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ORIGINAL ARTICLE

Epidural neostigmine and clonidine improves the quality of combined spinal epidural analgesia in labour

A randomised, double-blind controlled trial

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BACKGROUND In labour analgesia, the combination of epidural clonidine and neostigmine as adjuvants to local anaesthetics and opioids is under investigation to provide a longer duration of initial spinal analgesia with local anaesthetics and/or opioids.

OBJECTIVES To evaluate the quality of analgesia with epidural neostigmine and clonidine, added to initial spinal analgesia, and to test the hypothesis that the incidence of breakthrough pain could be reduced and patient satisfaction improved.

DESIGN Randomised double-blind controlled trial.

SETTING University Hospital of Leuven in Belgium.

PARTICIPANTS One hundred healthy, term ($\geq$37 weeks) parturients.

INTERVENTION All patients received initial spinal analgesia with ropivacaine and sufentanil. Fifteen minutes after spinal injection, 10 ml of a solution containing neostigmine 500 μg and clonidine 75 μg, or 10 ml physiological saline alone was injected epidurally. Patient-controlled analgesia with ropivacaine and sufentanil was then made available.

MAIN OUTCOME MEASURES The incidence of breakthrough pain, patient satisfaction and hourly ropivacaine use.

RESULTS Ropivacaine use decreased significantly by 32.6% in the neostigmine/clonidine (NC) group [11.6 ± 4.2 vs. $17.2 \pm 5.3\,mg\,h^{-1}$ in the NC group and placebo (P) group, respectively] and a significant difference in breakthrough pain was noted; only 3% in group NC had breakthrough pain compared with 36% in group P. Patient satisfaction was better after 1 h in group NC compared with group P ($P<0.05$) but not different after 24 h (visual analogue scale score 97 ± 5 vs. 88 ± 11 mm after 1 h; 92 ± 10 vs. 90 ± 14 mm after 24 h).

CONCLUSION The administration of epidural clonidine and neostigmine as adjuvants, following spinal injection of local anaesthetic, improves the quality of analgesia with less ropivacaine consumption, higher patient satisfaction 1 h after administration and a decrease in breakthrough pain compared to standard combined spinal and epidural analgesia and patient-controlled epidural analgesia with ropivacaine and sufentanil.

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Introduction

Neostigmine and clonidine are used frequently in clinical practice. During the last two decades, they have been used intrathecally and epidurally for labour analgesia.[1] The spinal route of administration has side-effects: clonidine can produce sedation and hypotension,[2–4] and neostigmine can cause moderate-to-severe nausea.[5,6] The epidural administration of these drugs seems to cause fewer side-effects and produces prolonged initial analgesia.[7,8]

Combined spinal and epidural analgesia (CSE) is the default labour analgesia technique in our department. We demonstrated that initial spinal labour analgesia can be prolonged and local anaesthetic consumption can be

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reduced if a bolus of clonidine and neostigmine is administered epidurally immediately following the spinal dose.[9] In that study, we were unable to assess whether the quality of analgesia was positively influenced in terms of improved patient satisfaction and decreased breakthrough pain because we intended to look for breakthrough pain and, therefore, did not immediately attach a patient-controlled epidural analgesia (PCEA) device after spinal injection to establish how long the first dose would work. In the present study, we tried to prevent breakthrough pain and, therefore, this study is methodologically different from our previous study. This study was designed to evaluate the effect of epidural clonidine and neostigmine on the quality of labour analgesia during CSE analgesia.

Methods

Ethical approval for this study was provided by the ethical committee of the Leuven University Hospital, Leuven, Belgium (Chairperson Professor Dr J. Vermylen; protocol number: ANE 11/2006-MVdV) on 8 January 2007. After obtaining written patient informed consent, 100 healthy, term (≥37 weeks) parturients who had requested regional analgesia during labour were asked to participate in this randomised, prospective, double-blind placebo-controlled trial. All were American Society of Anaesthesiologists (ASA) physical status class 1 or 2 and uncomplicated, vertex-presenting singleton pregnancies. All patients were primiparous.

