Obstetrical and Pediatric Anesthesia

Intrathecal clonidine prolongs labour analgesia but worsens fetal outcome: a pilot study

[L'administration intrathécale de clonidine prolonge l'analgésie du travail obstétrical, mais compromet l'évolution fœtale : une étude pilote]

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Purpose: Intrathecal clonidine prolongs total duration of spinal bupivacaine analgesia. However, there are contradictory reports about its effect on maternal blood pressure and only limited data are available on fetal and neonatal outcome. In this study, we evaluated the efficacy of spinal clonidine combined with ropivacaine and sufentanil and its effects on maternal and fetal outcome.

Methods: Fifty patients requesting combined spinal epidural analgesia for labour pain relief were randomly assigned to receive intrathecal ropivacaine 3 mg, sufentanil 1.5 µg with or without clonidine 30 µg. Onset time and duration of analgesia, visual analogue scores for pain, blood pressure, ephedrine requirements, heart rate, incidence of nausea, pruritus and motor blockade, umbilical artery pH, fetal heart rate abnormalities and Apgar scores were noted and analyzed.

Results: Patients receiving spinal clonidine had significantly longer lasting analgesia compared to patients treated without clonidine (122 ± 56 min vs 90 ± 36 min, $P < 0.05$). Clonidine-treated patients experienced a more pronounced decrease in mean arterial pressure as compared to patients treated without clonidine ($25 \pm 10\%$ vs $15 \pm 12\%$, $P < 0.05$). The groups also differed in ephedrine requirement (4.91 mg vs 0.75 mg, $P < 0.05$), number of new onset fetal heart rate abnormalities (28% vs 0% , $P < 0.05$) and umbilical artery pH (7.219 ± 0.096 vs 7.289 ± 0.085 , $P < 0.05$).

Conclusion: Intrathecal clonidine prolongs spinal analgesia with ropivacaine and sufentanil at the expense of maternal hypotension, worse fetal well being and worse neonatal umbilical artery pH. We do not recommend routine administration of spinal clonidine 30 µg to sufentanil and ropivacaine for labour pain relief.

Objectif : La clonidine intrathécale prolonge la durée totale de la rachianalgésie avec bupivacaine. Cependant, les résultats sont contradictoires au sujet de ses effets sur la tension artérielle maternelle et il n'y a que des données limitées sur l'évolution fœtale et néonatale. Nous voulions évaluer l'efficacité d'une rachianalgésie avec clonidine, ajoutée à la ropivacaine et au sufentanil, et ses effets sur l'évolution maternelle et fœtale.

Méthode : Cinquante patientes désirant une analgésie rachidienne et péridurale combinée pendant le travail ont été réparties au hasard et ont reçu 3 mg de ropivacaine intrathécale, 1,5 µg de sufentanil avec ou sans 30 µg de clonidine. Le délai d'installation et la durée de l'analgésie, les scores de douleur selon une échelle visuelle analogique, la tension artérielle, les besoins d'éphédrine, la fréquence cardiaque, l'incidence de nausées, le prurit et le blocage moteur, le pH de l'artère ombilicale, les anomalies de la fréquence cardiaque fœtale et l'indice d'Apgar ont été notés et analysés.

Résultats : L'analgésie avec clonidine rachidienne a duré significativement plus longtemps comparée à l'analgésie sans clonidine (122 ± 56 min vs 90 ± 36 min, $P < 0,05$). Les patientes traitées à la clonidine, comparées aux patientes sans clonidine, ont présenté une baisse plus prononcée de la tension artérielle moyenne ($25 \pm 10\%$ vs $15 \pm 12\%$, $P < 0,05$). Des différences intergroupes ont aussi été notées quant aux besoins d'éphédrine ($4,91$ mg vs $0,75$ mg, $P < 0,05$), au nombre d'anomalies de la fréquence cardiaque fœtale nouvellement installées (28% vs 0% , $P < 0,05$) et au pH de l'artère ombilicale ($7,219 \pm 0,096$ vs $7,289 \pm 0,085$, $P < 0,05$).

Conclusion : La clonidine intrathécale prolonge la rachianalgésie avec ropivacaine et sufentanil aux dépens de l'hypotension maternelle, d'une dégradation du bien-être fœtal et d'une modification du pH néonatal de l'artère ombilicale. L'administration rachidienne régulière de 30 µg de clonidine n'est pas recommandée comme supplément au sufentanil et à la ropivacaine pendant le travail obstétrical.

