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Analgesic and Hemodynamic Effects of Intrathecal Clonidine as the Sole Analgesic Agent during First Stage of Labor

A Dose–Response Study

Astrid Chiari, M.D., Christine Lorber, M.D.,* James C. Eisenach, M.D.,† Eckart Wildling, M.D.,* Claus Krenn, M.D.,* Ana Zavrsky, M.D.,* Christian Kainz, M.D.,‡ Peter Germann, M.D.,§ Walter Klimscha, M.D.‖*

Background: **Intrathecal clonidine produces dose-dependent postoperative analgesia and enhances labor analgesia from intrathecal sufentanil. The authors evaluated the dose–response potency of intrathecally administered clonidine by itself during first stage of labor with respect to analgesia and maternal and fetal side effects.**

Methods: **Thirty-six parturients requesting labor analgesia were included in this prospective, randomized, double-blind study. Parturients with < 6 cm cervical dilatation received either 50, 100, or 200 μg intrathecal clonidine. The authors recorded visual analog pain score (VAPS), maternal blood pressure and heart rate, ephedrine requirements, and sedation at regular intervals and fetal heart rate tracings continuously. Duration of analgesia was defined as time from intrathecal clonidine administration until request for additional analgesia.**

Results: **Clonidine produced a reduction in VAPS with all three doses. The duration of analgesia was significantly longer in patients receiving 200 μg (median, 143; range, 75–210 min) and 100 μg (median, 118; range, 60–180 min) than 50 μg (median, 45; range, 25–150 min), and VAPS was lower in the 200-μg than in the 50-μg group. In the 200-μg group, hypotension required significantly more often treatment with ephedrine than in the other groups. No adverse events or fetal heart rate abnormalities occurred.**

Conclusions: **Fifty to 200 μg intrathecal clonidine produces dose-dependent analgesia during first stage of labor. Although duration and quality of analgesia were more pronounced with 100 and 200 μg than with 50 μg, the high incidence of hypotension requires caution with the use of 200 μg for labor analgesia. (Key words: α-Adrenergic agonist; obstetric; pain; spinal injection.)**

EPIDURAL local anesthetics[1] or intrathecal opioids[2,3] can provide effective labor analgesia but may also cause unwanted side effects such as motor blockade, hypotension, and respiratory depression in some cases, with possible fetal compromise. The α_2-adrenergic agonist clonidine produces analgesia by a different mechanism, mimicking the effect of endogenously released norepinephrine to stimulate postsynaptic α_2 receptors in the spinal cord. Intrathecal[4] and epidural[5,6] clonidine produces dose-dependent analgesia in patients with postoperative and neuropathic cancer pain. Side effects of neuraxial clonidine include hemodynamic depression and sedation but not respiratory depression or motor block.[7] Epidural and intrathecal clonidine do not produce adverse maternal or fetal effects in sheep in doses up to 10 μg/kg.[8,9] Clonidine added to epidural local anesthetics prolongs and intensifies labor analgesia[10] and does not affect fetal outcome. Opioids and α_2-adrenergic agonists produce synergistic antinociceptive interactions at the spinal level in rodents[11] and if this is also true in humans, a combination of low doses of both drugs would yield a good and long-lasting analgesic effect with minimal side effects. A significant prolongation of the duration of analgesia from the combination of clonidine and intrathecal sufentanil has been recently described during early first stage of labor.[12,13]

For future comparisons of equianalgesic doses of intra-

* Staff Anesthesiologist, Department of Anesthesiology and General Intensive Care, University of Vienna, Austria.

† F. M. James III Professor of Anesthesiology, Wake Forest University, Winston-Salem, North Carolina.

‡ Associate Professor, Department of Gynecology and Obstetrics, University of Vienna, Austria.

§ Associate Professor, Director of Obstetric Anesthesia, Department of Anesthesiology and General Intensive Care, University of Vienna, Austria.

‖ Associate Professor, Department of Anesthesiology and General Intensive Care, University of Vienna, Austria.