Exclusion criteria were ASA classes 3 or 4, maternal height less than 150 cm, BMI more than 40 $kg\,m^{-2}$, fetus with known or suspected congenital abnormalities, gestational age less than 37 weeks, breech presentation, cervical dilatation more than 7 cm, visual analogue scale (VAS) for pain less than 50 mm, administration of parenteral or oral analgesics before the start of neuraxial anaesthesia or coagulation disorders.

Prior to initiation of analgesia, the following variables were recorded: maternal age, height, weight, cervical dilatation, gestational age, type of labour, status of the membranes, use of prostaglandins, use of oxytocin and medical history. The fetal heart rate (FHR) was recorded for 15 min before analgesia using external cardiotocography. Maternal blood pressure and heart rate during the last antenatal visit and just prior to analgesia were noted. Blood pressure and heart rate were measured with the patient in the full left lateral position. Pain was assessed using a VAS (0 mm = no pain and 100 mm = worst pain imaginable) and recorded 10 min prior to the CSE.

Before initiation of the neuraxial block, a fluid load consisting of lactated Ringer's solution in a volume of 10 $ml\,kg^{-1}$ was administered intravenously. The epidural space was identified at the L3–4 or L4–5 interspace with an 18-gauge Tuohy needle using the loss of resistance to saline technique with the patient sitting. A 27-gauge pencil-point spinal needle perforated the dura via the Tuohy needle. When free-flowing cerebrospinal fluid (CSF) was obtained, 2.5 ml of ropivacaine 0.175% with sufentanil 0.75 $\mu g\,ml^{-1}$ was injected intrathecally. A 20-gauge epidural catheter was inserted and a length of 4 cm was left in the epidural space. No epidural test dose was given. An aspiration test was performed. If CSF or blood was aspirated, the patient was excluded from the study and the catheter was resited.

PCEA was started immediately after insertion of the epidural catheter with the possibility of giving a bolus of 4 ml ropivacaine 0.175% with sufentanil 0.75 $\mu g\,ml^{-1}$ and a lockout period of 15 min.

Adequate pain relief was defined as a VAS score for pain of less than 10 mm. If pain relief was adequate at 15 min, the study solution was administered epidurally. If pain relief was inadequate 15 min after initiation of spinal analgesia, patients were excluded from the study and an additional 10-ml bolus of ropivacaine 0.175% with sufentanil 0.75 $\mu g\,ml^{-1}$ was administered epidurally.

The epidural study solution contained 10 ml physiological ('normal'; 0.9%) saline (placebo group; group P) or a mixture of clonidine 75 μg and neostigmine 500 μg dissolved in 10 ml saline (group NC). Study solutions were prepared by the hospital pharmacist and numbered from 1 to 100. Patients were assigned randomly to one of the two study groups. A person who was not involved in the study opened a sealed envelope containing a number and drew up the study medication by opening the vial corresponding to the number in the sealed envelope. Patient, midwife, obstetrician and anaesthetist were blinded to the identity of the study solution.

Pain was assessed at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min after the end of the spinal injection and then every 60 min until delivery. Data are reported for up to only 2 h after spinal injection because many of the patients delivered within 2 h after injection. Groups became smaller and smaller with time and there were no longer any differences. Pain was assessed at the moment the patient reported breakthrough pain. Breakthrough pain was defined as a VAS for pain of at least 20 mm, which did not improve following a PCEA bolus. If breakthrough pain occurred, an additional 10 ml bolus of ropivacaine 0.175% with sufentanil 0.75 $\mu g\,ml^{-1}$ was administered epidurally. The total local anaesthetic consumption was noted from the start of the spinal injection until after delivery. The hourly rate was calculated by dividing the total dose of ropivacaine administered by the number of minutes the patient was in labour from the start of spinal injection to the moment of delivery of the fetus. The total dose of ropivacaine included the spinal dose, the ropivacaine used using the PCEA device and ropivacaine administered through top-ups.

