Jikeikai Med J 2004 ; 51 : 91-6

Epidural Neostigmine Co-administered with Ropivacaine Does Not Improve Stress Responses or Postoperative Pain Status

Kazuhiro SHOJI, Hirokazu SAITO, and Eiji MASAKI

Department of Anesthesiology, The Jikei University School of Medicine

ABSTRACT

The neuraxial administration of neostigmine has been reported to have antinociceptive effects. This study was performed to determine whether preincisional epidural neostigmine co-administered with ropivacaine modulates stress responses and postoperative pain status. Twenty patients hospitalized for elective open abdominal gynecological surgery were randomly assigned to a control group, which received 10 ml of 0.75% epidural ropivacaine alone before the induction of general anesthesia, or a neostigmine group, which received 10 ml of 0.75% epidural ropivacaine and 0.3 mg of neostigmine before induction. One hour after the start of surgery continuous epidural infusion of 0.2% ropivacaine was started at a rate of 4 ml/hr and continued for 30 hours in both groups. Plasma levels of cortisol and interleukin-6 were measured perioperatively. The patients' postoperative pain rating was assessed with a visual analogue scale. Preincisional epidural neostigmine co-administered with ropivacaine did not change stress responses in the perioperative period. Visual analogue scale scores for postoperative pain were not significantly decreased by neostigmine. Epidural neostigmine co-administered with ropivacaine did not show antinociceptive effects in patients undergoing transabdominal gynecologic surgery. (Jikeikai Med J 2004 ; 51 : 91-6)

Key words : neostigmine, ropivacaine, epidural, postoperative pain, stress response

INTRODUCTION

Perioperative pain control remains an important issue for anesthesiologists. Peripheral nerve injury and subsequent inflammatory responses produced by surgical procedures result in a complicated pain response, which is extremely difficult to treat with conventional analgesics. Recent studies of the pain-modulatory system in the spinal cord have inspired the use of new classes of drugs, such as α_2-adrenergic agonists and adenosine and tricyclic antidepressants[1,2]. The neuraxial administration of neostigmine, one of a new class of analgesics, has been reported to be antinociceptive in humans and animals[3,4]. We previously demonstrated that preincisional epidural administration of neostigmine reduces plasma cortisol levels and decreases postoperative pain. However, these effects are transient and insufficient under epidural anesthesia with mepivacaine and bupivacaine[5].

Our previous unsatisfactory results prompted us to seek an alternative approach. We hypothesized that changing the local anesthetic used for basal epidural anesthesia might modulate the effects of the epidural neostigmine. We wished to examine whether ropivacaine, a long-acting, more-potent local anesthetic, would prolong and enhance the antinociceptive effects of neostigmine. Therefore, we

Received for publication, August 12, 2004

庄司　和広，斉藤　洋一，正木　英二

Mailing address : Eiji MASAKI, Department of Anesthesiology, The Jikei University School of Medicine, 3-25-8, Nishi-Shimbashi, Minato-ku, Tokyo 105-8461, Japan.

E-mail : ejmasaki@jikei.ac.jp

examined the effects of epidural neostigmine co-administered with ropivacaine on plasma concentrations of cortisol and interleukin (IL)-6. We also measured the pain scores of patients by using a visual analogue scale (VAS) postoperatively.

SUBJECTS AND METHODS

After obtaining the approval of our institution's human ethics committee and the written informed consent of each subject, twenty patients undergoing open lower-abdominal surgery for nonmalignant gynecologic conditions (total abdominal hysterectomy, myomectomy, salpingo-oophorectomy or cystectomy) were randomly assigned to a control group (which received ropivacaine) or a neostigmine group (which received both ropivacaine and neostigmine). All patients agreed to receive epidural neostigmine. However, patients older than 50 years, patients with known hypersensitivity to ropivacaine or neostigmine, and patients with a history of corticosteroid treatment, impaired sensation, or large surgical blood loss (more than 1,500 ml) were excluded from the study. All patients were classified as American Society of Anesthesiologists physical status I and were instructed on and understood the use of the VAS, which consisted of a 10 cm line with 0 equaling "no pain at all" and 10 equaling "the worst possible pain", for pain assessment preoperatively. The study was conducted in a prospective, randomized, double-blind, placebo-controlled fashion.