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Address reprint requests to Dr. Chiari: Department of Anesthesiology and General Intensive Care, University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Address electronic mail to: astrid.chiari@univie.ac.at

thecal clonidine with other drugs like opioids or local anesthetics during labor, dose–response relationships for analgesic as well as side effects of the single drugs during labor are warranted. These have been established for intrathecal sufentanil,[14,15] but not for intrathecal clonidine in laboring parturients. In addition, effects of intrathecal clonidine alone on the fetal heart rate (FHR) and uterine activity pattern have not previously been examined. The purpose of the current study was, therefore, to evaluate the dose–response potency of intrathecal administered clonidine by itself during first stage of labor with respect to analgesia and maternal and fetal side effects.

Methods

After institutional review board approval and written informed consent, 36 women at term pregnancy (American Society of Anesthesiologists physical status I or II; gravida 1 or 2) were recruited for this double-blind prospective study. Only patients with singleton pregnancies and vertex presentation who were in established labor and requesting analgesic medication, with a cervical dilatation < 6 cm and normal FHR tracings were enrolled. Each patient was randomized when she requested labor analgesia to receive one of the three intrathecal study solutions: 50, 100, or 200 μg clonidine (Boehringer Ingelheim, Ingelheim, Germany) in a total volume of 4 ml. The solutions were prepared using 0.9% saline by the hospital pharmacy and coded. Solution of clonidine in saline is isobaric at room temperature but slightly hypobaric compared with cerebrospinal fluid (CSF) at body temperature.[16] The anesthesiologist performing the block and the investigator were blinded to the clonidine dose administered.

Each patient received an intravenous bolus of at least 10 ml/kg Ringer's solution before initiation of analgesia, which was performed using the combined spinal epidural technique. With the patient in the sitting position, the epidural space was located at the L2–L3 or L3–L4 interspace with an 18-gauge epidural needle using the loss of resistance to saline technique. A 26-gauge Whitacre spinal needle (Espocan, Braun, Melsungen, Germany) was inserted through the epidural needle, clear free-flowing CSF was identified, and the study solution was injected through the spinal needle. The spinal needle was removed, and a 20-gauge epidural catheter was inserted 3 cm into the epidural space. To detect accidental intravascular or intrathecal placement of the catheter, aspiration from the epidural catheter was performed, but no epidural local anesthetic test dose was administered at this time. The epidural catheter was secured, and the patient positioned supine with slight head elevation and left uterine displacement. Time elapsed from intrathecal drug administration until the parturient was positioned in bed was around 5 min in all patients.

Pain at the peak of a contraction was assessed with a 10-cm visual analog pain score (VAPS) immediately before combined spinal epidural placement, every 5 min for 30 min and then every 15 min until request for further analgesic drug. Maternal blood pressure and heart rate were measured at the same intervals. Hypotension was defined as a systolic blood pressure < 90 mmHg or a 20% decrease from baseline and was treated immediately with a fluid bolus or intravenous ephedrine as required. At the same times, degree of somnolence was assessed using a four-point ordinal scale for sedation (1 = wide awake and alert; 2 = awake but drowsy, responding to verbal stimulus; 3 = arousable, responding to physical stimulus; and 4 = not arousable, not responding to physical stimulus). Other side effects such as pruritus, nausea, vomiting, or any other discomfort were also recorded at these times. When additional analgesia was requested, patients received epidural bupivacaine as per usual clinical routine for the remainder of their labor and the study protocol and data collection during labor were terminated. We defined duration of analgesia as time from injection of the study solution until the patient requested additional analgesia.

All patients had continuous external electronic FHR and tocodynamometric monitoring throughout the study period. FHR and uterine activity tracings from 20 min before until initiation of epidural analgesia were analyzed by a perinatologist blinded to the dose of the study solution. Tracing analysis included baseline FHR, number of accelerations per 20 min, long-term variability, decelerations (early, late, and variable), and number of uterine contractions per 20 min. The requirement for oxytocin augmentation, an instrumented (forceps) or cesarean delivery, and neonatal Apgar scores were also recorded. Patients were seen daily for 5 days to inquire about any postpartum problems including headache.