The FHR was recorded 10 min before, during and for 30 min after the CSE.

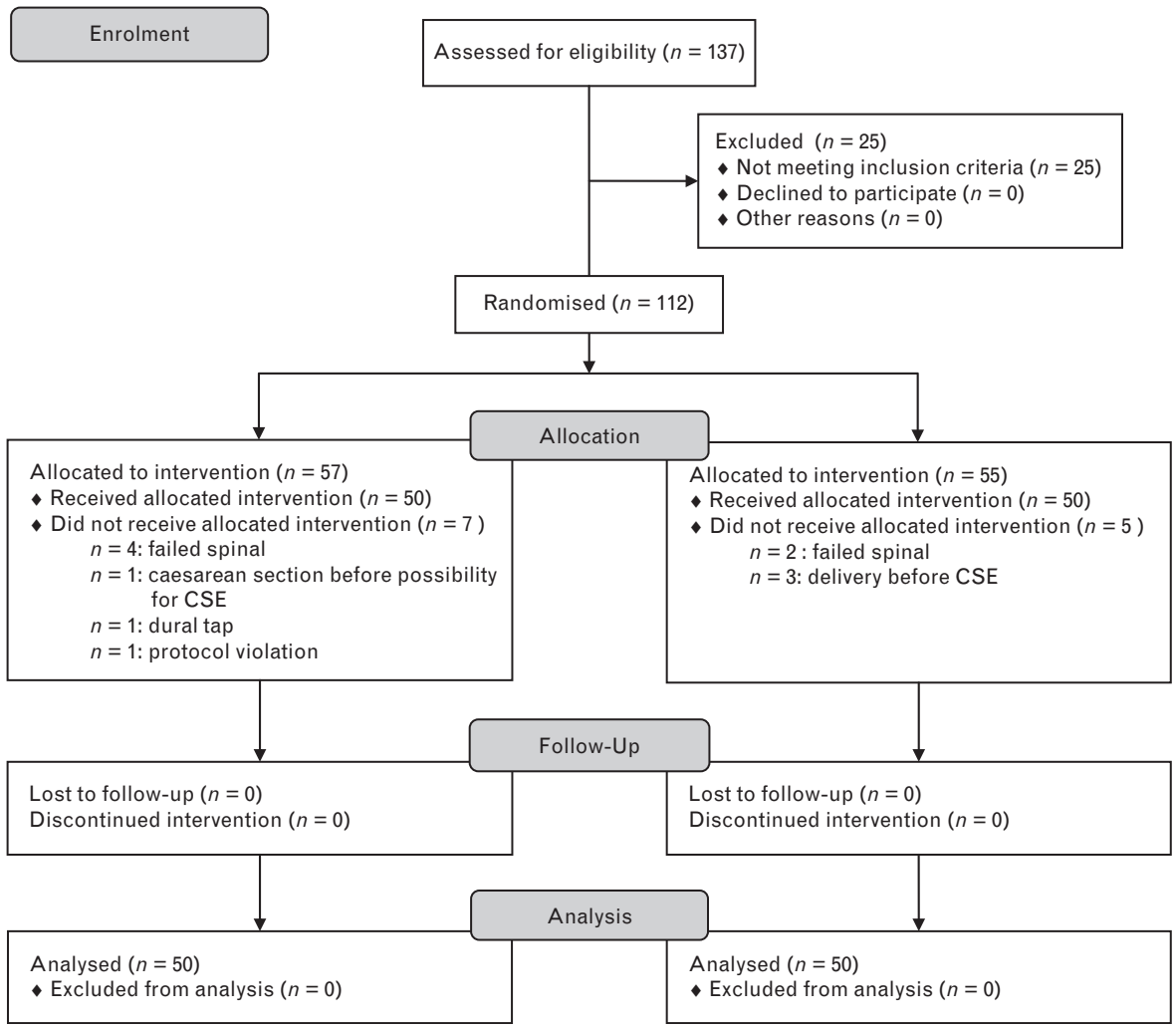
Our first primary outcome parameter was the number of episodes of breakthrough pain. Second, we assessed the total consumption of local anaesthetic (ropivacaine). Third, we evaluated the satisfaction of our patients using the VAS score.

