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## Low-dose Clonidine and Neostigmine Prolong the Duration of Intrathecal Bupivacaine-Fentanyl for Labor Analgesia

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**Background:** Intrathecal (IT) opioid and local anesthetic combinations are popular for labor analgesia because of rapid, effective pain relief, but the duration of analgesia is limited. This study was undertaken to determine whether the addition of clonidine and neostigmine to IT bupivacaine-fentanyl would increase the duration of analgesia without increasing side effects for patients in labor.

**Methods:** Forty-five healthy parturients in active labor were randomized to receive a 2-ml IT dose of one of the following dextrose-containing solutions using the combined spinal-epidural technique: (1) bupivacaine 2.5 mg and fentanyl 25 µg (BF); (2) BF plus clonidine 30 µg (BFC); or (3) BFC plus neostigmine 10 µg (BFCN). Pain, sensory levels, motor block, side effects, maternal vital signs, and fetal heart rate were systematically assessed.

**Results:** Patients administered BFCN had significantly longer analgesia (165 ± 32 min) than those who received BF (90 ± 21 min;  $P < 0.001$ ) or BFC (123 ± 21 min;  $P < 0.001$ ). Pain scores, block characteristics, maternal vital signs, Apgar scores, maternal satisfaction, and side effects were similar among groups except for nausea, which was significantly greater in the BFCN group ( $P < 0.05$  as compared with BFC).

**Conclusions:** The addition of clonidine and neostigmine significantly increased the duration of analgesia from IT bupivacaine-fentanyl during labor, but neostigmine caused more nausea. Although serious side effects were not observed in this study, safety must be further addressed before the routine use of multiple IT drugs is advocated. (Key words:  $\alpha_2$ -Agonist; cholinesterase inhibitor; combined spinal-epidural; hyperbaric; local anesthetic; technique.)

PROBLEMS associated with epidural infusions of local anesthetic solutions have prompted the development of alternative techniques for labor pain control. One technique gaining popularity is the combined spinal-epidural (CSE), whereby lipid-soluble opioids, often with low-dose bupivacaine, are administered by intrathecal (IT) injection to produce rapid pain relief with minimal motor block. The main disadvantage of this technique is the limited duration of analgesia. Once the spinal portion of the CSE analgesia dissipates, the epidural catheter may function poorly or its use may lead to motor block. Finding drug combinations or doses to lengthen the spinal analgesia of the CSE technique without producing additional side effects would be beneficial.

Clonidine, an  $\alpha_2$ -adrenergic agonist, and neostigmine, a cholinesterase inhibitor, are being investigated for use with current IT regimens for labor pain control. Clonidine prolongs the effects of local anesthetics for operative spinal anesthesia,<sup>1</sup> and during labor, IT clonidine with sufentanil produces longer analgesia than IT sufentanil alone.<sup>2,3</sup> IT neostigmine has also been administered to patients in labor and has been shown to reduce the dose of sufentanil required for 1 h of analgesia.<sup>4</sup> The coadministration of IT clonidine and neostigmine has not been evaluated in humans, but in animals it potentiated analgesia<sup>5,6</sup> without reducing spinal cord blood flow,<sup>7</sup> supporting the efficacy of this combination. The concomitant use of drugs from different pharmacologic classes may, in fact, produce superior analgesia with fewer side effects than any single agent because of

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different sites of action within the central nervous system.<sup>8</sup> The present study was designed to evaluate the duration of analgesia and to observe side effects from the addition of low-dose clonidine and neostigmine to IT bupivacaine-fentanyl for labor.

## Materials and Methods

After institutional approval and informed consent, 50 healthy Turkish patients with term, uncomplicated pregnancies in active labor (cervical dilation 3–6 cm) who requested analgesia were enrolled in this study. Exclusion criteria included weight > 115 kg, age < 18 yr, or allergy to the study medications. Eligible patients were prospectively randomized by a computer-generated list to one of three groups, each receiving an IT drug combination administered in a dextrose-containing solution for a total volume of 2 ml: (1) bupivacaine 2.5 mg plus fentanyl 25  $\mu$ g (BF); (2) BF plus plus clonidine 30  $\mu$ g (BFC); or (3) BFC plus neostigmine 10  $\mu$ g (BFCN).

