A Double-Blind Randomized Controlled Trial Comparing Epidural Clonidine vs Bupivacaine for Pain Control During and After Lower Abdominal Surgery

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Background: Alpha-2 adrenergic agonists produce safe and effective analgesia, but most investigations studying the analgesic effect of alpha-2 adrenoceptor agonists postoperatively included previous or concomitant administration of other analgesics. Because clonidine potentiates the effect of these drugs, its own intrinsic analgesic effect has been difficult to establish. This study was designed to compare the intraoperative and postoperative effects of epidural clonidine vs bupivacaine for patients undergoing lower abdominal surgery.

Methods: This randomized controlled trial included 40 patients aged 18-50 who were scheduled for elective lower abdominal surgery. Patients were randomly divided into 2 groups. Group I (n=20) received epidural clonidine; Group II (n=20) received epidural bupivacaine. Intraoperative and postoperative hemodynamics, pain scores, and complications were monitored.

Results: Mean pain scores were significantly lower in Group I compared to Group II (1.5–0.5 compared to 3.4–1.0, respectively) in the first 12 hours after surgery. Sedation was more prominent in Group I until 9 hours after surgery. Opioid requirements were significantly lower in Group I. Respiratory rate was similar in the 2 groups. Group I had larger decreases from baseline in systolic blood pressure and diastolic blood pressure than Group II. Heart rate in Group I was reduced from baseline, while it was increased in Group II. Less postoperative nausea and vomiting, urinary retention, pruritus, and shivering were observed in Group I.

Conclusion: Compared to bupivacaine, epidural clonidine provided effective intraoperative and postoperative analgesia in selected patients, resulting in a decreased intravenous pain medication requirement and prolonged duration of analgesia after epidural infusion was discontinued.

Keywords: Adrenergic alpha-agonists, analgesia–epidural, bupivacaine, clonidine, intraoperative care, pain–postoperative

INTRODUCTION

Alpha-2 adrenergic mechanisms of analgesia have been exploited for more than 100 years. Cocaine, the first spinal anesthetic, produces analgesia primarily by its local anesthetic action. Cocaine is also known to inhibit norepinephrine reuptake, and spinal cocaine produces analgesia, in part, by enhancing noradrenergic stimulation of alpha-2 adrenoceptors.1

Near the turn of the previous century, epinephrine was shown to produce spinal analgesia in animals, an effect now recognized to be secondary to the alpha-2 adrenoceptor. Nearly 50 years ago, spinal epinephrine alone was shown to produce clinically useful analgesia, although it is most commonly combined with local anesthetics for this purpose.2,3

Veterinarians have used alpha-2 adrenergic agonists (xylazine, detomidine, medetomidine) for many years for regional analgesia, but experience with these agents in humans dates back only 3 decades. In 1984, Tamsen and Gordh, after testing for neurotoxicity in animals, injected a parenteral preparation of the alpha-2 adrenergic agonist clonidine epidurally in 2 patients with chronic pain.4 Since then, a complete toxicologic assessment has suggested that clonidine is safe for intraspinal use.5–20

Most of the investigations studying the analgesic effect of alpha-2 adrenoceptor agonists postoperation included previous or concomitant administration of other analgesic drugs such as local anesthetics or opioids. Because clonidine has been shown to potentiate the analgesic effect of these drugs, the importance of its own intrinsic analgesic
Epidural Clonidine vs Bupivacaine for Pain Control

Effect has remained difficult to establish. Two studies reported the efficacy of intrathecal clonidine as a sole analgesic agent and showed complete and long-lasting analgesia after a single intrathecal injection of clonidine in women recovering from cesarean deliveries performed without perioperative administration of additional analgesics.

Our study compared the analgesic effect of defined-dose epidural clonidine as a sole epidural analgesic agent vs the more commonly used drug bupivacaine during and after lower abdominal surgery. We also compared the 2 groups with regard to hemodynamic changes, effects on respiratory function, sedative effects, and side effects.