Other outcome parameters were fetal health (cardiotocography), Apgar scores (at 1, 5 and 10 min after birth), duration of labour, type of delivery (all patients with a caesarean section were enrolled according to an intention-to-treat protocol) and the incidence of side-effects such as nausea, pruritus, sedation, motor block (using the modified Bromage score), maternal hypotension (defined as a decrease in SBP of more than 20%), bradycardia and postdural puncture headache (PDPH).

Auditing our own practice demonstrated that at least one episode of breakthrough pain occurred in about 70% of patients when CSE with PCEA is used. To be clinically relevant, our hypothesis was that the addition of clonidine and neostigmine should reduce the incidence of breakthrough pain to 25% or less Power analysis revealed that we needed to study 29 patients per group to detect a difference in breakthrough pain incidence from 70 to 25% with an α-error of 0.05 and β-error of 0.8. We assessed 137 patients and allocated 112 to one of the two treatment groups to allow for drop-outs (Fig. 1). We analysed data from 50 patients in each group.

Continuous variables were analysed statistically using analysis of variance and Scheffé's post-hoc test whenever appropriate. Categorical data were analysed using the Fisher's exact test and χ^2 analysis. Data are presented as mean $\pm$ standard deviation, % of group total or median

Fig. 1



CONSORT flow diagram of study. CSE, combined spinal and epidural block.

Table 1 Demographic and obstetric data

	Neostigmine and clonidine group (group NC)	Placebo group (group P)
Age (years)	29.4 ± 5.3	29.8 ± 5.1
Weight (kg)	84 ± 15	80 ± 10
PMA (postmenstrual age in weeks)	39.5 ± 1.4	39.8 ± 1.4
Cervical dilatation (cm)	3.6 ± 0.9	3.4 ± 1.2
C-section foetal distress (*n*)	2	5
C-section CPD (*n*)	1	5
Spontaneous delivery (*n*)	43	32
Ventouse delivery (*n*)	4	8

Data are expressed as mean ± standard deviation or number of patients per group ($n = 50$ per group). All patients were primiparous and primigravid. In all patients, labour was induced and augmented with oxytocin. No statistical differences were observed between groups. C-section, caesarean section; CPD, cephalopelvic disproportion.

with interquartile range, as appropriate. $P < 0.05$ was considered as statistically significant. Data were analysed using Statistica. The analysis accounted for repeated measurements over time.

Results

The demographic and obstetric data in both groups were similar (Table 1).

A significant difference between both groups in breakthrough pain was noted: only 6% of patients in group NC had breakthrough pain compared with 36% in the group P ($P < 0.001$; Table 2). Ropivacaine use was 32.6% lower in group NC (11.6 ± 4.2 vs. $17.2 \pm 5.3\,mg\,h^{-1}$, $P < 0.0001$; Table 2). Patient satisfaction was significantly better 1 h after delivery in group NC than in group P but not significantly different after 24 h (VAS score 97 ± 5 vs. 88 ± 11 mm after 1 h, $P < 0.0001$; 92 ± 10 vs. 90 ± 14 mm after 24 h, $P < 0.5$; Table 2).

The mean VAS pain score when breakthrough pain occurred did not differ significantly between groups (37 ± 23 mm in group NC vs. 45 ± 18 mm in group P). The differences between VAS scores were significant at 50, 60 and 120 min ($P < 0.05$, $P < 0.05$ and $P < 0.01$, respectively; Fig. 2).

SBP was significantly lower in the group NC at 30, 40, 50, 60 and 120 min (Fig. 3). The incidence of hypotension was similar in both groups. No vasopressor therapy was needed in either group. Maternal heart rate was lower in group NC, although the difference was not significant (Fig. 4).

