Anesthesiology 2005; 102:1205–10

Epidural Administration of Neostigmine and Clonidine to Induce Labor Analgesia

Evaluation of Efficacy and Local Anesthetic–sparing Effect

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Background: **Epidural clonidine produces analgesia without motor impairment, and is associated with a local anesthetic–sparing effect during labor. The authors have recently demonstrated that epidural neostigmine initiates selective labor analgesia devoid of adverse effects. Both drugs possess common analgesic mechanisms mediated through spinal acetylcholine release. This study evaluates their epidural combination in parturients.**

Methods: **At the beginning of labor, parturients were randomly allocated to one of five groups to receive one of the following after a test dose: 150 μg epidural clonidine, 750 μg neostigmine, or 75 μg clonidine combined with 250, 500, or 750 μg neostigmine. A pain score (visual analog scale, 0–100) was recorded before administration and at regular intervals until request for a supplemental injection. Subsequent analgesia was provided by continuous epidural infusion of ropivacaine.**

Results: **Parturients did not differ regarding demographic data and initial pain score. Clonidine 150 μg, neostigmine 750 μg, and 75 μg clonidine plus 250 μg neostigmine produced ineffective and short-lasting effects. Clonidine 75 μg plus 500 μg neostigmine and 75 μg clonidine plus 750 μg neostigmine presented comparable durations of 90 ± 32 and 108 ± 38 min (mean ± SD), respectively, and final analgesic efficacies, with 72.2% and 84%, respectively, of the parturients reporting a visual analog scale score of less than 30 out of 100 after 30 min. Ropivacaine use was significantly reduced in all clonidine groups (average, 9.5 mg/h) in comparison with neostigmine alone (17 ± 3 mg/h). No adverse effects were observed for 75 μg clonidine combined with any dose of neostigmine while maternal sedation (20%) and hypotension (33%) occurred with 150 μg clonidine alone.**

Conclusions: **Epidural clonidine, 75 μg, with 750 μg neostigmine is an effective combination to initiate selective labor analgesia without adverse effects. Clonidine use further reduces local anesthetic consumption throughout the course of labor.**

UNTIL now, local anesthetics have been used as a cornerstone to induce and maintain neuraxial analgesia during labor. Clinical trials conducted during the past years have sought to minimize the most noticeable side effects inherent to their administration, *i.e.*, motor impairment and sympathetic block. However, even at low doses, local anesthetics still may interfere with the normal course of labor and increase the rate of instrumental delivery when compared with systemic opioids.[1,2] Clonidine, an α_2-adrenoceptor agonist that can be used as a spinal analgesic whose administration does not induce motor impairment, produces analgesia through a nonopioid mechanism and is therefore devoid of adverse effects such as nausea, pruritus, or respiratory depression. Furthermore, use of clonidine allows a subsequent local anesthetic–sparing effect throughout the course of labor.[3,4] In laboring parturients, however, epidural or spinal use remains subject to caution because of dose-related side effects in the mother, mainly sedation and hypotension, and risks of alterations in heart rate and bradycardia in the fetus.[5] A few years ago, neostigmine, a cholinesterase inhibitor, was evaluated as a spinal analgesic in various acute pain conditions, including in laboring parturients.[6,7] Intrathecal administration induces major gastrointestinal adverse effects precluding any clinical use,[6,7] whereas epidural injection of neostigmine causes postoperative pain relief without particular side effects[8] and recently has provided effective analgesia when coadministered with sufentanil during the first stage of labor.[9] Epidural neostigmine does not induce respiratory depression, motor impairment, or hypotension and hence matches the characteristics requested to induce selective analgesia. Clonidine and neostigmine possess common mechanisms of action mediated through spinal release of acetylcholine, and beneficial interactions have been reported after neuraxial concurrent administration: enhancement of analgesia without enhancement of side effects in human volunteers[10] and reduction of the sympatholytic effect of clonidine by spinal neostigmine in animals.[11,12]

The current study evaluates the epidural combination of clonidine and neostigmine for labor analgesia. For this purpose, the efficacy of concurrent epidural administration of clonidine and neostigmine in the first stage of labor as well as the effect of both drugs on subsequent local anesthetic consumption throughout the course of labor are examined by comparison with use of epidural neostigmine or clonidine alone.