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COMBINED spinal-epidural (CSE) analgesia is popular for labour pain relief. CSE produces rapid onset analgesia with symmetrical spread. Furthermore, CSE reduces the required doses of analgesic drugs and preserves motor function.¹⁻³ Especially during late labour, CSE is particularly advantageous. Patient satisfaction is reported to be improved as compared to epidural analgesia.^{3,4}

Initial spinal analgesia is, however, of limited duration. Only 50% of women receiving a CSE during the late first stage of labour actually deliver during the spinal component of analgesia.⁵ Once spinal analgesia has worn off, epidural analgesia is required. Problems associated with the epidural catheter can occur, such as unilateral or patchy analgesia. The limited duration of initial spinal analgesia combined with problems associated with maintenance of epidural analgesia, have initiated the search for new combinations of analgesic drugs to prolong the duration of spinal analgesia without increasing side effects.

In recent years, clonidine, an α -2 adrenoreceptor agonist has been used to prolong spinal anesthesia. Chiari *et al.* noted that spinal clonidine in doses between 100 and 200 μ g produced effective analgesia but sedation and hypotension were common and often severe.⁶ Smaller doses of clonidine added to sufentanil alone successfully prolong analgesia but can induce hypotension especially if doses of 30 μ g or more are used.^{7,8} D'Angelo *et al.*,⁹ Paech *et al.*¹⁰ and Sia¹¹ examined the effects of clonidine added to intrathecally administered local anesthetics and opioids for labour analgesia. They could demonstrate a positive effect of clonidine on duration of spinal analgesia, although the difference did not reach statistical significance in the study by Paech *et al.*⁹⁻¹¹ D'Angelo *et al.*⁹ did not observe more hypotension in clonidine treated patients. However, Sia¹¹ and Paech *et al.*¹⁰ did. In 1998, Eisenach suggested that the intrathecal use of clonidine requires more investigation before it can routinely be used during spinal labour analgesia.¹²

We performed a double blind, randomized trial investigating the effects of CSE analgesia using intrathecal ropivacaine and sufentanil, with or without the addition of clonidine. We hypothesized that the addition of clonidine 30 μ g would increase the total duration of spinal analgesia, without an effect on maternal hemodynamics or fetal outcome. The addition of clonidine to intrathecal ropivacaine and sufentanil has not been studied previously.

Methods

Following institutional ethical approval and written patient informed consent, 50 healthy, term (> 36 weeks gestation), vertex presenting parturients of mixed parity in active labour and requesting analgesia were recruited to participate in this double-blind, randomized trial. Exclusion criteria were pre-term gestation (< 36 weeks), intra-uterine fetal death, multiple pregnancy, known or suspected fetal abnormalities, breech presentation and maternal ASA class III and IV. Maternal age, height, weight, cervical dilation, gestational age, type of labour, status of the membranes, use of oxytocin and medical history were recorded. The fetal heart rate (FHR) was recorded for 15 min prior to analgesia using external cardiotocography. Maternal blood pressure and heart rate during the last antenatal visit and just prior to analgesia were recorded. Pain was assessed using a visual analogue scale (VAS; 100 mm; 0 = no pain and 100 = worst pain imaginable) and recorded ten minutes prior to the CSE.

Following *iv* hydration with 1000 mL of lactated Ringer's solution, a CSE was performed at the L₃-L₄ interspace with the patient in the sitting position. The epidural space was located using the loss of resistance to saline technique with an 18-gauge Tuohy needle. Spinal puncture was performed using a 27-gauge pencil point needle. The spinal solution was given when spontaneous backflow of cerebrospinal fluid (CSF) occurred in the spinal needle and CSF could easily be aspirated. A 20-gauge epidural catheter was placed 5 cm in the epidural space. Intravascular or intraspinal placement of the catheter was checked by aspiration. No test dose was given. The catheter was secured and the patient was positioned in left lateral decubitus.

Patients were randomized to one of two study groups. Twenty-five patients received a spinal injection of ropivacaine 3 mg combined with sufentanil 1.5 μ g dissolved in 2 mL saline (ROSU-group). Twenty-five patients received a spinal injection of 2 mL saline containing ropivacaine 3 mg, sufentanil 1.5 μ g and clonidine 30 μ g (CLON-group). Vials were prepared by the hospital pharmacist following a computer generated list. The vials were numbered with numbers 1 to 50 and stored in the refrigerator at the labour and delivery suite. Each number corresponded either to the CLON-group or the ROSU-group, based on the computer generated list. The midwife, assisting with the block, randomly took one vial out of storage and offered it to the anesthesiologist performing the CSE. Midwives, anesthesiologists and patients were blinded to the drugs used for spinal analgesia.