METHODS
Study Design
This randomized, double-blind, prospective clinical trial enrolled 40 patients presenting for elective lower abdominal surgery at a tertiary care university hospital. The study was approved by the institutional review board. Sixty-two patients who fulfilled the inclusion criteria were approached. Forty-six patients agreed to participate. Six patients were excluded because of concomitant beta blocker therapy (3 patients), abnormal coagulation profile (2 patients), and cardiac conduction defect (1 patient) (Figure). After providing informed consent, patients were randomly divided into 2 groups of 20 patients each. Randomization was done using sealed and shuffled envelopes with treatment allocations inside. Each envelope was opened by an investigator just before surgery to learn the group assignment and to order the infusion. All patients were treated strictly as randomly assigned.

Outcomes
The primary outcome was the comparison of pain control between groups. Secondary outcomes were the comparisons of hemodynamic changes, effects on respiratory function, sedative effects, and side effects between the two groups.

Participants
All patients were 18-50 years of age, American Society of Anesthesiologists (ASA) physical status category 1 or 2, and scheduled for elective lower abdominal surgery (ie, oblique inguinal hernia, femoral hernia, lower abdominal incisional hernia repairs, and abdominal hysterectomy) at a tertiary care university hospital in Cairo, Egypt.

Exclusion criteria were any history of allergy to the drugs used in the study, abnormal coagulation profiles, abnormal hepatic or renal function, chronic pain, cardiac conduction defects, or use of beta blocker therapy.

Blending
All patients were blinded to the treatments used. Physicians who took care of the patients intraoperatively and postoperatively, including investigators who collected the postoperative outcomes of interest, were blinded to the treatments used. In addition, the biostatistician who performed the statistical analysis was blinded. Groups were labeled as Group I (patients who received epidural clonidine) and Group II (patients who received epidural bupivacaine). All previously mentioned participants were unaware of the treatment assigned to Group I as well as Group II.

Preoperative
All patients received intravenous (IV) premedication with midazolam 0.05 mg/kg 30 minutes before induction.

Intraoperative
Monitors were applied after establishing an IV line and infusing 1 L of crystalloid solution; in the operating room, an epidural catheter was inserted in all patients at the L2-L3 vertebral interspace. Level identification was done using anatomic landmarks with the line across the highest points of the iliac crests (Tuffier’s line) used to identify the L4 vertebral body or the L4-L5 interspace. The epidural space was identified using the midline approach with loss of resistance to air. An epidural catheter was then inserted 4 cm past the needle tip.

Patients in Group I (n=20) received an initial dose of epidural clonidine of 10 μg/kg in 7 mL saline in 15 minutes, followed immediately by an infusion of 6 μg/kg/h (7 mL/h). Patients in Group II (n=20) received an initial dose of bupivacaine 0.5% in 7 mL saline (~35 mg) in 15 minutes, followed immediately by an infusion of bupivacaine 0.25% (7 mL/h=17.5 mg/h). Epidural infusion at the stated doses was maintained in both groups during the first 12 postoperative hours.

In all patients, general anesthesia was induced concomitantly with the epidural infusion. Induction of anesthesia was performed using thiopental sodium (3-5 mg/kg), and tracheal intubation was facilitated by atracurium (0.5 mg/kg). An IV bolus of lidocaine was given 1 minute before intubation. Additional bolus doses of fentanyl (0.5 μg/kg) were given to patients who had an increase of 20% in mean arterial blood pressure or heart rate compared to the baseline recorded after the initial dose of epidural drugs and before skin incision.

During anesthesia, the following observations were made every 30 minutes: hemodynamic data, including arterial blood pressure and heart rate; the number and dose of fentanyl injections per patient; and the occurrence of side effects. Hypotension was treated with IV ephedrine in 5 mg increments, while bradycardia was treated with atropine 0.5 mg IV until the condition resolved.

Postoperative
After reversal of muscle relaxation and tracheal extubation, patients were transferred to the postanesthesia care unit where they were assessed hourly for 12 postoperative hours for the following parameters.

1. Hemodynamic monitoring consisted of heart rate, systolic arterial blood pressure (SBP), and diastolic arterial blood pressure (DBP) measurements. Hypotension and bradycardia were defined as a decrease of ≥20% from baseline.
2. Respiratory rate and arterial oxygen saturation were measured with pulse oximetry.
3. Degree of pain was assessed using the visual analog scale (VAS), a 0-10 scale with 0=no pain and 10=maximum intolerable pain. In cases of VAS
scores ≥5 at rest or ≥8 with coughing, a registered nurse administered 1.5 mg IV morphine as needed with a lockout time of 10 minutes and a maximum dose of 10 mg/h. Duration of analgesia was measured as the time to the first requirement of IV analgesia after discontinuation of the epidural infusion at the end of the initial 12 postoperative hours.