Materials and Methods

After approval by the Clinical Research Practices Committee (St Luc Hospital, Université Catholique de Louvain, Brussels, Belgium) and obtaining informed consent,

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Received from the Department of Anesthesiology, Université Catholique de Louvain, St Luc Hospital, Brussels, Belgium. Submitted for publication November 19, 2004. Accepted for publication February 23, 2005. Support was provided solely from institutional and/or departmental sources. Presented in part at the 36th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, Ft. Myers, Florida, May 12–16, 2004.

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100 healthy parturients with American Society of Anesthesiologists physical status of I or II with a gestational age greater than 36 weeks and who requested epidural analgesia during labor were enrolled in the study. Lumbar epidural puncture was performed with an 18-gauge Tuohy needle, and an epidural catheter was inserted 4 cm at the L3–L4 level in all parturients. Exclusion criteria included obstetric complications (multiple pregnancy, premature labor, or nonvertex presentation), contraindications to regional analgesia, and accidental dural puncture when the epidural was performed. All parturients were in established labor (cervical dilatation inferior to 5 cm), and all received an oxytocin infusion during the course of labor.

The current study was conducted in a similar way as we did previously when evaluating the efficacy of epidural neostigmine and sufentanil combination in labor.[9] Pain was assessed with a 100-mm visual analog scale (VAS; 0–100). When the VAS score reached the level of 30 (out of 100), an epidural test dose of 3 ml lidocaine, 2%, with 1:200,000 epinephrine was administered, and the parturients were randomly allocated to one of five study groups to receive, in a total volume of 12 ml, 150 μg epidural clonidine (n = 20), 750 μg neostigmine (n = 20), or a combination of 75 μg clonidine with 250 μg neostigmine (n = 20), 500 μg neostigmine (n = 20), or 750 μg neostigmine (n = 20). Neostigmine was provided from the commercial solution of neostigmine methylsulfate (Prostigmine®, 0.5 mg/ml; Roche, Summerville, NJ), and clonidine was provided from the commercial solution clonidine hydrochloride (Catapressan®, 150 μg/ml; Boehringer, Ingelheim, Germany). Safety assessment has been reported for spinal use of both drugs.[12] The decision to administer a dose of 750 μg neostigmine alone resulted from our previous study on epidural neostigmine to induce labor analgesia, which found that at least 6–7 μg/kg (*i.e.*, 500 μg) was needed when combined with sufentanil.[9] The choice of epidural clonidine at dose of 150 μg resulted from a review of the literature regarding its use in laboring parturients and balancing analgesic and well-known side effects. The data were collected by an anesthesiologist, either a resident or an attending, who was blinded to the patient groups and to the epidural drugs. Maternal and fetal vital parameters were continuously monitored throughout the course of labor. Pain score (VAS) was recorded 3, 5, 10, 15, 20, and 30 min after the epidural injection, and sensory block (ether test) and motor block in the lower limb (modified Bromage scale: from 1 = complete motor blockade to 6 = no weakness at all) were assessed 15 and 30 min after injection. The duration of analgesia was considered the time elapsed to the patient's first request for further analgesia. From that second epidural injection until delivery, the maintenance of analgesia was provided by continuous infusion with 0.1% ropivacaine (8–10 ml/h) and rescue doses of local anesthetic as needed. The duration of the labor from the time of the first epidural injection until delivery, the mode of delivery (operative, vaginal instrumental, or spontaneous), and cervical dilatation at the time of second epidural injection were recorded. The total consumption of ropivacaine throughout the course of labor was calculated.

Maternal adverse events (nausea and vomiting, pruritus, sedation, hypotension) and fetal side effects (bradycardia during labor and low Apgar score) were also closely monitored.

Statistical Analysis

Results are expressed as mean ± SD, 95% confidence interval, or median (interquartile range), as indicated. Demographic data and continuous variables were compared among the groups by analysis of variance and repeated measures, followed, if appropriate, by multiple comparison with the Tukey Honest Significant Difference test (Statistica; StatSoft, Tulsa, OK). Comparison of ordinal categorical data among groups was achieved by application of the Kruskal-Wallis test followed by the Wilcoxon rank sum test for multiple comparisons. Incidence of adverse effects and installation of satisfactory analgesia were compared among the groups by chi-square analysis corrected for multiple tests. A P value less than 0.05 was considered significant.

The number of patients in the different groups was based on preliminary data regarding duration of analgesia resulting from a first epidural bolus of 750 μg neostigmine or 150 μg clonidine alone. A prospective sample size calculation (SigmaStat; SPSS Science Software, London, United Kingdom) indicated that 20 subjects were required in each group to have a 80% power to detect a 25% difference at an α level of 0.05 for the duration of analgesic effect after combination of the two drugs.

