, clonidine has been demonstrated to potentiate inhibitory effects of local anesthetics on C fiber activity. Therefore, oral clonidine may exert its effects within the central nervous system, at peripheral nerve roots, or by potentiation of effects of local anesthetics, and further studies will be needed to determine exact sites of action.

Our finding of prolonged sensory block after oral clonidine may have clinical implications. Although sensory block to pinprick was unaffected by clonidine, tolerance to TES was prolonged in the lumbar sacral dermatomes. TES has been previously demonstrated to provide a stimulus equivalent to skin incision during general anesthesia. Thus, duration of tolerance to TES should be a realistic estimate of duration of surgical anesthesia. Our results indicate that oral clonidine should prolong the duration of surgical anesthesia in the lumbar sacral dermatomes from lidocaine spinal anesthesia, but this prolongation may be variable and difficult to predict. Another clinical implication from our study arises from sensory testing with a pneumatic thigh cuff. Tourniquet pain is a poorly understood phenomenon that may cause an otherwise adequate spinal anesthetic to fail. Although previous studies have suggested that addition of intrathecal clonidine may reduce the incidence of tourniquet pain during bupivacaine spinal anesthesia, effects of oral clonidine have not been previously examined. Our results indicate that premedication with oral clonidine may be clinically valuable but prolongation of tolerance to tourniquet pain will vary in duration.

Premedication with oral clonidine also prolonged motor block after lidocaine spinal anesthesia. Previous studies have demonstrated similar prolongation of motor block after intrathecal administration of clonidine, however conflicting results have been reported after oral administration of clonidine before tetracaine and bupivacaine spinal anesthesia. The mechanism whereby oral clonidine may affect motor block is unclear. Both direct inhibition of α motor fibers and augmentation of intrathecal local anesthetic effects may play a role in the effects of oral clonidine. Because we did not explore mechanisms of action, our study did not determine whether effects of clonidine on motor block occurred within the central nervous system or within peripheral nerves. Thus, further studies will be needed to determine exact sites of action of oral clonidine on motor block after spinal anesthesia.

Systolic blood pressure and heart rate decreased after administration of clonidine. This observation is consistent with previous dose–response studies of oral clonidine that reported dose-dependent reduction of tonic sympathetic outflow and depression of blood pressure and heart rate. In addition, previous dose–response and single dose studies of oral clonidine administered before tetracaine spinal anesthesia have also reported modest hemodynamic depression during anesthesia and surgery. Thus, our data from healthy volunteers are consistent with data from surgical patients and indicate that premedication with 0.2 mg oral clonidine results in significant but well-tolerated hemodynamic depression. The incidence of mild sedation was also greater after premedication with clonidine. This finding is in agreement with previous dose–response studies of oral clonidine. However, this sedation was relatively short lived, did not result in respiratory depression in our healthy, nonmedicated subjects, and may have little clinical significance.

An additional side effect after spinal anesthesia is inhibition of micturition, yet few studies have investigated this side effect in a controlled fashion. β-Adrenergic receptors are found in the bladder and urethra, and stimulation of these receptors inhibits smooth and striated muscle function and the ability to micturate. Therefore, clonidine may affect the ability to void by direct β-adrenergic effects or by enhancement of local anesthetic blockade in the sacral dermatomes. After standardization of intravenous fluid administration and verification of significant amounts of urine in the bladder, all subjects were able to void on the first allowed attempt, and there were no differences in the time until voiding with the use of 0.2 mg oral clonidine.

Several aspects of study design deserve comment. First, our study could be criticized for lacking a dose–response or time–response design. We elected to study a fixed dose and time of administration because of logistical limitations (the need for more than two spinal anesthetics per volunteer). However, the dose and timing of administration of oral clonidine were based on previous dose– and time–response studies of oral clonidine alone and with tetracaine spinal anesthesia. These previous studies suggested that 0.2 mg oral clonidine given 1–3 h before spinal anesthesia would prolong spinal anesthesia without deleterious side effects.
However, administration of greater doses of oral clonidine would probably result in unacceptably high incidences of hemodynamic side effects and sedation. Indeed, our findings of significant hemodynamic depression and sedation after 0.2 mg clonidine suggest that larger doses of clonidine may be unacceptable. A further criticism of our study could be the use of an inactive placebo, because the high incidence of sedation after clonidine may have resulted in unblinding of the subjects and biased our results. Although inclusion of an inactive placebo is common, our use of a crossover design may have increased the potential for bias. On the other hand, collection of paired data through a crossover design was necessary because of the well-documented, large intersubject variability in lidocaine spinal anesthesia. Indeed, previous controversy regarding the effects of epinephrine on tetracaine and lidocaine spinal anesthesia were resolved only after use of similar crossover study designs.

In conclusion, premedication with 0.2 mg oral clonidine 1.5 h before initiation of lidocaine spinal anesthesia prolonged sensory and motor block. The exact mechanism of the interaction of oral clonidine and spinal anesthesia remains to be determined. Although premedication with oral clonidine may result in clinically useful prolongation of lidocaine spinal anesthesia, these increases probably will be modest and variable.

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References


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