Oral premedication consisting of 7.5 mg of zopiclone (an ultrashort-acting benzodiazepine receptor agent) and 150 mg of ranitidine was administered 90 minutes before the patients arrived in the operating room. The epidural space was identified using the loss of resistance technique, and an epidural catheter was placed through a 17-gauge Tuohy needle at the L1-L2 interspace. Following a negative test dose consisting of 3 ml of 0.75% ropivacaine (failure to produce sensory and motor anesthesia in the saddle area), an additional 7 ml of 0.75% ropivacaine was administered without (control) or with 0.3 mg neostigmine. Ropivacaine and neostigmine were purchased from Astra Zeneca (Cheshire, UK) and Shionogi and Co., Ltd. (Osaka, Japan), respectively. The dermatomal analgesic level was evaluated with an alcohol swab 10 minutes after epidural administration. After the analgesic level was confirmed above Th 9, general anesthesia was induced with propofol (2 mg/kg), and vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation. Anesthesia was maintained with 1.0% to 2.0% sevoflurane in 33% O_2 and 67% N_2O, with intermittent doses of vecuronium (1 to 2 mg) as clinically indicated. Upon the earliest sign of pain (i.e., increasing blood pressure and heart rate and pupil dilation), additional epidural 0.75% ropivacaine (3 to 5 ml) was administered by the anesthesiologist, who was blinded to the addition of neostigmine to ropivacaine. One hour after the start of surgery, continuous epidural infusion was started with 0.2% ropivacaine at a rate of 4 ml/hour and continued for 30 hours. Blood pressure was measured every 5 minutes, and electrocardiograms and hemoglobin oxygen saturation were monitored continuously throughout the operation. A decrease in mean arterial pressure of more than 20% of the preanesthetic baseline value was treated with intravenous boluses of ephedrine or with intravenous fluid administration or both.

If postoperative pain relief was not complete, an intravenous drip infusion of 2 mg of butorphanol over 1 hour at a minimum 6-hour interval was ordered by a gynecologist, who was a member of the surgical team, and given upon the patient's request. If patients still complained of pain, a 50-mg diclofenac suppository was available at a minimum 4-hour interval.

Blood samples were obtained to measure plasma levels of cortisol and IL-6 upon admission to the operation room, 30 minutes after the start of operation, upon arrival to the postanesthesia care unit, and 24 hours after the end of surgery. The blood samples were subjected to centrifugation at 1,600×g for 15 minutes, and the separated plasma samples were stored at −80°C until assayed. Plasma levels of cortisol and IL-6 were determined with a commercially available enzyme immunoassay kit (Diagnostic Systems Laboratories, Inc., Webster, TX, USA) and an enzyme-linked immunosorbent assay kit (Amersham Pharmacia Biotech Inc, Piscataway, NJ, USA),

respectively.

The postoperative pain of patients was assessed at rest with VAS scores at 2, 24, and 72 hours after the end of surgery. Analgesic demand for rescue and side effects, such as pruritus and nausea and vomiting were assessed and recorded during the first 24 hours after surgery. Nausea and vomiting were treated with 10 mg intravenous metoclopramide upon patient request.

The data were analyzed using repeated-measure analysis of variance with subsequent intragroup comparisons made with the Bonferroni correction by using the Prism software program (version 2.0 ; GraphPad Software, San Diego, CA, USA). A P value$<$ 0.05 was considered to indicate significance.

Results

Demographic data, duration of surgery, and total amount of 0.75% ropivacaine used are summarized in Table 1. There were no significant differences between the groups. The types of surgical procedures performed during the study are shown in Table 2.

Additional ropivacaine in the first 30 minutes after surgical incision was required by one patient in each group. Neither blood pressure nor heart rate changed after the start of surgery in patients who did not receive the additional ropivacaine.

Epidural neostigmine administered under epidural anesthesia with ropivacaine did not significantly alter the cortisol levels perioperatively (Fig. 1). However, IL-6 levels were increased during and after the operation, but there was no significant difference between

Table 1. Summary of treatment groups

	control	neostigmine
Age (years)	37±2	37±2
Body weight (kg)	54±3	55±2
Height (cm)	157±2	157±1
Surgery duration (minutes)	86±11	87±10
Total amount of ropivacaine (ml)	10.4±0.4	10.5±0.4

Data are expressed as means±SE (n=10).
There were no differences between groups.