The incidences of nausea and pruritus were comparable in the two groups. Motor block was observed in five patients but had a similar distribution in both groups. The incidence of new FHR changes was comparable in the two groups and no differences in neonatal outcome could be identified (Table 3).

Discussion

Our results show that epidural administration of neostigmine and clonidine shortly after the spinal administration of ropivacaine and sufentanil decreased the incidence of breakthrough pain during neuraxial labour analgesia maintained using PCEA. Furthermore, patient satisfaction was higher in the neostigmine/clonidine group compared to the placebo group. Hourly ropivacaine use decreased by almost one-third, a result which has also been shown in previous studies.[9,10]

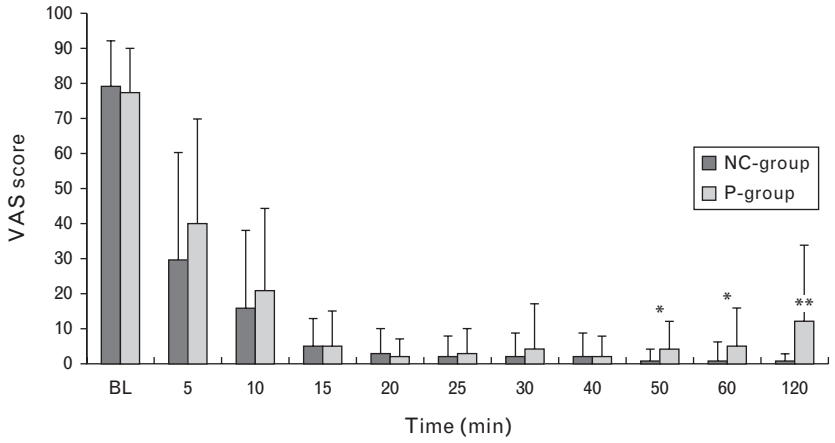
These two previous studies by van de Velde *et al.*[9] and Roelants *et al.*[10] evaluated the combined administration of clonidine and neostigmine epidurally to improve analgesia in labour. Roelants *et al.*[10] conducted a study in which different doses of neostigmine and clonidine were used. Epidural clonidine 150 μg alone produced maternal hypotension and sedation in 33 and 20% of parturients, respectively. Epidural neostigmine 750 μg alone was ineffective. The optimal combination for prolongation of analgesia appeared to be clonidine 75 μg with neostigmine 500 μg or 750 μg (although the

Table 2 Hourly ropivacaine use, number of episodes of breakthrough pain, visual analogue scale satisfaction scores at 1 and 24 h and breakthrough pain visual analogue scale score in patients treated with spinal ropivacaine and sufentanil combined with epidural neostigmine/clonidine or placebo (epidural saline)

	Neostigmine and clonidine group (group NC)	Placebo group (group P)
Hourly ropivacaine use (mg)	11.6 ± 4.2*	17.2 ± 5.3
Episodes of breakthrough pain, *n* (%)	3 (6)*	18 (36)
VAS satisfaction at 1 h (mm)	97 ± 5*	88 ± 11
VAS satisfaction at 24 h (mm)	92 ± 10	90 ± 14
VAS pain score at breakthrough episodes (mm)	37 ± 23	45 ± 18
Mean duration of epidural analgesia (min)	254 ± 147	240 ± 121

Data are expressed as mean ± standard deviation or number of patients per group. mm, millimetres on a scale from 0 to 100 mm; VAS, visual analogue scale. * $P < 0.05$ vs. group P.