Patients and anesthesia providers were blinded to treatment group. After a 500-ml intravenous bolus dose of balanced salt solution, CSE analgesia was performed with the patient in the lateral position using the “needle through needle” technique at the L2–L3 or L3–L4 interspace. Briefly, the epidural space was located with an 18-gauge, 8.89-cm Perican needle (B. Braun, Melsungen, Germany) using loss of resistance to air. A 27-gauge, 12.7-cm Spinocan needle (B. Braun) was inserted through the epidural needle, and subarachnoid placement was confirmed by cerebrospinal fluid visualization. After the subarachnoid injection of study solution, the spinal needle was removed, and a 20-gauge multiport Perifix catheter (B. Braun) was inserted 4 cm cephalad within the epidural space and secured. Patients were placed supine with left uterine displacement and 30° head elevation for the duration of labor.

### Assessments

Baseline verbal pain scores (10-point scale: 0 = no pain; 10 = worst possible pain), maternal blood pressure, maternal heart rate, and continuous external fetal heart rate were measured before CSE placement. These measurements were continued after IT drug administration; in addition, bilateral sensory levels to pin prick and degree of motor block (0 = lifts lower extremity; 1 = lifts knees; 2 = moves feet; 3 = no leg movement) were assessed at 5, 10, 15, 30, 45, and 60 min and then every 30 min until delivery. Hypotension was defined as a >

20% change from baseline systolic blood pressure and was treated with ephedrine at the discretion of the anesthesiologist. Bradycardia was defined as heart rate < 60 beats/min. The duration of CSE analgesia was measured from the time of IT drug administration until additional pain medication was requested. If the patient did not obtain pain relief within 10 min of CSE drug administration or delivered vaginally or operatively during this time interval, she was removed from the study. When additional pain medication was requested, a pain score was obtained, and a 2-ml test dose of 2% lidocaine with 25  $\mu$ g epinephrine was administered through the epidural catheter. If there was no evidence of subarachnoid or intravascular drug injection after the epidural test dose, the patient received 10 ml 0.25% bupivacaine solution over 10 min. The duration of analgesia after the epidural bolus was also recorded to determine whether the addition of clonidine with or without neostigmine might increase the duration of analgesia after the bolus. Patients were assessed hourly throughout labor for the presence or absence of nausea, pruritus, and sedation (0 = awake; 1 = sleepy but responsive to verbal stimulus; 2 = responsive only to tactile stimulus; 3 = unresponsive). After delivery, maternal satisfaction with the CSE intervention (0 = unsatisfied; 5 = highest satisfaction) and Apgar scores were recorded.

### Statistical Analysis

Statistical analyses were performed using SAS (Statistical Analysis System, Inc., Cary, NC) and included analysis of variance, Kruskal-Wallis, chi-square test, or Fisher exact test as appropriate. A *P* value < 0.05 was considered significant. Group sizes were predetermined by power analysis ( $\beta = 0.8$ ;  $\alpha = 0.05$ ) to detect a 30-min difference between groups in the duration of analgesia and assuming a 45-min SD within each group. Unless otherwise stated, data are expressed as mean  $\pm$  SD.

## Results

Fifty patients were randomized, and 45 patients completed the study. Five patients were excluded because the data were lost (one in the BF group), cesarean section was performed before patient request for additional pain medication (one in the BF group, one in the BFC group), and inadequate analgesia occurred after CSE placement (two in the BFCN group).

Demographic variables and labor characteristics, including parity, oxytocin use, cervical dilation at CSE

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**Table 1. Demographics and Labor Characteristics**

	BF (n = 15)	BFC (n = 15)	BFCN (n = 15)	Statistical Test
Age (yr)	26 ± 4	27 ± 4	26 ± 5	ANOVA
Height (cm)	162 ± 5	164 ± 6	163 ± 3	ANOVA
Weight (kg)	74 ± 7	76 ± 8	70 ± 6	ANOVA
Nulliparous (%)	53	53	80	Fisher exact
Oxytocin use (%)	13	27	27	Fisher exact
Cervical dilation (cm)*	5 (4, 6)	5 (4.5, 6)	4 (4, 5.5)	Kruskal-Wallis
Duration of labor (min)				
CSE-10 cm	171 ± 172	225 ± 131	224 ± 94	ANOVA
Stage 2	41 ± 21	60 ± 61	50 ± 33	ANOVA

Unless identified, data are presented as mean ± SD. No significant differences exist between groups.

\* Median (twenty-fifth, seventy-fifth percentile) cervical dilation at the time of spinal injection.