Statistical Analysis

Data are expressed as mean $\pm$ SD or median and range, as indicated. Two way analysis of variance (ANOVA) for repeated measurements was used to assess changes over time within as well as between groups. For comparison

Table 1. Patient Characteristics

	50 μg	100 μg	200 μg
Age (yr)	26 ± 5.6	24 ± 5.2	28 ± 7.2
Height (cm)	161 ± 5.7	167 ± 5.1*	163 ± 4.9
Weight (kg)	75 ± 11	82 ± 15	72 ± 10
Gestational age (wk)	39.7 ± 1.2	40.8 ± 1	40.1 ± 2.2
Para 0/1 (%)	58/42	75/25	58/42
Oxytocin (%)	42	42	33
Cervical dilatation (cm)	4 ± 1	4 ± 1	4 ± 1
Baseline VAS	9.6 ± 0.9	8.7 ± 1.1	9.2 ± 0.8

Data are mean ± SD or percentage of the population.

* $P < 0.05$ *versus* 50 μg.

of raw data between groups as well as duration of analgesia, one-way ANOVA was performed with *post hoc* analysis (Scheffé) to allow for multiple comparisons. Paired Student *t* test was performed to make single comparisons of pre- with posttreatment data from the FHR tracings. For evaluation of sedation, time from intrathecal drug administration until delivery and Apgar scores, the Kruskal-Wallis test with Bonferroni correction allowing for multiple comparisons was performed as indicated. Proportional data were evaluated using the chi-square test. A P value < 0.05 was considered significant.

Results

Of the 36 patients enrolled in the study, 12 were assigned to each group. Participants in this study did not differ in most demographic variables, gestational age, parity, percentage receiving oxytocin, baseline VAPS, or cervical dilatation at the time when the intrathecal study solution was administered (table 1). Patients in the 100-μg group were found to be significantly taller (6 cm) than patients in the 50-μg group, although this difference was irrelevant.

Intrathecal clonidine provided a significant reduction in VAPS for parturients in all three groups (fig. 1; $P < 0.001$). Onset of analgesia was similar among groups. Pain scores were significantly smaller 25 and 30 min after intrathecal clonidine administration in the 200-μg group compared with those in the 50-μg group (fig. 1). A reduction in pain score of 70% from baseline was reported by 5 of 12 patients in the 50-μg group, 8 of 12 patients in the 100-μg group, and 11 of 12 patients in the 200-μg groups. This difference between groups was statistically significant ($P < 0.05$). Analgesic duration in the 50-μg group was shorter than in the 100-μg and 200-μg groups (fig. 2). Blood pressure decreased significantly following clonidine injection in all groups (fig. 3A). Although onset of hypotension compared with baseline occurred earlier after higher clonidine doses, blood pressure was not significantly different among groups over the time. Maximum reduction of mean arterial blood pressure in individual patients occurred within 1 h after intrathecal clonidine administration in all cases (table 2), and all episodes of decreased blood pressure were easily reversed by supplemental fluid and ephedrine administration. As indicated, maximum decrease in mean arterial