Results

One hundred patients were enrolled in the study. Variables including age, weight, and parity were similar among the groups, as was cervical dilatation at the first injection and when a second epidural injection was required (table 1). Maternal hemodynamic parameters did not differ among the groups and remained stable in all the groups until 30 min after injection. Among the parturients who received epidural 150 μg clonidine, 33% experienced significant hypotension, mainly observed at 90 min after injection, which was easily treated by fluid loading and ephedrine administration (table 2).

Only epidural combinations of 75 μg clonidine with 500 and 750 μg neostigmine provided efficient analgesia that significantly reduced the initial VAS score (fig. 1). To better compare the effectiveness of the various epidural solutions, the percentages of parturients presenting satisfactory analgesia (which we defined as a VAS score <

Table 1. Demographic Data

	C150	N750	C75N250	C75N500	C75N750
n	20	20	20	20	20
Age, yr	32 ± 4	31 ± 3	32 ± 5	29 ± 4	32 ± 5
Weight, kg	78 ± 7	80 ± 7	72 ± 7	79 ± 13	76 ± 10
Nullipara, %	45	53	42	55	45
Cervical dilatation 1, cm*	3.0 (3.0–4.0)	3.0 (2.5–4.5)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	3.3 (3.0–4.0)
Cervical dilatation 2, cm*	4.0 (4.0–5.0)	5.0 (3.3–5.0)	4.5 (4.0–5.0)	5.0 (4.0–5.0)	4.5 (4.0–4.5)

Data are expressed as mean ± SD or * median (interquartile range). Cervical dilatation was recorded (1) before administration of the first epidural injection and (2) when the parturient requested a second epidural dose. Groups: 150 μg epidural clonidine (C150), 750 μg neostigmine (N750), 75 μg epidural clonidine combined with 250, 500, and 750 μg neostigmine (C75N250, C75N500, and C75N750, respectively).

30) were evaluated at different time points after injection (fig. 2). The 75 μg clonidine–750 μg neostigmine group afforded the best effectiveness to relieve pain in parturients, with more than 80% of them presenting satisfactory analgesia after 15 min. Although the 75 μg clonidine–500 μg neostigmine group presented results not statistically different from the 75 μg clonidine–750 μg neostigmine group, the onset time was slower, and only 72% of the parturients matched our criteria of satisfactory analgesia (VAS score < 30). The durations of analgesia resulting from this first top-up dose were comparable between the 75 μg clonidine–500 μg neostigmine and 75 μg clonidine–750 μg neostigmine groups (table 3), with the effect of 75 μg clonidine–750 μg neostigmine lasting significantly longer than the effect of 150 μg clonidine alone and 75 μg clonidine–250 μg neostigmine. Epidural neostigmine alone, 750 μg (10 μg/kg), was ineffective to initiate labor analgesia and, in contrast with other groups receiving epidural clonidine, did not display a sparing effect of ropivacaine throughout the course of labor (table 3).

The level of sensory block assessed at 30 min after epidural injection was similar in all groups, as was the degree of motor blockade. No significant motor impairment was observed in any group (table 3).

Total duration of labor, mode of delivery, and neonatal outcome were comparable among all the groups (table 2). Epidural neostigmine up to a dose of 750 μg did not induce particular side effects in the mother or in the fetus. By comparison, 150 μg epidural clonidine produced some degree of maternal sedation and, more importantly, caused significant maternal hypotension resulting in alterations of fetal heart rate (fetal bradycardia, n = 3, 13.5%) but without adverse consequence. No hypotension or sedation was observed in any of the groups involving an epidural combination of clonidine and neostigmine.

Discussion

The current results show that 75 μg epidural clonidine with 500 μg neostigmine or, better, 750 μg neostigmine, induced selective analgesia, *i.e.*, devoid of motor impairment or sympathetic block, for an average duration of 108 min (confidence interval, 83–133 min) in 80% of the parturients.