4. Postoperative side effects such as nausea, vomiting, urinary retention, pruritus, and shivering were recorded.

5. Opioid requirements were measured as the number of intraoperative fentanyl boluses and the number of postoperative morphine injections per patient.

6. Degree of sedation was assessed using the Ramsay sedation scale, a 0-3 scale with 0=alert or drowsy, easily roused by verbal command; 1=sleepy, but roused by verbal command; 2=sleepy, but roused by tactile stimulation; and 3=sleepy, and not roused by tactile stimulation.26

**Statistical Analysis**

Continuous data were presented in the form of mean ± standard deviation or median and range. Categorical data were presented in the form of number and percentage. Two independent sample group comparisons of continuous data parameters were performed by using the Mann-Whitney U test. Paired comparison within the same group was performed by using the Wilcoxon rank-sum test. Between groups, comparisons of categorical data parameters were performed by using the chi-square test or the Fisher exact test ($X^2$ value). Sample size was calculated based on 85% power of analysis, and $P$ value was considered significant if <0.05.

Figure. Study flowchart.
Epidural Clonidine vs Bupivacaine for Pain Control

Table 1. Demographic Data of Enrolled Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (clonidine)</th>
<th>Group II (bupivacaine)</th>
<th>Group I vs Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=20</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>35.7 ± 11.8</td>
<td>33.3 ± 9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>12 (60)/8 (40)</td>
<td>11 (55)/9 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.2 ± 9.1</td>
<td>74.9 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of anesthesia, min</td>
<td>141.8 ± 18.3</td>
<td>148.3 ± 19.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant. With the exception of sex, data are presented as mean ± SD.

RESULTS

Demographics

The 2 groups had no significant differences with respect to age, sex, weight, and duration of anesthesia (P>0.05) (Table 1).

Pain

Pain scores measured using the VAS during rest were significantly lower in Group I than in Group II (mean of 1.5 ± 0.5 compared to 3.4 ± 1.0, respectively) during the first 12 postoperative hours (Table 2). Patients who received epidural clonidine did not require any intraoperative boluses of IV fentanyl; however, patients who received epidural bupivacaine required 1-2 doses of fentanyl 50 μg (median, 1 dose).

During the postoperative period, patients on epidural clonidine (Group I) did not require any rescue medication for pain, while patients on epidural bupivacaine (Group II) required 2-4 doses of 1.5 mg morphine sulfate each during the first 12 postoperative hours (median, 3 doses; P<0.001).

Postoperative Analgesia

Clonidine produced significantly longer analgesia than bupivacaine as measured by the first requirement for analgesic medication after discontinuation of the epidural infusion. Mean duration was 297 ± 28.3 minutes in Group I vs 74.3 ± 10.4 minutes in Group II.

Intraoperative Hemodynamics

SBP during the intraoperative period significantly decreased in both groups compared to the baseline reading (Table 3). The lowest mean intraoperative SBP and DBP readings, expressed as percentage change from the baseline readings, did not show significant variation between the 2 groups. Respective SBP and DBP changes were −21.2% ± 3.9% and −13.3% ± 2.8% in Group I vs −17.1% ± 3.6% and −8.8% ± 3.1% in Group II.

Heart rates of patients in Group I significantly decreased by −10% ± 3.3% during the intraoperative period, while the patients in Group II showed a significant increase in heart rate by +27% ± 15.1% (Table 3).

Postoperative Hemodynamics

Intergroup comparison showed significant differences between the 2 groups in postoperative SBP and heart rate (Table 3). SBP was significantly lower than the baseline reading in Group I with a percentage change of −15.5% ± 8.7%. Group II had no significant difference in SBP compared to the baseline (−2.7% ± 8.1%) for most of the postoperative period, except that SBP was significantly higher than the baseline during the first 2 hours after recovery. For DBP, values were −10.6% ± 2.6% in Group I and −6.7% ± 3.4% in Group II.

The postoperative heart rate of patients in Group I was not significantly different from baseline (percentage change of −0.4% ± 15.8%), while patients in Group II continued to demonstrate significantly elevated heart rates (19% ± 19.6%).