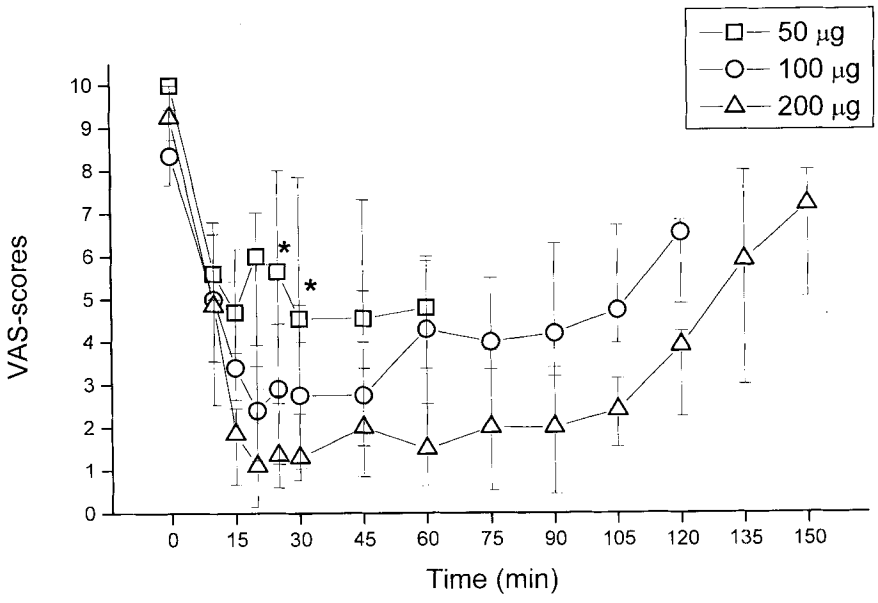

Fig. 1. Visual analog pain scores (median, 25th, and 75th percentile) after injection of 50 μg, 100 μg, and 200 μg intrathecal clonidine (n = 12 in each group). Pain scores decreased significantly in all groups from baseline ($P < 0.001$, ANOVA for repeated measurements). *Visual analog pain scores at respective time points were significantly lower in the 200-μg than in the 50-μg group.

Fig. 2. Duration of analgesia provided by the different doses of intrathecal clonidine. Horizontal lines represent medians. *Duration of analgesia was significantly longer in the 100-μg and 200-μg groups compared with the 50-μg group ($P < 0.001$, one-way ANOVA followed by *post hoc* test with Scheffé).

blood pressure was significantly greater in the 200-μg group than in the 50-μg group ($P < 0.05$), and ephedrine administration was required significantly more often in the 200-μg group than in the lower dose groups ($P < 0.05$; table 2). Similarly, maternal heart rate decreased significantly from baseline in the 100-μg and 200-μg groups, but not in the 50-μg group (fig. 3B). Again, there was no difference in heart rate over the time among groups. Maximum reduction in heart rate occurred up to 90 min after intrathecal clonidine (data not shown), but all episodes resolved spontaneously, and none of these parturients required atropine treatment.

Intrathecal clonidine produced sedation at all doses studied. Starting at 15 min after intrathecal clonidine injection, sedation scores were increased in a dose-dependent manner (fig. 4; $P < 0.05$). Although we did not actively assess motor function in this study, all patients could move their legs easily and reported normal sensation without numbness. Patients in all groups could micturate spontaneously during the period of clonidine analgesia. No patient was allowed to walk during the study period due to the need for continuous maternal and fetal monitoring for safety reasons. None of the parturients reported any nausea, vomiting, or itching, but dryness of the mouth was observed by 1 of 12, 2 of 12, and 3 of 12 patients in the 50-μg, 100-μg, and 200-μg groups, respectively. Daily questioning for 5 days postpartum revealed no case of postdural puncture headache.

There was no significant difference among groups for number of participants whose labors were induced or required oxytocin augmentation (2–20 mU/min). There was no difference in fetal variables between observation periods before and after intrathecal clonidine administration (table 3). All FHR decelerations prior to and after intrathecal clonidine administration were transient and no fetus experienced severe bradycardia. None of the FHR changes seen after intrathecal clonidine administration were considered clinically significant, and none resulted in intervention for fetal compromise. No episodes of uterine hyperstimulation or decreased uterine activity were noted after intrathecal clonidine. The progress of labor as indicated by the time of intrathecal injection to delivery (table 4), was similar among groups. The number of operative deliveries was similar for the three groups (table 4). Indications for cesarean section were cephalopelvic disproportion, slow progress of labor, *abruptio placentae,* and twisted umbilical cord. All operative and instrumental deliveries were performed after the analgesic effect of the clonidine dose had disappeared and epidural analgesia had been established. Apgar scores were within normal range in all neonates.