Besides the fact that neither drug causes motor impairment, they possess specific properties that are of interest for labor analgesia. Spinal clonidine, which action mimics activation of descending inhibitory pathways, inhibits behavioral and neurophysiologic effects after noxious visceral stimuli in animal models of colorectal distension[13] and, more recently, uterine cervical distension.[14] Clinical application of the drug in the context of visceral pain has therefore led to its use for labor analgesia in association with local anesthetics.[15] Neostigmine inhibits the breakdown of endogenous acetylcholine and indirectly stimulates both muscarinic and nicotinic receptors into the spinal cord, inducing effective analgesia *via*

Table 2. Adverse Effects, Obstetric and Neonatal Data

	C150	N750	C75N250	C75N500	C75N750
Labor duration, min	246 ± 73	309 ± 129	239 ± 98	286 ± 150	348 ± 189
Instrumental delivery, %	7	13	15	17	7
Cesarean delivery, %	0	0	7.5	0	11
Maternal nausea and vomiting, %	0	7	0	0	0
Maternal sedation, %	20	0	0	0	0
Maternal hypotension, %	33*	0	0	0	0
Fetal bradycardia, %	13.5	0	0	0	0
Apgar scores < 7 at 1/5/10 min, n	0/0/0	0/0/0	0/0/0	1/0/0	0/0/0

Data are mean ± SD for duration of labor or expressed as percent of parturients per group. * $P < 0.05$ with all the other groups. Maternal hypotension was defined as a decrease greater than 20% from baseline systolic blood pressure, and fetal bradycardia was defined as a fetal heart rate value between 80 and 100 beats/min during 3–5 min. Groups: 150 μg epidural clonidine (C150), 750 μg neostigmine (N750), 75 μg epidural clonidine combined with 250, 500, and 750 μg neostigmine (C75N250, C75N500, and C75N750, respectively).

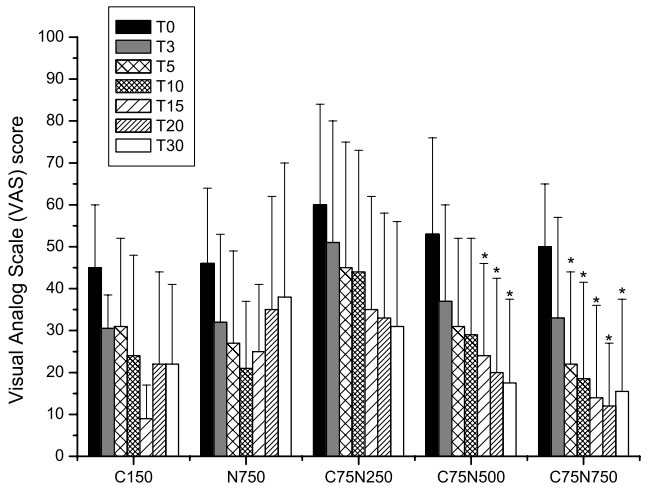

Fig. 1. Evolution of pain scores before (T0) and from 3 min until 30 min (T3 to T30) after epidural injection in the different groups of parturients. Groups: 150 μg epidural clonidine (C150), 750 μg neostigmine (N750), 75 μg epidural clonidine combined with 250, 500, and 750 μg neostigmine (C75N250, C75N500, and C75N750, respectively). * $P < 0.05$ with visual analog scale score at T0, before epidural injection.

the epidural route without the major gastrointestinal side effects related to its intrathecal administration.[8,9] Because some experimental data have suggested a sex difference in cholinergic analgesia in favor of females,[16] the drug seems particularly indicated in the field of obstetric analgesia.

We have recently investigated the use of epidural neostigmine in combination with neostigmine in parturients[9] and found that 500 μg neostigmine (determined as the minimal effective dose) induces selective analgesia in 90% of patients for a duration of 119 min (confidence interval, 106–135 min), an effect comparable to that of 750 μg neostigmine with 75 μg clonidine. The current results support our previous observations showing that, coadministered with ropivacaine, sufentanil, or clonidine, epidural neostigmine at a dose less than 500 μg (*i.e.*, 5–6 μg/kg) is ineffective in laboring parturients,[9,17] in contrast to the analgesic effects observed for lower doses in postoperative conditions such as after cesarean delivery[18] or orthopedic surgery.[8] Moreover, epidural neostigmine alone, even at a dose of 750 μg (*i.e.*, 8–9 μg/kg), does not provide satisfactory pain relief in the first stage of labor, as previously observed by other authors with intrathecal neostigmine alone.[19] One reason might be the fact that, as a consequence of the hydrophilic nature of the compound, the dose reaching the spinal cord (*i.e.*, around 75 μg in this case) was not large enough to be effective. In fact, an intrathecal dose of at least 100 μg was needed to provide some analgesia in volunteers.[10] Furthermore, in humans, painful labor does not seem to activate spinal cholinergic pathways.[20] Another reason might be that neostigmine was reported to be more effective to relieve pain of somatic origin than of visceral origin, and the first stage of labor mostly implies visceral pain.[21]