Respiratory Function

Respiratory rate and hemoglobin oxygen saturation did not show significant differences between the 2 groups during the postoperative period (Table 4).

Postoperative Side Effects

Group I demonstrated fewer incidences of nausea, vomiting, and pruritus compared to Group II, but the differences were not significant (P>0.05). Urinary retention and shivering were significantly lower in Group I (P<0.05 and P<0.001, respectively) (Table 5).

Sedation

Sedation scores were significantly higher in Group I compared to Group II until 9 hours after surgery (P<0.001) (Table 6).

Table 2. Pain Scores According to the Visual Analog Scale (VAS)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Group I (clonidine)</th>
<th>Group II (bupivacaine)</th>
<th>Group I vs Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=20</td>
<td>n=20</td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>1.7 ± 0.5</td>
<td>3.4 ± 0.9</td>
<td>a</td>
</tr>
<tr>
<td>1 h</td>
<td>1.6 ± 0.5</td>
<td>3.8 ± 1.3</td>
<td>a</td>
</tr>
<tr>
<td>2 h</td>
<td>1.6 ± 0.5</td>
<td>3.1 ± 1.0</td>
<td>a</td>
</tr>
<tr>
<td>3 h</td>
<td>1.7 ± 0.5</td>
<td>3.4 ± 0.9</td>
<td>a</td>
</tr>
<tr>
<td>4 h</td>
<td>1.8 ± 0.4</td>
<td>3.4 ± 1.0</td>
<td>a</td>
</tr>
<tr>
<td>5 h</td>
<td>1.4 ± 0.5</td>
<td>3.2 ± 1.0</td>
<td>a</td>
</tr>
<tr>
<td>6 h</td>
<td>1.6 ± 0.5</td>
<td>3.5 ± 0.7</td>
<td>a</td>
</tr>
<tr>
<td>7 h</td>
<td>1.5 ± 0.5</td>
<td>3.4 ± 1.0</td>
<td>a</td>
</tr>
<tr>
<td>8 h</td>
<td>1.6 ± 0.5</td>
<td>3.2 ± 1.2</td>
<td>a</td>
</tr>
<tr>
<td>9 h</td>
<td>1.5 ± 0.5</td>
<td>3.6 ± 0.9</td>
<td>a</td>
</tr>
<tr>
<td>10 h</td>
<td>1.4 ± 0.5</td>
<td>3.3 ± 1.0</td>
<td>a</td>
</tr>
<tr>
<td>11 h</td>
<td>1.6 ± 0.5</td>
<td>3.2 ± 1.1</td>
<td>a</td>
</tr>
<tr>
<td>12 h</td>
<td>1.5 ± 0.5</td>
<td>3.6 ± 0.8</td>
<td>a</td>
</tr>
<tr>
<td>Average pain score</td>
<td>1.5 ± 0.5</td>
<td>3.4 ± 1.0</td>
<td>a</td>
</tr>
</tbody>
</table>

*P<0.001.