Discussion

This is the first study showing that intrathecal clonidine by itself produces dose-dependent analgesia

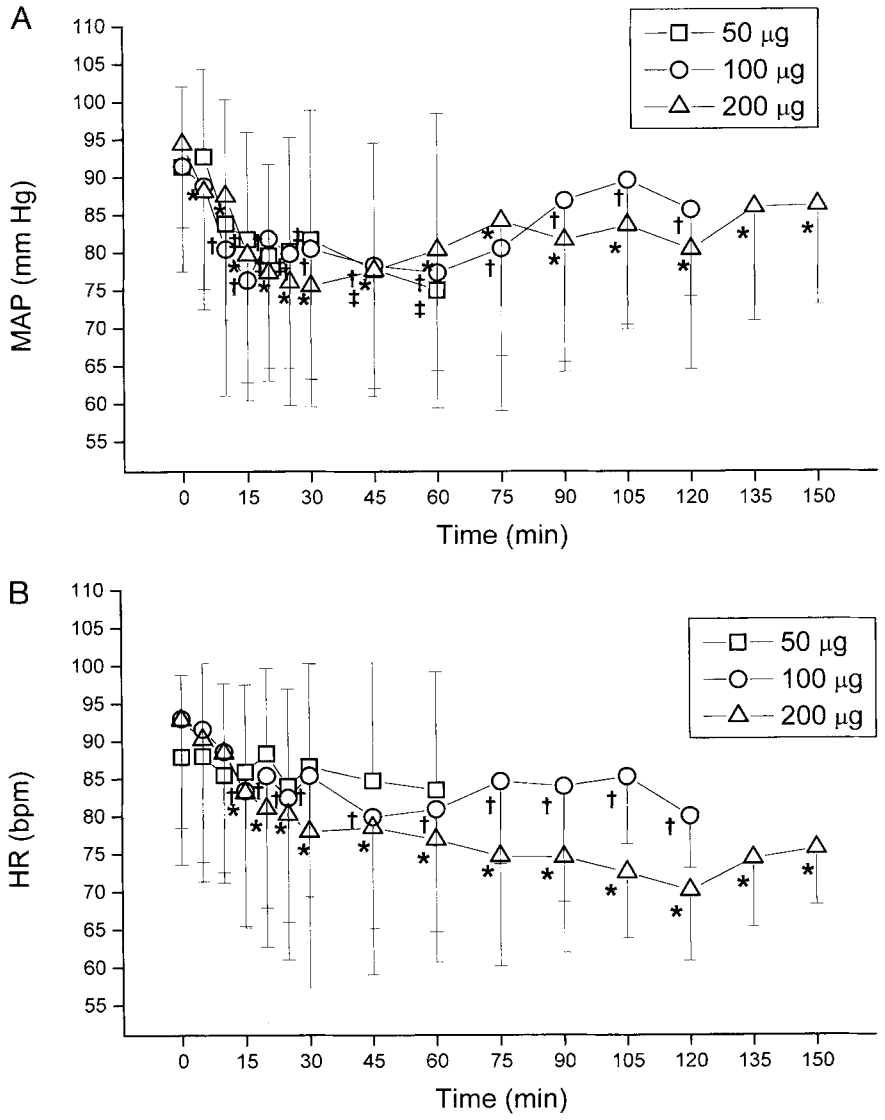

Fig. 3. (*A*) Mean arterial blood pressure (MAP) decreased significantly from baseline in all groups after injection of 50 μg, 100 μg, and 200 μg intrathecal clonidine. Onset time of this decrease was dose-dependent. Significant decrease from baseline: ‡50 μg ($P < 0.05$), †100 μg ($P < 0.01$), and *200 μg ($P < 0.01$). Data are mean ± SD. (*B*) Heart rate (HR) decreased after injection of 100 μg and 200 μg intrathecal clonidine. Significant decrease from baseline: †100 μg ($P < 0.01$) and *200 μg ($P < 0.05$). Data are mean ± SD.

for pain during first stage of labor. The current study determined that a dose of 50 μg intrathecal clonidine provides labor analgesia by itself, although degree and duration of analgesia were significantly greater with the larger doses, but also accompanied by hypotension.