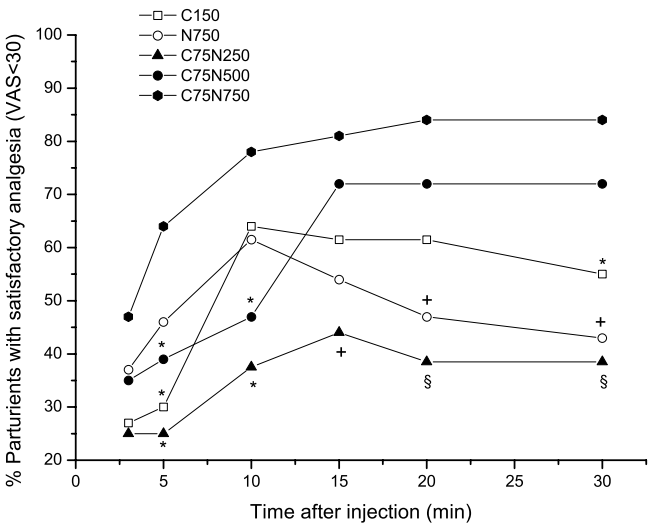

Fig. 2. Efficacy of epidural injection based on the percentage of parturients experiencing a satisfactory level of analgesia (defined as a score strictly < 30 out of 100 on visual analog scale [VAS]) at different times after injection of the different analgesic solutions. Groups: 150 μg epidural clonidine (C150), 750 μg neostigmine (N750), 75 μg epidural clonidine combined with 250, 500, and 750 μg neostigmine (C75N250, C75N500, and C75N750, respectively). * $P < 0.05$ with the C75N750 group; + $P < 0.05$ with the C75N500 and C75N750 group; § $P < 0.05$ with the C150, C75N500, and C75N750 groups.

Several studies have evaluated neuraxial clonidine as an analgesic during labor[15] and have established that the optimal epidural dose, a compromise between analgesia and acceptable side effects, lies between 60 and 75 μg (a dose lower than 60 μg is ineffective,[3] whereas a dose larger than 100 μg induces sedation and hypotension[5]). In most of these clinical trials, clonidine added to the first epidural bolus improves the effect of local anesthetic used. By example, 75 μg clonidine combined with 12.5 mg bupivacaine prolongs analgesia to 127 min (SD, 11 min)[22] and combined with 8 mg ropivacaine lasts for 132 min (SD, 48 min).[5] To our knowledge, few reports have assessed the efficacy of clonidine without local anesthetic during the first stage of labor. Chiari *et al.*[23] reported the effects of intrathecal clonidine (50–200 μg) as a sole analgesic. Buggy and MacDowell[24] combined 120 μg epidural clonidine with μ-opioid fentanyl, and Connelly *et al.*[25] administered 75 μg epidural clonidine with sufentanil in the first stage of labor. Without an epidural test dose, the former authors observed effective analgesia lasting for 80 min (interquartile range, 60–90 min) after a median onset time of 20–35 min, but although no motor impairment appeared, maternal hypotension occurred in 57% of the patients in relation to the dose of clonidine they received.[24] Using a test dose and epidural dose of clonidine similar to what we used, the latter authors reported a duration of analgesia of 178 min (SD, 55 min) when clonidine was coadministered with 20 μg sufentanil.[25]

Table 3. Assessment of the Analgesic Effect Resulting from a Single Epidural Injection

	C150	N750	C75N250	C75N500	C75N750
VAS 1	49 ± 15	46 ± 17	60 ± 24	53 ± 23	50 ± 14
VAS 2	47 ± 14	60 ± 18	63 ± 21	63 ± 19	56 ± 17
Sensory level*	T10 (10–10)	T10.5 (10–11)	T10 (8–10)	T10 (8–11)	T8.5 (7–8)
Motor block*	6 (6–6)	6 (6–6)	6 (6–6)	6 (6–6)	6 (5–6)
Duration of analgesia, min†	67 ± 33 (49–86)	47 ± 19 (36–58)	63 ± 37 (40–83)	90 ± 32§ (73–108)	108 ± 38‡§ (83–133)
Ropivacaine use, mg/h†	9.7 ± 3 (7–13)	17 ± 3‖ (13–19)	10.4 ± 1 (9–11)	10.2 ± 3 (9–12)	9.3 ± 4 (7–11)