If spinal analgesia did not produce satisfactory pain relief within 15 min, additional epidural analgesia

(ropivacaine 0.15% with 0.75 $\mu\text{g}\cdot\text{mL}^{-1}$ sufentanil, bolus of 5 mL) was given. Additional epidural top-ups were subsequently administered until satisfactory analgesia was achieved. However these patients were excluded from the study and their data were not used for further analysis. Satisfactory analgesia was defined as a VAS score for pain of less than 20 mm within 15 min following the intrathecal injection.

The first primary outcome variable was the duration of initial spinal analgesia. The duration of initial analgesia was defined as the time between the end of the spinal injection and the moment additional analgesia was requested by the patient. If the patients requested additional pain relief, patient-controlled epidural analgesia was initiated using a bolus of 4 mL with a lockout of 15 min. The epidural solution consisted of ropivacaine 0.15% and sufentanil 0.75 $\mu\text{g}\cdot\text{mL}^{-1}$.

The second primary outcome variable was the incidence of hypotension and the effect of spinal analgesia on maternal blood pressure. Hypotension was defined as a mean arterial pressure (MABP) decrease > 10%. Severe hypotension was defined as a decrease in MABP > 20%. We also recorded the lowest MABP following spinal analgesia and calculated the percentage decrease in arterial pressure.

Following initiation of analgesia, data were collected at regular time intervals until additional analgesia was requested. At this point the study stopped. The following data were collected: VAS for pain, block height, motor blockade, FHR, pruritus, nausea, maternal blood pressure, maternal heart rate (MHR) and the need for tocolytic drugs or ephedrine. Postpartum, maternal satisfaction was assessed using a VAS score (0 = totally unsatisfied, 100 = totally satisfied). Maternal side effects such as back pain, headache, etc., were recorded. Neonatal weight, Apgar scores and umbilical artery pH were recorded also.

Block height was tested using changes of sensory level to cold (ether). Motor block was quantified using the modified Bromage score (0 = no motor block, 1 = inability of straight leg raising, 2 = no knee flexion, 3 = no ankle or foot flexion). FHR and variations in FHR were monitored continuously using external cardiotocography and examined closely during a 15-min interval pre- and a 60-min post-puncture interval. FHR abnormalities considered were late decelerations (FHR < 100 beats $\cdot\text{min}^{-1}$ following a contraction) and/or bradycardia (FHR < 100 beats $\cdot\text{min}^{-1}$ for more than 90 sec). FHR abnormalities such as late decelerations, bradycardia or decreased variability were treated with oxygen, lateral decubitus and ephedrine if necessary.

TABLE I Demographic and obstetric data

	<i>ROSU-group</i> (<i>n</i> = 20)	<i>CLON-group</i> (<i>n</i> = 18)
Age (yr)	30.1 $\pm$ 4.5	29.9 $\pm$ 4.9
Height (cm)	165 $\pm$ 6	166 $\pm$ 6
Weight (kg)	82 $\pm$ 15	75 $\pm$ 13
Pregnancy duration (weeks)	39.6 $\pm$ 1.6	39.4 $\pm$ 1.7
Cervical dilatation (cm)	3.0 $\pm$ 1.0	3.3 $\pm$ 1.6
Nulliparous patients (<i>n</i>)	11	10
Induced labour (<i>n</i>)	12	12
Ruptured membranes (<i>n</i>)	7	8

Data are presented as mean $\pm$ standard deviation or number of patients (*n*). No statistically significant differences were observed. ROSU-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 μg sufentanil; CLON-group = patients randomized to combined spinal-epidural analgesia using ropivacaine 3 mg with 1.5 μg sufentanil and 30 μg clonidine.

TABLE II Analgesia and patient satisfaction

	<i>ROSU-group</i> (<i>n</i> = 20)	<i>CLON-group</i> (<i>n</i> = 18)
Onset time of analgesia (sec)	497 $\pm$ 295	355 $\pm$ 212
Duration of analgesia (min)	90 $\pm$ 36	122 $\pm$ 56*
VAS maternal satisfaction at one hour	91 $\pm$ 11	93 $\pm$ 11
VAS maternal satisfaction at 24 hr	82 $\pm$ 22	89 $\pm$ 13

Data are presented as mean $\pm$ standard deviation. **P* < 0.05 *vs* ROSU-group. ROSU-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 μg sufentanil. CLON-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 μg sufentanil and 30 μg clonidine. VAS = visual analogue scale.