Analgesia

Intrathecal and epidural administration of α_2-adrenergic agonists prolong and intensify labor analgesia from local anesthetics[17,18] and opioids.[12,13,19] However, with the exception of an early report describing epinephrine as a sole analgesic for labor,[20] no information has been available regarding the dose-response relationship of intrathecal α-adrenergic agonists in this clinical setting.

This is the first study to demonstrate that intrathecal clonidine alone produces dose-dependent analgesia for pain during the first stage of labor. We determined that a dose of 50 μg intrathecal clonidine provides moderate analgesia to labor pain, although degree and duration of analgesia were significantly more satisfactory with 100 μg and 200 μg. The 200-μg dose, however, did not offer advantages over 100 μg with respect to duration or intensity of analgesia. We found a shorter duration of pain relief than in a study by Gautier *et al.*,[12] wherein 30 μg intrathecal clonidine alleviated labor pain for about

Table 2. Decrease in MAP

	50 μg	100 μg	200 μg
Baseline MAP (mmHg)	91 ± 11	92 ± 14	94 ± 11
Lowest MAP (mmHg)	77 ± 14	70 ± 16	70 ± 15
Maximal decrease from baseline (%)	−16 ± 13	−24 ± 12	−25 ± 14*
Time of maximal decrease (min)	20 (10–25)	25 (5–45)	22.5 (10–60)
Intravenous fluid (ml)	542 ± 542	773 ± 343	792 ± 721
Ephedrine (% of patients)	16	8	58†

Data are mean ± SD, median (range), or percentage of the population.

*$P < 0.05$ *versus* 50 μg.

†$P < 0.05$ *versus* 50 and 100 μg.

1 h. Different methodologies in pain assessment and labor management may account for these discrepancies. First, the degree of reduction in VAPS indicating sufficient pain relief is variable among different investigators. Gautier *et al.*[12] did not provide VAPS during the period of "adequate analgesia" of their patients, making a direct comparison difficult. Whereas a 50% reduction in VAPS has been used to indicate successful analgesia during labor,[10,18] other authors define criteria as a VAPS ≤ 25 mm.[13,15] Second, we measured time from intrathecal drug injection until additional analgesia was requested by the parturient rather than when it was administered. The continuous presence of the anesthesiologist with the patient in our study may have encouraged earlier reporting of pain. Third, oxytocin-augmented labor is known to be associated with more painful contractions, depending on the administered oxytocin dose. Unfortunately, Gautier *et al.*[12] do not provide these doses and therefore the possibility of different oxytocin regimens, which may account for different pain levels, cannot be excluded.

Intrathecal clonidine, used as the sole analgesic agent after cesarean section,[4] provided dose-dependent analgesia with 150 μg relieving postoperative pain for 6 h, compared with only 2.5 h with 200 μg in our study for labor pain. It is possible that different qualities of pain may account for that difference, since labor pain increases with progression of labor, but postoperative pain has a tendency to decrease over time. As labor progresses and the nature of labor pain turns from visceral into somatic, the analgesic effect of opioids without local anesthetic effects decreases.[21] Although clonidine itself has weak local anesthetic properties in