Table 2. Procedures performed

	control	neostigmine
Total abdominal hysterectomy	4	2
Salpingo-oophorectomy	0	0
Myomectomy	5	7
Cystectomy	1	1

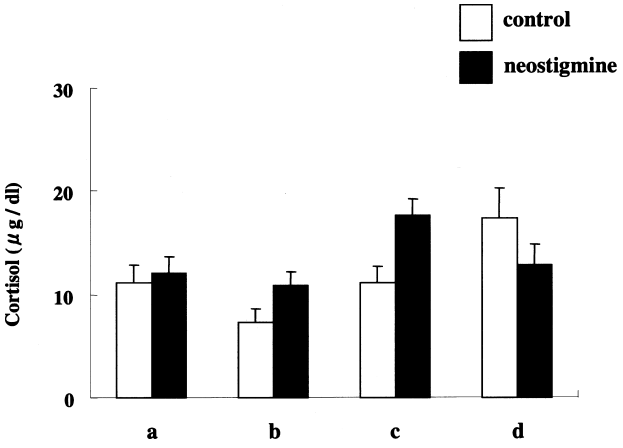

Fig. 1. Plasma levels of cortisol. Blood samples were obtained : a, before induction of general anesthesia ; b, 30 minutes after the start of surgery ; c, when the patient entered postanesthesia care unit ; and d, 24 hours after the end of surgery. Plasma levels of cortisol were determined with enzyme immunoassay. Data are expressed as means±SE (n=10). There were no differences between the groups.

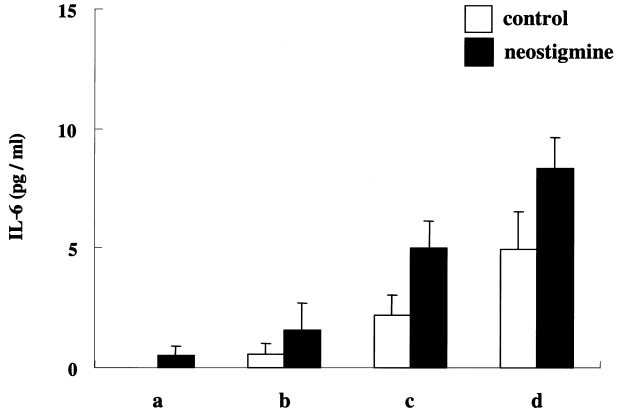

Fig. 2. Plasma levels of IL-6. Blood samples were obtained : a, before induction of general anesthesia ; b, 30 minutes after the start of surgery ; c, when the patient entered the postanesthesia care unit ; and d, 24 hours after the end of surgery. Plasma levels of IL-6 were determined with enzyme-linked immunosorbent assay. Data are expressed as means±SE (n=10). There were no differences between the groups.

Table 3. Postoperative pain scores (VAS) and the time for first rescue analgesics

	control	neostigmine
2 hours	0.4±0.3	0.4±0.2
24 hours	4.0±0.9	2.0±0.6
72 hours	1.8±0.4	0.5±0.3
First rescue time (hours)	9.1±2.1	12.0±1.8

Data are expressed as means±SE (n=10).
There were no differences between groups.

the groups (Fig. 2).

The postoperative VAS scores did not differ between the groups. Furthermore, the time to first rescue analgesic was not affected by epidural neostigmine co-administered with ropivacaine (Table 3).

Nausea and vomiting were observed in only one patient in the control group but did not require treatment. The other patients complained of no other side effects. Analgesic (butorphanol) consumption during the first 24 hours postoperatively did not differ significantly between the groups (2.8±0.6 [mean±SE] and 2.0±0.3 mg in the control and neostigmine groups, respectively ; n=10). Additional diclofenac was required by one patient in the neostigmine group.