Continuous variables were analyzed using analysis of variance and Scheffé's post hoc test or unpaired *t* testing whenever appropriate. Categorical data were analyzed using Fisher's exact test and Chi-square analysis. Data are presented as mean $\pm$ standard deviation, percent of group total or median with interquartile range. *P* < 0.05 was considered statistically significant.

Results

Seven women delivered before requesting additional analgesia (four in the CLON-group and three in the ROSU-group) and five women did not achieve adequate analgesia following the initial spinal dose (two in the ROSU-group and three in the CLON-group). Thus only 38 patients completed the study and only these results were used for final analysis. There were no differences in demographic and obstetric data

FIGURE 1 Visual analogue scale score for pain in patients randomized to combined spinal epidural analgesia using either ropivacaine 3 mg with 1.5 µg sufentanil (ROSU-group) or ropivacaine 3 mg with 1.5 µg sufentanil and 30 µg clonidine (CLON-group). Data are presented as a mean $\pm$ standard deviation. No significant differences were observed.

between the two groups (Table I). The duration of spinal analgesia was significantly longer in the CLON-group compared to the ROSU-group ($P < 0.05$). There were no differences in onset time of analgesia (Table II). VAS scores for pain were similar between the groups (Figure 1). Maternal satisfaction one hour and one day after delivery was high in both groups.

MHR remained stable throughout the study period and was similar in both groups. Maternal blood pressure decreased significantly following intrathecal clonidine and was significantly lower in the CLON-group compared to the ROSU-group (Figure 2). Percentage change in arterial pressure was more pronounced in the CLON-group compared to the ROSU-group ($P < 0.05$; Table IV). Eleven patients in the CLON-group had a reduction in MABP of more than 20%, compared to only five patients in the ROSU-group ($P < 0.05$). More ephedrine was used in CLON-group patients ($P < 0.05$; Table IV).

More new onset FHR abnormalities were observed in the CLON-group ($P < 0.05$; Table III). Umbilical artery pH was 7.289 ± 0.085 in the ROSU-group and 7.219 ± 0.096 in the CLON-group ($P < 0.05$). However, no differences in Apgar scores at one, five or ten minutes were observed. The number of children with umbilical artery pH < 7.2 was also identical in the two groups (Table III). No differences in outcome of labour were observed. The incidence of pruritus and nausea was similar in both groups. Motor block did not occur in any patient.

FIGURE 2 Mean arterial pressures in patients randomized to combined spinal epidural analgesia using either ropivacaine 3 mg with 1.5 µg sufentanil (ROSU-group) or ropivacaine 3 mg with 1.5 µg sufentanil and 30 µg clonidine (CLON-group). Data are presented as a mean $\pm$ standard deviation. * $P < 0.05$ vs ROSU-group.

TABLE III Labour and fetal outcomes

	ROSU-group (n = 20)	CLON-group (n = 18)
Spontaneous delivery (n)	14	12
Neonatal weight (g)	3316 $\pm$ 433	3394 $\pm$ 673
Apgar < 7 (n)	1	3
Umbilical artery pH	7.289 $\pm$ 0.085	7.219 $\pm$ 0.096*
Umbilical artery pH < 7.200	3	5
FHR abnormalities (%)	0	28*

Data are presented as mean $\pm$ standard deviation or number of patients (n). * $P < 0.05$ vs ROSU-group. ROSU-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 µg sufentanil; CLON-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 µg sufentanil and 30 µg clonidine.

TABLE IV Maternal hemodynamics

	ROSU-group (n = 20)	CLON-group (n = 18)
Mean % decrease in mABP	15 $\pm$ 12	25 $\pm$ 10*
> 20% decrease mABP (n)	5	11*
> 30% decrease mABP (n)	3	4
Ephedrine (n)	2	5
Ephedrine (mg)	0.75 [0.00–0.00]	4.91* [0.00–7.5]

Data are presented as a mean $\pm$ standard deviation or number of patients (n). * $P < 0.05$ vs ROSU-group. mABP = mean arterial pressure; ROSU-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 µg sufentanil; CLON-group = patients randomized to combined spinal epidural analgesia using ropivacaine 3 mg with 1.5 µg sufentanil and 30 µg clonidine.