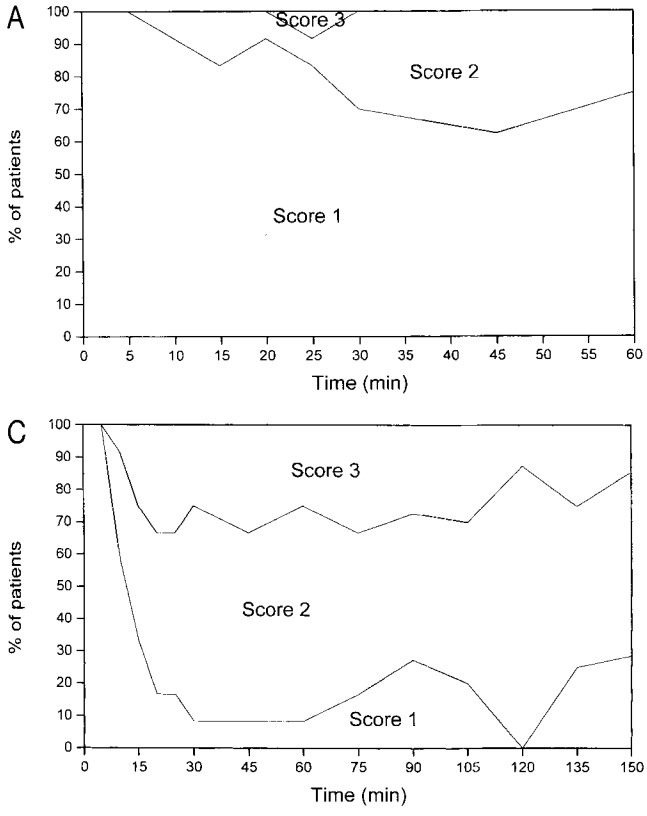

Fig. 4. Sedation scores after administration of (*A*) 50 μg, (*B*) 100 μg, and (*C*) 200 μg intrathecal clonidine. Intrathecal clonidine produced sedation in all groups. Significant dose-dependent differences (Kruskal-Wallis test with Bonferroni correction allowing for multiple comparisons) between groups occurred between 15 min and 30 min ($P < 0.05$).

Table 3. Fetal Heart Rate

	50 μg		100 μg		200 μg	
	Pre	Post	Pre	Post	Pre	Post
Baseline (bpm)	139 ± 7	143 ± 12	138 ± 2	135 ± 6	133 ± 11	128 ± 12
Number of accelerations/20 min	4 (1–5)	3 (1–5)	2 (1–3)	1 (1–3)	4 (1–6)	2 (1–5)
Decreased long-term variability (number of patients)	0	1	3	0	0	1
Decelerations (number of patients)						
Variable	0	2	1	2	3	1
Early	1	2	0	1	0	0
Number of uterine contractions/20 min	3 (2–4)	4 (3–5)	3 (3–8)	3 (2–8)	6 (4–6)	6 (3–9)

Data are mean ± SD, median (range), or number of patients. There were no differences between pretreatment and posttreatment in either group.

extremely high concentrations *in vitro*,[22] a direct inhibitory effect of clonidine on nerve conduction in clinical relevant doses used for spinal analgesia seems unlikely. Intrathecal clonidine *by itself* might, even at higher doses than we administered, therefore not be effective to treat more advanced labor pain since it has also failed to provide surgical anesthesia, despite doses up to 450 μg.[23]

Hemodynamics

As expected, blood pressure decreased significantly over time in each group (fig. 3A). Although analysis of variance showed no difference among groups, maximum blood pressure decrease from baseline was significantly more profound with the highest dose and consequently, ephedrine treatment was required significantly more often to restore adequate blood pressure in this group (table 2). Our data confirm results obtained by Gautier *et al.*[12] and Filos *et al.*,[4] who found maximum decreases of blood pressure by 15% after 30 μg intrathecal clonidine and 21% after 150 μg, respectively. Neuraxial clonidine decreases blood pressure by inhibiting preganglionic sympathetic neural activity in the spinal cord.[24] The degree of hypotension after neuraxial clonidine seems to be associated with the level of injection, with more profound hypotension occurring after injection at thoracic levels,[25,26] close to the preganglionic sympathetic neurons. In addition, activation of postsynaptic α_2 receptors in the brainstem and peripheral presynaptic α_2 receptors reduce sympathetic drive.