DISCUSSION

The findings of the present study were not consistent with those of our previous study[5], in which epidural neostigmine decreased plasma cortisol levels in the early postoperative period and improved the postoperative pain status of patients who received epidural anesthesia with mepivacaine and bupivacaine. In the present study, plasma levels of cortisol and the postoperative pain status were not significantly affected by the co-administration of epidural neostigmine with ropivacaine. In the control group, plasma levels of cortisol were not elevated perioperatively, and the VAS scores 2 hours after the end of surgery were low. Furthermore, additional ropivacaine was required by only one patient (10%) in each group, and hemodynamic values (blood pressure and heart rate) of the other patients who did not receive the additional ropivacaine were stable before and after surgical incision. On the other hand, in our previous study, plasma levels of cortisol were elevated after the start of surgery and the VAS scores 2 hours after the end of surgery in the control group were higher than in the present study. Supplemental mepivacaine was also required by many patients (63%). These results suggest that basal epidural anesthesia with 10 ml of 0.75% ropivacaine is sufficient to block acute incisional stimuli and mask the antinociceptive effects of epidural neostigmine that were observed under epidural anesthesia with mepivacaine and bupivacaine in the previous study[5].

Although the precise equipotent doses of local anesthetics for pain responses are not clear, the relative potency of ropivacaine is about 4 times greater than that of mepivacaine[6]. In one clinical study, the analgesia produced by 0.75% ropivacaine was of longer duration than that produced by 2% mepivacaine in patients receiving interscalene brachial plexus anesthesia[7]. We used 10 ml of 1% mepivacaine and 0.75% ropivacaine for initial epidural injection in our previous and present studies, respectively. In our previous study, the epidural blockade achieved by 1% mepivacaine might have been incomplete, resulting in elevated cortisol levels and high VAS scores in the absence of epidural neostigmine[5]. The effects of neostigmine were exaggerated under incomplete basal epidural anesthesia with 1% mepivacaine.

Another possible explanation for epidural neostigmine not showing further antinociceptive effects under ropivacaine epidural anesthesia may be that ropivacaine and mepivacaine have different effects on molecular targets other than Na^+-channels. Although the mechanisms underlying the antinociceptive effects of neostigmine have not been fully identified, neostigmine inhibits the breakdown of spinally released endogenous acetylcholine. The interneurons stimulated by the acetylcholine in the spinal cord would release γ-aminobutyric acid or glycine or both onto secondary sensory afferent neurons, which would then be hyperpolarized[8,9]. Ropivacaine suppresses glycine-induced ion currents in acutely dissociated rat hippocampal neurons[10]. The inhibitory effects of ropivacaine on glycine-induced ion currents may abolish the antinociceptive property of epidural neostigmine. Neuronal calcium

signaling is also differentially modulated by ropivacaine and mepivacaine. In human neuroblastoma cells, intracellular Ca^{2+} concentration transients evoked by carbachol (a muscarinic receptor agonist) are more potently inhibited by ropivacaine than by mepivacaine[11]. Although the implications for local anesthetic inhibition of muscarinic-receptor-mediated calcium signaling in antinociception are not clear, activation of both muscarinic and nicotinic receptors is implicated in the mechanisms of antinociception produced by epidural neostigmine[12,13].

Plasma levels of IL-6 were elevated after surgery with epidural anesthesia, and co-administration of ropivacaine and neostigmine did not alter IL-6 levels postoperatively. These results indicate that even with adequate blockade of painful stimuli by epidural anesthesia, the regulation of IL-6 production was not altered, as suggested by Moor et al.[14]. Many factors contribute to the production of IL-6[15,16], and treatments that successfully control IL-6 levels have been reported in patients undergoing surgery[17,18]. Because high levels of plasma IL-6 may be associated with undesirable outcomes, including increased postoperative pain[19,20], additional methods should be developed to regulate the production of IL-6.

In summary, epidural neostigmine co-administration with ropivacaine does not change stress responses and fails to improve the postoperative analgesic effects of the local anesthetic.

Acknowledgments: This work was supported in part by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan to H.S. (No. 15790838) and K.S. (No. 15790836). The authors thank Dr. Salim Hayek (Cleveland Clinic Foundation, Cleveland, OH, USA) for his help with manuscript preparation.