BF = bupivacaine 2.5mg, fentanyl 25µg; BFC = bupivacaine 2.5mg, fentanyl 25µg, clonidine 30µg; BFCN = bupivacaine 2.5µg, fentanyl 25µg, clonidine 30µg, neostigmine 10µg; ANOVA = analysis of variance.

placement, and labor duration, were similar among the groups (table 1). No technical difficulty was encountered during the CSE procedure, and cerebrospinal fluid was identified in all patients. Verbal pain scores were similar before CSE placement, 15 min after CSE placement, and when the CSE drug effects dissipated (table 2). The groups differed significantly in the duration of analgesia measured from the time of IT drug administration until the patient requested additional pain medication (table 2). The longest duration of analgesia occurred in the BFCN group (165 ± 32 min) and was significantly longer than in the BF control group (90 ± 21 min;  $P < 0.001$ ) and the BFC group (123 ± 21 min;  $P < 0.001$ ). A representation of the analgesia time course after IT drug injection is shown as the percentage of patients not requesting additional pain medication *versus* time (fig.

1). Although the groups differed in the duration of analgesia from IT drug administration, there were no differences in analgesia resulting from the epidural bupivacaine that was given when pain returned. In other words, the addition of IT clonidine and neostigmine did not prolong analgesia after the subsequent bolus of epidural bupivacaine (table 2) and provided no obvious benefit after the initial IT drug effect subsided. The median maximum sensory levels obtained after IT drug injection are also shown in table 2. The highest block level reported was T3 in one patient in the BFC group.

Side effects and patient satisfaction are shown in table 3. There were no significant differences among groups in the incidence of hypotension, bradycardia, pruritus, sedation, and motor block after IT drug administration, but the study had limited power to detect differences in

**Table 2. Labor Analgesia Characteristics**

	BF (n = 15)	BFC (n = 15)	BFCN (n = 15)	Statistical Test
Verbal Pain Scores*				
Before CSE	8.9 ± 1.6	8.7 ± 1.4	9.0 ± 1.4	Kruskal-Wallis†
After CSE	0.4 ± 1.0	0.2 ± 0.6	1.1 ± 2.4	Kruskal-Wallis
At return of pain	3.5 ± 2.1	3.4 ± 2.0	3.2 ± 1.3	Kruskal-Wallis
Duration of CSE (min)	90 ± 21	123 ± 21§	165 ± 32§	ANOVA
Range	(65–135)	(90–160)	(115–215)	—
Duration of redose (min)†	106 ± 41	131 ± 32	118 ± 10	ANOVA
Maximum sensory level‡	T7 (T6, T7)	T7 (T6, T8)	T8 (T6, T8)	Kruskal-Wallis

Unless identified, data are presented as mean ± SD.

\* Verbal pain scores using a 10-point scale (0 = no pain, 10 = worst pain).

† Duration of analgesia following 10 ml epidural bupivacaine (0.25%) in laboring patients. Data are represented by 5, 7, and 4 patients remaining in groups BF, BFC, and BFCN, respectively.

‡ Median (twenty-fifth, seventy-fifth percentile) maximum sensory level.

§  $P < 0.001$  as compared to the BF value.

||  $P < 0.001$  as compared to the BFC value.

BF = bupivacaine 2.5 mg, fentanyl 25 µg; BFC = bupivacaine 2.5 mg, fentanyl 25 µg, clonidine 30 µg; BFCN = bupivacaine 2.5 µg, fentanyl 25 µg, clonidine 30 µg, neostigmine 10 µg; ANOVA = analysis of variance.

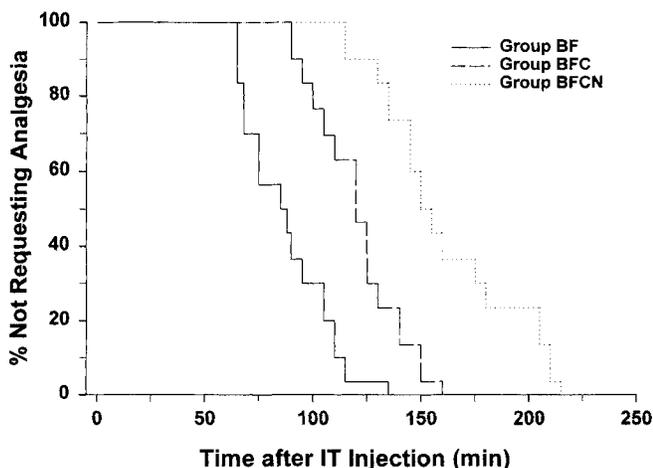


Fig. 1. The duration of spinal analgesia as the percentage of patients not requesting additional pain medication after the intrathecal injection of bupivacaine 2.5 mg and fentanyl 25  $\mu$ g (BF), BF plus clonidine 30  $\mu$ g (BFC), or BFC plus neostigmine 10  $\mu$ g (BFCN). The groups' duration of analgesia differed significantly (analysis of variance,  $P = 0.0001$ ).