Discussion

The addition of clonidine 30 µg to intrathecal ropivacaine 3 mg and sufentanil 1.5 µg prolongs the duration of effective labour analgesia. Our results confirm previously published reports that clonidine significantly extends the duration of spinal analgesia.⁷⁻¹¹ The present investigation is the first to evaluate the effects of clonidine in association with intrathecal ropivacaine and sufentanil. Landau *et al.*¹³ previously reported that the addition of clonidine to epidural ropivacaine significantly prolonged epidural analgesia. Our results corroborate the previous observations that spinal clonidine enhances analgesia from various anesthetic agents. From the available literature, both spinal and epidural clonidine seem to prolong the duration of adequate labour analgesia, irrespective of the local anesthetic or opioid used.⁶⁻¹³

Considerable variation in the effect of clonidine on duration of labour analgesia has been observed in various studies. Methodological variations may explain why such differences have been observed. The timing of analgesia, the dose of local anesthetic and/or opioid, the type of opioid, the parity of patients and differences in patient education can all account for the observed variations.

Only four patients in the clonidine group delivered prior to epidural supplementation was required. This was similar to the patients treated without clonidine. Therefore, clonidine did not prolong analgesia beyond the need for epidural supplementation. Consequently, the observed differences in duration of spinal analgesia may be of little clinical benefit.

Unfortunately, our results demonstrate that spinal clonidine in a dose of 30 µg significantly influences maternal hemodynamics. Hypotension occurred more often and more ephedrine was required to restore maternal arterial pressure. This is in agreement with Sia¹¹ and Paech *et al.*¹⁰ who also noted that the combination of clonidine, bupivacaine and sufentanil has important effects on maternal hemodynamics. D'Angelo *et al.*⁹ and Owen *et al.*,¹⁴ however, did not note a significant increase in the incidence and severity of hypotension. Actually, this may have been the result of a small sample size, as they reported an increase in the incidence of hypotension, but the difference failed to reach statistical significance.

Apgar scores were unaffected by clonidine treatment in the studies by Sia,¹¹ D'Angelo *et al.*⁹ and Paech *et al.*¹⁰ Our results confirm these findings. However Apgar scores are a relatively crude measure of neonatal outcome and intrapartum hypoxia. In contrast to these studies, we also report on FHR changes following CSE and on umbilical artery blood

gases. More new onset FHR abnormalities developed following CSE. Importantly, neonates from clonidine-treated patients had significantly lower umbilical artery pH values compared to patients treated with plain ropivacaine and sufentanil. Previous investigations, studying the combination of intrathecal local anesthetic, opioid and clonidine failed to report such findings.⁹⁻¹¹ We cannot conclusively establish a causal relationship between the addition of clonidine to the spinal anesthetic and worse neonatal outcome. However we could not identify any other factors associated with low umbilical artery pH values in our trial. No correlation existed between low umbilical artery pH and parity, duration of labour, FHR abnormalities prior to initiation of analgesia, maternal co-existing disease, maternal fever, etc. We therefore assume that maternal hypotension due to spinal clonidine could be involved in worse neonatal outcome as compared to patients not treated with spinal clonidine.

We are aware that, as in previous studies, the present trial suffers from the limited number of patients recruited and randomized. Based on a 30-min difference in duration of analgesia (as determined in our trial), post hoc power analysis reveals a power of 0.65 if data from all 50 scheduled patients (25 in each group) could have been used for data analysis. Since data from only 38 patients were used for the final analysis, the power of the study is 0.50. This pilot trial was designed to evaluate the effectiveness and safety of intrathecal clonidine in our patient population and in our practice before embarking on a more extensive trial including a statistically useful number of patients. In order to reach a power of 0.90, 48 patients completing the trial would be required in each group. This would mean, based on our dropout rate of 24%, that we should include approximately 125 patients. Our preliminary results provide no solid basis to perform such a trial since significantly more maternal hypotension and worse fetal outcome was associated with the use of clonidine. Furthermore, we question the clinical importance of a 30-min increase in duration of initial spinal analgesia.

We conclude that intrathecal clonidine 30 µg prolongs analgesia provided by a ropivacaine and sufentanil mixture. We question the clinical significance of the observed 30-min extension of spinal analgesia. We feel it is justified to warn against the routine use of intrathecal clonidine since maternal hypotension, signs of intrapartum hypoxia and acidosis and worse neonatal outcomes were observed following its use. We do not recommend the routine addition of intrathecal clonidine 30 µg to sufentanil 1.5 µg and ropivacaine 3 mg for pain relief during labour.

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