Fig. 2



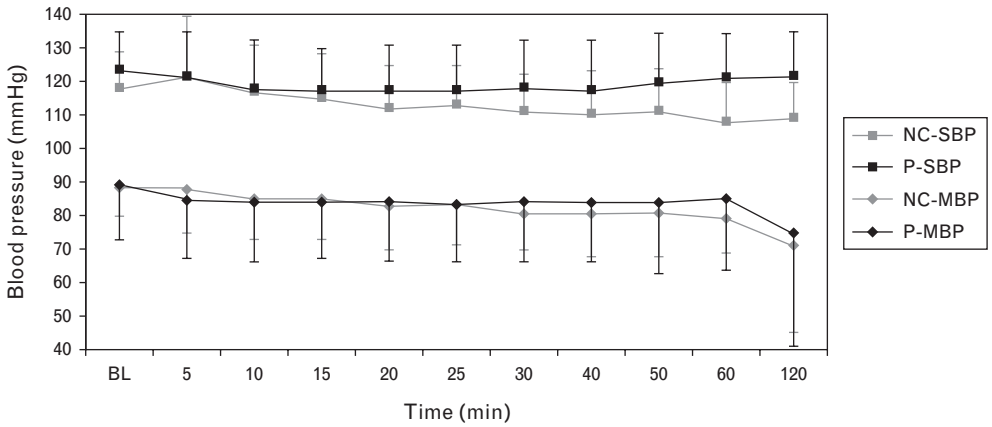
Visual analogue scale (VAS) scores for labour pain over time. A progressive decrease in VAS score was noted in both the neostigmine/clonidine (NC) group and placebo (P) group. At 50, 60 and 120 min, VAS pain score was significantly lower in the neostigmine/clonidine group compared with the placebo group. $*P<0.05$ vs. group P, $**P<0.01$ vs. group P. BL, baseline.

higher dose did not have a significant additive effect) and a reduction of the ropivacaine dose by 41% in all groups receiving clonidine occurred, with minimal side-effects. We used clonidine 75 μg with neostigmine 500 μg in our previous study[9] and found a ropivacaine dose-sparing effect of approximately 30%. In that study, we could not demonstrate that clonidine and neostigmine influenced the quality of analgesia for the methodological reasons previously mentioned. The present study filled that gap and showed that clonidine and neostigmine were able to improve the quality of PCEA maintenance analgesia following an initial spinal dose.

The doses used in the present study are based on a review of the literature. Clonidine has been added epidurally in doses ranging from 30 to 150 μg, but the optimal dose lies between 60 and 75 μg because lower doses appear to be ineffective and side-effects occur with higher doses.[11–13] Epidural neostigmine appears to be effective for analgesia in early labour when administered in a dose of 6 to 7 $\mu g\,kg^{-1}$ but smaller doses (4 $\mu g\,kg^{-1}$) do not provide adequate pain relief.[8,14]

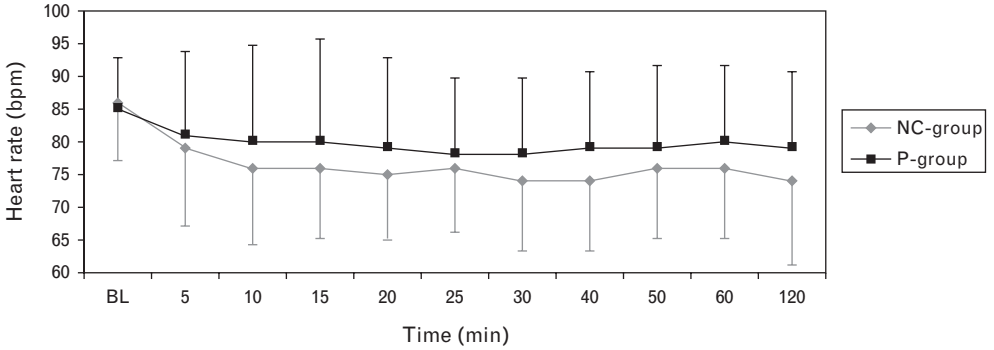
It is generally known that it is important to reduce the dose of local anaesthetic used in spinal and epidural analgesia because one of the main problems with local anaesthetics administered in labour via the epidural or intrathecal route is the dose-dependent motor blockade which increases the risk of subsequent instrumental delivery or caesarean section.[15] In addition, reducing the dose of local anaesthetic improves patient satisfaction. Based on the present and previous trials in our

Fig. 3



SBP and mean blood pressure (MBP) in the neostigmine/clonidine (NC) group and placebo (P) group. SBP values were significantly lower in the group NC at 30, 40, 50, 60 and 120 min compared with the placebo group ($P<0.05$).