side effects. Hence, a negative result must be viewed cautiously because a larger sample size may have revealed differences among groups. The maximum decrease in blood pressure was not  $> 25\%$  from baseline, except in one patient in the BFCN group who, while supine, had a blood pressure of 85/47 mmHg. Four of the seven episodes of hypotension were treated with intravenous ephedrine with prompt blood pressure normalization and without alterations in fetal heart rate. Maternal bradycardia occurred in three patients in the BF group without blood pressure or fetal heart rate changes and was not treated. Patients in the BFCN group experienced significantly more nausea than did patients in the BFC group ( $P < 0.05$ ). Nausea developed 60–90 min after IT injection in patients in the BFCN group and was accompanied by emesis. Pruritus and sedation were mild and required no treatment. Motor block, when present, was mild (able to bend knee but not raise leg) and subsided by the time of delivery. In fact, all but one patient walked with minimal assistance from the labor room to the delivery room. All patients had normal spontaneous vaginal delivery except two who underwent cesarean section: one in the BF group for failure to progress, and one in the BFCN group for fetal distress during the epidural portion of the CSE technique. Apgar scores were similar among the groups, and none was  $< 7$ . There were no differences in the degree of satisfaction experienced by patients participating in the study. Overall,  $\geq 80\%$  of patients in each group reported excellent

satisfaction, and no patient was dissatisfied; however, again, the sample size may have been insufficient to detect a difference if one existed.

## Discussion

The addition of clonidine and neostigmine significantly prolonged analgesia produced by IT bupivacaine-fentanyl for labor analgesia. The BFCN combination produced 83% and 34% longer analgesia than did BF and BFC, respectively. These findings are consistent with the results of animal studies<sup>5,6,8</sup> and human trials.<sup>9,10</sup> In animals, antinociceptive synergism between spinal  $\alpha_2$ -adrenergic agonists and opioids is well documented.<sup>8</sup> In addition, because spinal  $\alpha_2$ -adrenergic agonists produce analgesia, in part, by spinal acetylcholine release,<sup>11</sup> it is not surprising that clonidine-induced analgesia is enhanced by spinal neostigmine.<sup>12</sup> Human studies have yielded similar conclusions. Hood *et al.* found that IT neostigmine enhanced both clonidine-<sup>9</sup> and opioid-induced<sup>10</sup> analgesia in volunteers, and for postoperative pain control, IT neostigmine provided an opioid dose-sparing effect.<sup>13,14</sup>

For use during labor, the addition of clonidine or neostigmine to IT opioids has also improved analgesia, although the number of published studies are few. When clonidine 30  $\mu$ g was added to IT sufentanil, 2.5 or 5  $\mu$ g, Gautier *et al.*<sup>2</sup> found that the duration of labor analgesia increased from 104 to 145 min without motor block. Similarly, Mercier *et al.*<sup>3</sup> observed longer labor analgesia from IT clonidine 30  $\mu$ g and sufentanil 5  $\mu$ g (125 min) than from IT sufentanil alone (97 min). D'Angelo *et al.*<sup>15</sup> recently reported 197 min of labor analgesia from the IT injection of clonidine 50  $\mu$ g, sufentanil 7.5  $\mu$ g, and bupivacaine 2.5 mg (compared with 132 min for the sufentanil-bupivacaine control) but also encountered a 60% incidence of maternal hypotension. In the few neostigmine labor studies conducted, IT neostigmine alone was ineffective for labor pain relief,<sup>16</sup> but when combined with IT sufentanil, 10  $\mu$ g neostigmine reduced the ED<sub>50</sub> of sufentanil by 25%.<sup>4</sup>

These studies demonstrate enhanced analgesia from combination IT drug therapy, but it remains questionable whether low-dose drug combinations result in fewer side effects. Clonidine, for example, extends labor analgesia when added to IT opioids, but hypotension is also worsened. Gautier *et al.*<sup>2</sup> reported a 25% incidence in maternal hypotension (defined as a 20% decrease in mean arterial pressure) after IT sufentanil alone (5  $\mu$ g),

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Table 3. Side Effects and Patient Satisfaction (%)

	BF (n = 15)	BFC (n = 15)	BFCN (n = 15)	Statistical Test
Hypotension (>20% ↓)	13	27	7	Fisher exact
Bradycardia (< 60 beats/min)	20	0	0	Fisher exact
Nausea	7	0	33‡	Fisher exact
Pruritus	67	47	60	Chi-square
Sedation*	7	7	7	Chi-square
Motor block†				
0	93	80	60	Fisher exact
1	7	20	40	Fisher exact
Patient satisfaction				
Excellent	100	93	87	Fisher exact
Good	0	7	13	Fisher exact

Data are expressed as percentage of patients with a positive response in each category.