Data are presented as mean ± SD. The VAS is a 10-point numeric scale with 0 equal to no pain and 10 equal to maximum intolerable pain.
<table>
<thead>
<tr>
<th>Time Point</th>
<th>SBP, mmHg Group I vs Group II</th>
<th>SBP, mmHg Group I vs Group II</th>
<th>SBP, mmHg Group I vs Group II</th>
<th>DBP, mmHg Group I vs Group II</th>
<th>DBP, mmHg Group I vs Group II</th>
<th>DBP, mmHg Group I vs Group II</th>
<th>HR, bpm Group I vs Group II</th>
<th>HR, bpm Group I vs Group II</th>
<th>HR, bpm Group I vs Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>127.3 ± 11.2</td>
<td>125.5 ± 10.7</td>
<td>NS</td>
<td>75.8 ± 7.1</td>
<td>74.1 ± 7.3</td>
<td>NS</td>
<td>65.6 ± 6.3</td>
<td>68.5 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Intubation (1 min)</td>
<td>120.3 ± 10.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>117.8 ± 10.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>78.1 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76.7 ± 7.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>85.1 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90.0 ± 9.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td>30 min intraoperative</td>
<td>100.1 ± 8.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>106.3 ± 13.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>66.0 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67.7 ± 8.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>67.4 ± 5.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>83.2 ± 9.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>a</td>
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<td>60 min intraoperative</td>
<td>105.3 ± 10.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>109.3 ± 10.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>66.2 ± 6.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.9 ± 7.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>58.6 ± 5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>87.2 ± 8.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>90 min intraoperative</td>
<td>110.8 ± 12.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>108.2 ± 9.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>67.4 ± 6.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.8 ± 7.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>63.3 ± 6.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84.9 ± 9.0&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>120 min intraoperative</td>
<td>108.1 ± 11.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>103.9 ± 8.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>65.7 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.7 ± 7.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>60.4 ± 5.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>84.8 ± 10.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>a</td>
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<tr>
<td>Recovery</td>
<td>111.8 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>138.3 ± 9.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>70.5 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73.2 ± 6.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>NS</td>
<td>70.2 ± 8.7&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>94.3 ± 11.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>a</td>
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<tr>
<td>1 h postoperative</td>
<td>111.5 ± 5.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>135.6 ± 9.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>a</td>
<td>68.0 ± 7.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70.5 ± 7.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>64.2 ± 5.8&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>96.8 ± 15.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2 h postoperative</td>
<td>110.7 ± 4.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>121.6 ± 9.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>a</td>
<td>68.4 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.8 ± 7.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>66.4 ± 11.4&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>81.1 ± 11.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>116.0 ± 5.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>124.6 ± 8.4&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>b</td>
<td>68.3 ± 6.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.7 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>69.1 ± 11.0&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>94.1 ± 13.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>4 h postoperative</td>
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<td>131.1 ± 9.1&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>a</td>
<td>68.1 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.9 ± 7.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>70.9 ± 10.0&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>100.7 ± 13.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>5 h postoperative</td>
<td>106.7 ± 5.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>123.1 ± 9.4&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>a</td>
<td>67.8 ± 7.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.2 ± 7.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>67.4 ± 10.1&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>89.4 ± 13.1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>a</td>
<td>67.8 ± 7.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.5 ± 7.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>71.1 ± 12.7&lt;sup&gt;NS&lt;/sup&gt;</td>
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<td>7 h postoperative</td>
<td>110.2 ± 6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>129.9 ± 9.6&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>a</td>
<td>68.1 ± 6.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>9 h postoperative</td>
<td>109.4 ± 6.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>132.3 ± 8.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>a</td>
<td>68.1 ± 7.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70.2 ± 7.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>61.7 ± 6.6&lt;sup&gt;NS&lt;/sup&gt;</td>
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<tr>
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<td>a</td>
<td>67.9 ± 6.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69.9 ± 7.6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
<td>69.3 ± 9.4&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>93.0 ± 16.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup><sub>p<0.001</sub>,<sup>b</sup><sub>p<0.01</sub>,<sup>c</sup><sub>p<0.05</sub>.

DBP, diastolic blood pressure; HR, heart rate; NS, not significant; SBP, systolic blood pressure.

Data are presented as mean ± SD.
<table>
<thead>
<tr>
<th>Time Point</th>
<th>RR, bpm (Group I vs Baseline)</th>
<th>RR, bpm (Group II vs Baseline)</th>
<th>O₂ Saturation, % (Group I vs Baseline)</th>
<th>O₂ Saturation, % (Group II vs Baseline)</th>
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<td>96.2 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
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<td>6 h postoperative</td>
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<td>96.3 ± 1.1&lt;sup&gt;NS&lt;/sup&gt;</td>
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</tr>
</tbody>
</table>

bpm, breaths per minute; NS, not significant.
Data are presented as mean ± SD.
DISCUSSION

Our study was designed to compare defined-dose epidural clonidine as a sole analgesic agent vs epidural bupivacaine during and after lower abdominal surgeries. Regarding hemodynamic effects, the present study demonstrated no significant intraoperative differences in SBP between groups. Statistically significant decreases in blood pressure were seen in both groups compared to baseline that were managed by IV fluids, but vasopressors were not needed by any patient. Clonidine resulted in significantly lower SBP compared to bupivacaine during the postoperative period, although DBP was not significantly different between groups. These results are consistent with other studies that showed bolus administration of epidural clonidine causes a dose-independent reduction in blood pressure and a 5%-20% reduction in heart rate.\textsuperscript{12,27} However, other studies demonstrate that clonidine (150-600 \textmu g) added to epidural bupivacaine or lidocaine does not reduce blood pressure more than local anesthetic alone and does not diminish blood pressure response to ephedrine.\textsuperscript{28,29}