The greater hypotension with the largest clonidine dose is possibly due to rostral spread in CSF to thoracic levels and to the brainstem. Since clonidine becomes slightly hypobaric at body temperature,[16] rostral spread might have occurred with the parturient in the sitting position for a few minutes after intrathecal injection. Although clonidine's lipophilicity can be held as an argument against rapid rostral spread in CSF,[7] the lipophilic opioid sufentanil ascends rapidly from lumbar to cervical dermatomes in dogs.[27] However, the hemodynamic depression after all doses of intrathecal clonidine during labor requires careful monitoring for the entire period of analgesia.

Since clonidine is a mixed α_1-α_2-adrenergic agonist, high clonidine doses cause peripheral vasoconstriction, which results in a U-shaped hemodynamic dose-response curve.[4,26] Although Filos *et al.*[4] reported hemodynamic stability with 300 μg and 450 μg intrathecal

Table 4. Obstetric Results

	50 μg	100 μg	200 μg
Mode of delivery (number of patients)			
Vaginal	9	10	8
Instrumental	1	1	2
Cesarean section	2	1	2
APGAR [median (range)]			
5 min	10 (10)	10 (9–10)	10 (8–10)
10 min	10 (10)	10 (10)	10 (9–10)
Umbilical *p*H	7.25 ± 0.06	7.2 ± 0.07	7.24 ± 0.13
Time from intrathecal drug administration until delivery (min)	295 ± 151	325 ± 214	318 ± 200

Data are number of patients, medians (range), or mean ± SD.

clonidine, we chose to use 200 μg as our maximum dose, since intrathecal injected clonidine is rapidly absorbed into plasma,[28] which could yield plasma concentrations adequate to produce uterine artery vasoconstriction and decreased uterine blood flow.[29]

Heart rate also decreased significantly from baseline in the 100 μg and 200 μg groups (fig. 3B). Again, no differences between all groups were detected over the time. When administered after cesarean section, intrathecal clonidine minimally reduced heart rate in doses from 150 to 450 μg.[4] Clonidine decreases heart rate by a presynaptic mediated inhibition of norepinephrine release and by direct depression of atrioventricular nodal conduction,[30] and this decrease correlates with plasma clonidine concentrations.[28] However, no parturient in our study experienced sustained bradycardia and all episodes resolved spontaneously without treatment.

Clonidine will most likely be administered intrathecally in combination with either opioids or local anesthetics to provide labor analgesia, due to a positive analgesic interaction of these drugs in animals and humans.[12,13,31] Although clonidine does not produce an additional hypotensive effect when combined with local anesthetics,[7] there is a potential for exacerbating hemodynamic depression from the combination of intrathecal clonidine with opioids.[13,32] Hemodynamic side effects of this combination therapy warrant further investigation.

We found dose-dependent sedation in parturients from intrathecal clonidine doses of 50–200 μg, in agreement with studies by Filos *et al.*[4] This represents an α_2-adrenergic effect, since sedation from epidural clonidine can be reversed by the specific antagonist yohimbine in postoperative patients.[33] Experimental data show that the sedative-hypnotic effect of α_2-adrenergic agonists is caused by actions on the locus ceruleus.[34] We did not measure oxygen saturation or arterial blood gases in our study because clonidine does not cause respiratory depression by itself or in combination with opioids.[35,36]

In our study, doses up to 200 μg intrathecal clonidine for labor analgesia in healthy parturients were not associated with any FHR abnormalities, fetal distress, increased rate of operative delivery, or adverse neonatal outcome. Uterine activity and progress of labor were unaffected by 50–200 μg intrathecal clonidine, as times from intrathecal drug administration to delivery did not differ between groups and were similar to intrathecal sufentanil in other studies.[12,13] Nevertheless, the relatively small number of patients included in our study precludes the conclusion of safety for mother and neonate of intrathecal clonidine in obstetric analgesia.

In conclusion, 50–200 μg intrathecal clonidine produces a dose-dependent reduction in VAPS during first stage of labor. Duration and quality of analgesia were more pronounced with 100 μg and 200 μg than with 50 μg, but 200 μg doses were also associated with a high incidence of hypotension. Further studies are warranted to evaluate the safety for the possible clinical use of intrathecal clonidine as the sole analgesic during labor.

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