Data are presented as mean ± SD and * median value (interquartile range) or † (95% confidence interval) as indicated. ‡ $P < 0.05$ with C150 and C75N250; § $P < 0.01$ with N750; ‖ $P < 0.01$ with all the other groups. Visual analog scale (VAS) represents pain score (0–100) evaluated by the parturients (1) before administration of the first epidural injection and (2) when the parturient requested a second epidural dose. The duration of epidural analgesia was calculated as the time elapsed between these two injections. Sensory level (ether test) and motor block (modified Bromage scale) were assessed at 30 min after injection. Groups: 150 μg epidural clonidine (C150), 750 μg neostigmine (N750), 75 μg epidural clonidine combined with 250, 500, and 750 μg neostigmine (C75N250, C75N500, and C75N750, respectively).

There are several reasons to combine clonidine with neostigmine for neuraxial analgesia, besides those aforementioned, which concern their use in the context of labor pain. The first is an enhancement of efficacy through a common analgesic mechanism: The principal site of action for clonidine-mediated analgesia is located at spinal cord level, partly through spinal release of the endogenous neurotransmitter acetylcholine.[26] The second is a hemodynamic advantage resulting from opposite effects on the central sympathetic system: Spinal clonidine decreases sympathetic outflow in the spinal cord intermediolateral cell column, whereas neostigmine, through an enhanced acetylcholine release in preganglionic sympathetic neurons, increases sympathetic outflow.[11,12] Experimental results in animals have demonstrated a synergistic effect in analgesia resulting from concurrent administration,[27] whereas in human volunteers, intrathecal neostigmine only enhances epidural analgesia from clonidine in an additive manner, but without enhancement of the side effects.[10] In parturients, both drugs have been coadministered as part of an intrathecal mixture to induce labor analgesia. Spinal clonidine, 50 μg, prolonged analgesia provided by spinal sufentanil and bupivacaine; however, the addition of 10 μg neostigmine to the mixture did not further potentiate the duration in a study by D'Angelo *et al.*,[7] in contrast to a study by Owen *et al.*,[6] who demonstrated that 10 μg spinal neostigmine extended the duration of effect of spinal bupivacaine–fentanyl–clonidine 30 μg from 123 to 165 min. In both studies, however, the dose of intrathecal neostigmine was hampered by severe nausea and vomiting.

Although it is difficult to compare our results to those aforementioned, which also involve an intrathecal local anesthetic and a μ-opioid agonist, we report here the first epidural combination of both drugs in early labor. Administration of 750 μg epidural neostigmine (intrathecal equivalence of 75 μg)[8] with 75 μg epidural clonidine provides pain relief in early labor for 108 min (confidence interval, 83–133 min) without particular side effects. Specifically, we did not observe maternal hypotension among the women who received a combination of both drugs (*i.e.*, 75 μg clonidine with any of the three doses of neostigmine). Epidural clonidine at dose greater than 100 μg is known to cause hypotension,[5] and lower doses, such as 60 or 75 μg, have been shown to cause some hypotension, respectively 26% and 30%, when coadministered with ropivacaine.[3,4] In the literature, 75 μg spinal neostigmine injected at the same time as bupivacaine failed to prevent hypotension from local anesthetic in humans[28] but abolished clonidine-induced hypotension in a large animal model such as sheep.[11]

One of the advantages of epidural clonidine lies in its local anesthetic dose-sparing effect throughout the course of labor: A single epidural dose of 60–75 μg at the beginning of labor provides 44–64% of the ropivacaine dose-sparing effect.[3,4] In the current study, we also demonstrated similar benefits with a reduction of 41% in ropivacaine requirements in all groups receiving epidural clonidine, regardless of the dose. In contrast, epidural neostigmine alone does not produce this effect. One potential explanation might be that epidural neostigmine alone, at the dose we used, was not effective in the parturients or to the underlying mechanisms of action of the drug. Neostigmine exerts an indirect analgesic effect in contrast with substances such as clonidine or μ-opioid agonists, which possess direct analgesic effect and have both demonstrated local anesthetic dose-sparing effects in labor.[3,4,29]

In conclusion, epidural coadministration of 75 μg clonidine with 500 μg neostigmine or, better, 750 μg neostigmine provides satisfactory and selective analgesia in early labor, without motor or sympathetic block or fetal side effects. Further, the use of epidural clonidine, devoid of bothersome consequence such as hypotension when combined with neostigmine, demonstrates a useful ropivacaine-sparing effect throughout the course of labor.

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