\*  $P < 0.05$  as compared to BFC value;

† All patients had sedation scores of 1. Sedation was defined by: 0 = awake, 1 = sleepy, but responds to verbal stimulus, 2 = responds only to tactile stimulation, 2 = unresponsive;

‡ Motor block was defined as leg weakness lasting  $\geq 30$  min after IT drug administration and was defined by: 0 = lifts lower extremity, 1 = bends knee, 2 = moves feet, 3 = no leg movement.

which more than doubled when clonidine 30  $\mu\text{g}$  was coadministered. Decreasing the clonidine dose to 15  $\mu\text{g}$  did not reduce hypotension but did decrease the duration of analgesia from the combination.<sup>2</sup> Mercier *et al.*<sup>3</sup> also observed a 63% incidence of hypotension (systolic blood pressure < 95 mmHg or decreased by > 25%) with clonidine 30  $\mu\text{g}$  and sufentanil 5  $\mu\text{g}$  versus a 12% incidence with sufentanil alone. D'Angelo *et al.*<sup>15</sup> similarly found a 60% incidence of hypotension (< 20% decrease in systolic blood pressure) with clonidine 50  $\mu\text{g}$ , bupivacaine 2.5 mg, and sufentanil 7.5  $\mu\text{g}$ , compared with 33% in the IT bupivacaine-sufentanil control group. We found a 27% incidence of hypotension in the BFC group compared with 7% in the BFCN and 14% in the BF groups. Although hypotension observed after IT bupivacaine 2.5 mg and fentanyl 25  $\mu\text{g}$  is similar to separate reports using identical IT doses,<sup>17,18</sup> it is noteworthy that in the group that received clonidine without neostigmine (BFC), hypotension was almost four times greater than in the group that received clonidine with neostigmine (BFCN). In sheep<sup>19</sup> and human volunteers,<sup>9</sup> neostigmine has been shown to counteract clonidine-induced hypotension. This study would have required a larger sample size to detect a statistically significant difference, but the observation is interesting nonetheless. The incidence of hypotension, as well as that of pruritus, sedation, and mean maximum sensory level, was lower in the current study than in other reports.<sup>2,3,15</sup> A likely explanation for our low incidence of side effects was the use of a hyperbaric diluent. In most studies using the CSE technique, IT injections are made in dextrose-free solu-

tions. Dextrose-containing solutions have been shown to reduce side effects and shorten the duration of analgesia, especially when administered to patients in the sitting position.<sup>9,20</sup> Dextrose was used in this study to minimize nausea, which is reported with neostigmine administration.<sup>21</sup> Hood *et al.* found that utilizing dextrose-containing solutions markedly decreased the incidence of neostigmine related nausea probably by limiting cephalad drug spread.<sup>21</sup> Because we used hyperbaric solutions, we avoided the sitting position to preserve analgesia. IT hyperbaric solutions administered in the lateral position have not been shown to reduce analgesia,<sup>20</sup> and our results are in agreement. The 90-min duration of analgesia observed in our hyperbaric BF group is almost identical to other reports using bupivacaine-fentanyl dextrose-free solutions.<sup>17,18,22</sup> However, the lateral position may have increased nausea in patients who received neostigmine even though we sustained a 30° head elevation after the CSE procedure. Despite the longer duration of analgesia reported with the addition of neostigmine, the increased incidence of nausea may make it unacceptable for routine use in obstetrics.

In addition to nausea, motor weakness is also associated with neostigmine, but at doses exceeding 100  $\mu\text{g}$  in volunteers.<sup>21</sup> In the present study, patients who received IT neostigmine had a 40% incidence in mild lower-extremity weakness (able to bend knee but not raise leg) compared with 7% in the BF control group. Although this was not statistically significant, it may be clinically relevant and could interfere with ambulation. Patients in this study did not ambulate during labor, but all of them,

except one, walked to the delivery room with minimal assistance. Furthermore, the labor durations and characteristics were similar among groups, suggesting minimal motor-related interference.

In summary, the CSE technique may offer advantages over standard labor epidural analgesia because of the rapid onset, greater reliability in producing quality analgesia, and less motor block. A major disadvantage—the limited duration—may be overcome with the development of longer-acting analgesic agents or multidrug combinations. We found that the combination of clonidine and neostigmine increased the duration of labor analgesia by 83% when added to IT BF but was associated with more nausea. Multiple drug combinations may be useful in extending labor analgesia as part of the CSE technique; however, caution must be exercised to prevent drug contamination and dilution errors, and larger studies are needed to further evaluate side effects.

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