Fig. 4



Maternal heart rate in the neostigmine/clonidine group and placebo group. Maternal heart rate was lower in the neostigmine/clonidine (NC) group compared with the placebo (P) group, but the differences were not significant.

patient population, clonidine and neostigmine are capable of reducing local anaesthetic consumption by around 30%.[9]

Combining clonidine with neostigmine has benefits. Clonidine has a ropivacaine-sparing effect and a prolonged duration of analgesia can be achieved with a smaller dose of local anaesthetic. The addition of neostigmine to this combination has two advantages: it provides an enhancement of analgesia which prolongs the duration of analgesia and it has a counteractive effect on the induced hypotension of clonidine.[16,17]

The explanation for these effects comes from interactions of clonidine and neostigmine in the central nervous system. It is known that spinal activation of noradrenergic pathways plays a major role in antinociception and a major role could be provided by α_2-receptors because they have multiple actions such as inhibition of neurotransmitter release (which causes a decrease in sympathetic outflow) and stimulation of acetylcholine release.[18,19] Neostigmine, an acetylcholinesterase inhibitor, also increases acetylcholine concentrations which is responsible for the additive analgesic effect of neostigmine to clonidine, at least partially mediated through a common pathway in the perception of pain. Neostigmine also causes enhanced release of acetylcholine in preganglionic sympathetic neurones. In contrast to clonidine, this causes an increase in sympathetic outflow, which can reduce clonidine-mediated hypotension.

However, the latter effect has been demonstrated only with spinal administration of the agents, and not with delivery into the epidural space. This is important because the meninges, which exclude acetylcholinesterases, prevent neostigmine from counteracting the effect of clonidine on the sympathetic nervous system. This may also be the explanation for the lack of nausea and vomiting that is seen when neostigmine is administered epidurally instead of intrathecally.[8]

We are aware that our study has some limitations. We used one dose of clonidine and neostigmine, so we cannot conclude whether there is an optimal dose combination to use for maximal pain relief and patient satisfaction. However, this was not the purpose of the study. Furthermore, we did not collect any data about sedation, which could be a potential confounder. However, from the clinical point of view, all patients were alert and had good orientation.

Although our data suggest that there is little effect on maternal haemodynamics and that foetal outcome seems to be unaffected, our study is insufficiently powered to demonstrate such differences. Theoretical effects on the fetus are possible because neostigmine can cross the placenta to a limited extent and can provoke foetal bradycardia.[20]

Several studies have shown that both clonidine and neostigmine, when administered alone, have no

Table 3 Foetal outcome

	Neostigmine and clonidine group (group NC)	Placebo group (group P)
Weight newborn (g)	3513 ± 500	3471 ± 468
UA pH	7.275 ± 0.067	7.270 ± 0.550
FHR changes after study drugs	0	1
UA pH<7.2 (*n*)	5	4
Apgar<7 (*n*)	3	2

Data are expressed as mean ± standard deviation or number of persons per group (*n*). No statistical differences were found between the groups. FHR, fetal heart rate; UA, uterine artery.

neurotoxic effects and preserve medullary blood flow.[21–23] However, their combined effects have not yet been studied in animal models.[21,22]

In conclusion, we have found that the administration of epidural clonidine and neostigmine as adjuvants to local anaesthetics not only provides a prolonged duration of analgesia and less ropivacaine consumption, as seen in our previous study, but also improves the quality of analgesia with higher patient satisfaction 1 h after administration and a decrease of more than 30% in breakthrough pain compared to standard CSE and PCEA with ropivacaine and sufentanil.

Studies of the incorporation of neostigmine and clonidine in PCEA regimens with continuous infusions are still needed. Dose-response studies examining the efficacy and safety in continuous epidural analgesia are also needed. The future of epidural clonidine and neostigmine in labour is promising.

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Conflicts of interest: none.

Presentation: none.

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