Heart rate in Group I was significantly decreased from baseline during the intraoperative period. This effect was in contrast to the significant increase from baseline experienced by Group II. The decrease in heart rate in Group I was not associated with hemodynamic instability that necessitated intervention. It should be kept in mind that the patients involved in this study were young and were classified as ASA 1 or 2, and the surgical procedures were simple with no major fluid shift or blood loss.

In 1999, De Kock and colleagues demonstrated that epidural clonidine used as a sole agent provides dose-dependent control of the hemodynamic changes associated with surgical stimulation and dose-dependent postoperative analgesia without major side effects.\textsuperscript{30} Hemodynamic stability can be explained by clonidine’s actions at different sites involved in blood pressure control. Clonidine acts at central and medullary sites to reduce blood pressure and on peripheral alpha-2 adrenergic receptors on blood vessels to cause vasoconstriction.\textsuperscript{20} Measured blood pressure is the net result of these opposing effects. Moreover, profound bradycardia is a rare complication of clonidine administration, even after a massive overdose.\textsuperscript{31}

Regarding the analgesic effects in the present study, patients in Group I showed statistically significant lower pain scores and decreased opioid requirements during the postoperative periods than patients in Group II. Although systemic administration of clonidine also reduces anesthetic requirements, De Kock and colleagues demonstrated in

\begin{table}[h]
\centering
\caption{Postoperative Side Effects}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Side Effect} & \textbf{Group I (clonidine)} & \textbf{Group II (bupivacaine)} & \textbf{Group I vs Group II} \\
\hline
\textbf{n=20} & \textbf{n=20} & \\
\hline
Nausea, n (%) & 1 (5) & 3 (15) & NS \\
Vomiting, n (%) & 0 (0) & 2 (10) & NS \\
Urine retention, n (%) & 0 (0) & 5 (25) & \textsuperscript{a} \\
Pruritus, n (%) & 0 (0) & 1 (5) & NS \\
Shivering, n (%) & 0 (0) & 12 (60) & \textsuperscript{b} \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}P<0.05.  \\
\textsuperscript{b}P<0.001.  \\
NS, not significant.

\begin{table}[h]
\centering
\caption{Sedation Scores According to the Ramsay Sedation Scale}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Time Point} & \textbf{Group I (clonidine)} & \textbf{Group II (bupivacaine)} & \textbf{Group I vs Group II} \\
\hline
& \textbf{n=20} & \textbf{n=20} & \\
\hline
Recovery & 2 (1-2) & 1 (0-1) & \textsuperscript{a} \\
1 h postoperative & 2 (1-2) & 0 & \textsuperscript{a} \\
2 h postoperative & 1.5 (1-2) & 0 & \textsuperscript{a} \\
3 h postoperative & 1 (1-2) & 0 & \textsuperscript{a} \\
4 h postoperative & 1 (1-1) & 0 & \textsuperscript{a} \\
5 h postoperative & 1 (1-1) & 0 & \textsuperscript{a} \\
6 h postoperative & 1 (1-1) & 0 & \textsuperscript{a} \\
7 h postoperative & 1 (1-1) & 0 & \textsuperscript{a} \\
8 h postoperative & 1 (0-1) & 0 & \textsuperscript{a} \\
9 h postoperative & 1 (0-1) & 0 & \textsuperscript{a} \\
10 h postoperative & 0 & 0 & NS \\
11 h postoperative & 0 & 0 & NS \\
12 h postoperative & 0 & 0 & NS \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}P<0.001.  \\
NS, not significant.

Data are presented as median and range.