References

1. Pan H, Xu Z, Leung E, Eisenach JC. Allosteric adenosine modulation to reduce allodynia. Anesthesiology 2001; 95: 416-20.
2. Lograsso M, Nadeson R, Goodchild CS. The spinal antinociceptive effects of cholinergic drugs in rats: receptor subtype specificity in different nociceptive tests. BMC Pharmacol 2002; 2: 1-9.
3. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine methylsulfate in humans. Anesthesiology 1995; 82: 331-43.
4. Hwang JH, Hwang KS, Leem JK, Park PH, Han SM, Lee DM. The antiallodynic effects of intrathecal cholinesterase inhibitors in a rat model of neuopathic pain. Anesthesiology 1999; 90: 492-9.
5. Masaki E, Saito H, Shoji K, Matsushima M. Postoperative analgesic effect of epidural neostigmine, and the responses of plasma cortisol and IL-6. J Clin Anesth 2004 (in press).
6. Stoelting RK, Miller RD, editors. Local anesthetics. basic anesthesia 4th ed. Philadelphia: Churchill Livingstone; 2000. p. 80-8.
7. Casati A, Fanelli G, Cedrati V, Verti M, Aldegheri G, Rorri G. Pulmonary function changes after interscalene brachial plexus anesthesia with 0.5% and 0.75% ropivacaine: a double-blinded comparison with 2% mepivacaine. Anesth Analg 1999; 88: 587-92.
8. Travagli RA. Muscarine receptor activation in the substantia gelatinosa of the spinal trigeminal nucleus of the guinea pig. J Neurophysiol 1996; 76: 3817-22.
9. Kiyosawa A, Katsurabayashi S, Akaike N, Pang ZP, Akaike N. Nicotine facilitates glycine release in the rat spinal dorsal horn. J Physiol 2001; 536: 101-10.
10. Yang HJ, Shin MC, Chang HK, Jang MH, Lee TH, Kim YJ, Chung JH, Kim CJ. Bupivacaine and ropivacaine suppress glycine- and glutamate-induced ion currents in acutely dissociated rat hippocampal neurons. Neurosci Lett 2003; 344: 33-6.
11. Xu F, Garavito-Aguilar Z, Recio-Pinto E, Zhang J, Blanck TJ. Local anesthetics modulate neuronal calcium signaling through multiple sites of action. Anesthesiology 2003; 98: 1139-46.
12. Bernardini N, Roza C, Sauer SK, Gomeza J, Wess J, Reeh PW. Muscarinic M2 receptors on peripheral nerve endings: a molecular target of antinociception. J Neurosci 2002; 22: 229.
13. Hama AT, Lloyd GK, Menzaghi F. The antinociceptive effect of intrathecal administration of epibatidine with clonidine or neostigmine in the formalin test in rats. Pain 2001; 91: 131-8.
14. Moore CM, Desvorough JP, Powell H, Burrin JM, Hall GM. Effects of extradural anesthesia on interleukin-6 and acute phase response to surgery. Br J Anesth 1994; 72: 272-9.
15. Cruickshank AM, Fraser WD, Burns HJG, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci 1990; 79: 161-5.
16. Tsukada K, Katog H, Shimojima M, Suzuki T, Takenoshita S, Nagamachi Y. Concentration of cytokines in peritoneal fluid after abdominal surgery. Eur J Surg

1993 ; 159 : 475–9.
17. Kim MH, Hahn TH. The effect of clonidine pretreatment on the perioperative proinflammatory cytokines, cortisol, and ACTH responses in patients undergoing total abdominal hysterectomy. Anesth Analg 2000 ; 90 : 1441–4.
18. Beiin B, Bessler H, Mayburd E, Smirnov G, Dekel A, Yardeni I, Shavit Y. Effect of preemptive analgesia on pain and cytokine production in the postoperative period. Anesthesiology 2003 ; 98 : 151–5.
19. Cui JG, Holmin S, Mathiesen T, Meyerson BA, Linderoth B. Possible role of inflammatory mediators in tactile hypersensitivity in rat model of mononeuropathy. Pain 2000 ; 88 : 239–48.
20. Murphy PG, Ramer MS, Borthwick L, Gauldie J, Richardson PM, Basby MA. Endogenous interleukin-6 contributes to hypersensitivity to cutaneous stimuli and changes in neuropeptides associated with chronic nerve constriction in mice. Eur J Neurosci 1999 ; 11 : 2243–53.