The Ramsay sedation scale is a 0-3 scale with 0 equal to alert or drowsy, easily roused by verbal command; 1 equal to sleepy, but roused by verbal command; 2 equal to sleepy, but roused by tactile stimulation; and 3 equal to sleepy, and not roused by tactile stimulation.
1993 that epidural clonidine showed a 50%-75% reduction in supplemental propofol and alfentanil use compared with the same dose of IV clonidine during surgery.\(^3\) In a study of intraoperative and postoperative analgesia, epidural clonidine appeared to be significantly more effective than bupivacaine.\(^3\) During anesthesia, epidural clonidine was particularly efficient in blunting stress responses (hypertension or tachycardia) in response to surgical incision. A purely hemodynamic effect was considered unlikely based on data obtained using the electroencephalographic bispectral index. Patients in Group I required significantly fewer propofol supplementations than patients in Group II to maintain the index in a range compatible with adequate anesthesia. Because systemic absorption of spinal clonidine is fast and significant, this anesthetic-sparing effect is possibly the result of a central hypnotic action consecutive to systemic absorption.\(^31,33,34\)

An important reduction of the noxious afferent inputs to the central site, consecutive to a spinal regional effect, can influence the state of general anesthesia.\(^3\) In anesthetized patients, high-dose epidural clonidine (8 \(\mu g/kg\)) resulted in a greater depression of the electroencephalogram than the same dose injected via the systemic route.\(^3\) A separate study demonstrated that epidural clonidine was clearly associated with a greater reduction of intraoperative anesthetic/analgesic supplementation compared with systemic administration.\(^3\) These 2 observations argue for a specific spinal anesthetic-sparing effect of epidural clonidine.

In a double-blind, placebo-controlled trial, epidural clonidine reduced intraoperative IV fentanyl requirements by 50% and provided postoperative analgesia for 4 hours without significantly reducing blood pressure.\(^3\) Epidural clonidine increased the duration of analgesia from fentanyl more than 2-fold in patients after abdominal aortic surgery and reduced epidural fentanyl infusion requirements by 45% after colorectal surgery.\(^3\) The addition of epidural clonidine to sufentanil produces longer analgesia than sufentanil alone.\(^4\) In animals, spinal alpha-2 adrenergic agonists interact synergistically with the \(\mu\) receptor but not all opioid receptor subtypes. This interaction may explain the lack of enhancement from the addition of epidural clonidine to butorphanol in humans.\(^42,43\)

Epidural clonidine has been combined with morphine in postoperative patients in 4 double-blind controlled studies. Whereas a single bolus of 75 \(\mu g\) clonidine did not affect analgesia from epidural morphine after meniscectomy, larger doses (150 and 280 \(\mu g\)) in the same study did enhance analgesia from morphine after total hip replacement and after pancreactectomy in a separate study.\(^44,46\) In both studies with larger clonidine doses, onset of effective analgesia was more rapid with clonidine-morphine than with morphine alone. Because the time course of action differs so widely between clonidine and morphine, their interaction could more easily be investigated during continuous infusion. Motsch and colleagues demonstrated that continuous epidural clonidine infusion reduced pain scores and the use of supplemental analgesics and improved forced vital capacity when added to epidural morphine.\(^47\)

Epidural clonidine combined with local anesthetics has demonstrated increased duration of postoperative analgesia, reduced pain scores, and less need for systemic rescue pain medication than bupivacaine alone without increasing the incidence of hypotension or bradycardia.\(^48\) Similarly, the addition of epidural clonidine to a postoperative infusion of bupivacaine plus morphine reduced pain during mobilization and coughing compared with bupivacaine plus morphine alone.\(^4\)

When an epidural bolus of clonidine is used as a sole agent, analgesia lasting from 2-6 hours has been demonstrated with no increase in duration beyond a dose of 400 \(\mu g.\)\(^3\) Adequate analgesia has been achieved in patients who administered epidural clonidine by patient-controlled analgesia at 24-14 \(\mu g/h\) after a loading dose of 417 \(\mu g\) post scoliosis surgery.\(^5\) Similarly, 25 \(\mu g/h\) epidural clonidine was equipotent to epidural morphine (1 mg bolus plus 0.1 mg/h) in patients after total hip replacement, whereas 50 \(\mu g/h\) clonidine was more potent in reducing rescue analgesic requirements.\(^4\) A much larger epidural clonidine infusion rate (120-150 \(\mu g/h\)) provided complete analgesia in patients after major abdominal procedures.\(^5\)

The results of the present study were different from those obtained by Filos and colleagues who used intrathecal clonidine as a sole agent for postoperative analgesia after cesarean delivery.\(^5\) The largest bolus dose those authors used was 450 \(\mu g\) (approximately 6 \(\mu g/kg\)) of spinal clonidine, resulting in complete postoperative analgesia lasting 864 \(\pm\) 80 minutes. When clonidine is administered intrathecally, more drug is immediately available at its site of spinal action (the spinal dorsal horn). Also, in Filos et al, healthy young women with Pfannenstiel incisions were considered in the early postpartum period. Along with the evident psychological benefits of delivery, the end of pregnancy is associated with high levels of endorphins in humans.\(^13\)

Regarding respiratory function, epidural clonidine used as a sole agent did not show evidence of respiratory depression even with the use of defined doses. No significant differences in respiratory rate and arterial oxygen saturation were seen in our 2 groups, consistent with previous work demonstrating that the addition of clonidine to epidural bupivacaine or lidocaine for surgery produces sedation with no change in respiratory rate or the arterial partial pressure of oxygen.\(^28\)

Postoperative sedation was more prominent in Group I vs Group II in our study. Although no patient reached a sedation score of 3 during the postoperative period, most patients had a score of 2 during the immediate postoperative period. Sedation scores decreased to 1 after 2 hours, and most patients had a sedation score of 0 after the 8th hour. This finding is in agreement with the 1999 work of De Kock and colleagues who demonstrated the absence of major and long-lasting postoperative sedation after similar large doses of epidural clonidine.\(^30\) The explanation they proposed was the development of tachyphylaxis to the sedative effects of the alpha-2 adrenergic agonists, but this hypothesis remains unproven. In our study, moderate sedation was more frequent in patients who received clonidine than in patients who received bupivacaine. However, no evidence exists to indicate that this difference significantly influenced the analgesic requirements. Sedation has been documented after systemic, epidural, and intrathecal administration of clonidine in humans.\(^22,32,52\) Experimental data have shown the sedative hypnotic effect of alpha-2 adrenergic agonists is caused by action primarily on the locus coeruleus.\(^3\)
Systemically administered alpha-2 adrenergic agonists have been advocated for premedication before surgery to provide sedation without respiratory depression.\(^{30}\) In a study of epidural clonidine premedication, Penon and associates observed intense sedation 60-120 minutes after injection in 7 patients accompanied by decreased blood pressure (by 12%-25%) and decreased heart rate (by 10%-16%).\(^{53}\) Although snoring was observed in 5 of 7 patients and ventilatory response to inhaled carbon dioxide was mildly depressed, clonidine did not alter end tidal carbon dioxide, and all patients had oxyhemoglobin saturation >95% without supplemental oxygen.

Our study showed no significant difference in the incidence of nausea and vomiting in the two groups. Group I had no cases of urinary retention while Group II had 5, a statistically significant difference. Pruritus occurred in 1 patient in Group II and no patients in Group I, and this difference could be explained by the higher use of morphine sulfate in Group II. Shivering occurred in 12 patients in Group II compared to no patients in Group I. The higher incidence of shivering in Group II can be explained by the sympathetic blockade effect of bupivacaine that causes cold sensation and shivering. In these circumstances, patients frequently asked for something to make them more comfortable.

These findings are supported by the work of Rosa-e-Silva and colleagues who used clonidine to treat nausea and vomiting in patients with gastroparesis and by the work done in 1999 by De Kock et al who noted the lack of major side effects after administration of a similar large dose of epidural clonidine.\(^{30,54}\) In the De Kock et al study, the incidence of nausea and vomiting was significantly lower in Group 1 than in Group 2 (10% vs 45%), and none of the patients on clonidine suffered shivering (compared to 65% in Group 2).

Although other studies report the use of epidural clonidine for pain control, our study is unique because it addresses a different population, confirms efficacy, and provides a detailed hemodynamic profile in the immediate postoperative period.

**CONCLUSION**

Clonidine can be used as a sole epidural analgesic agent in defined dose in patients classified as ASA 1 or 2 who have no contraindications for clonidine. Patients on epidural clonidine require close postoperative hemodynamic monitoring for the duration of epidural infusion and for the first few hours after stopping the infusion.

**ACKNOWLEDGMENTS**

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**REFERENCES**


Epidural Clonidine vs Bupivacaine for Pain Control


