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Effects of Continuous Epidural Infusion of Neostigmine on Postoperative Pain Status and Inflammatory Responses

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ABSTRACT

Epidural neostigmine has antinociceptive effects. We hypothesized that continuous epidural infusion of neostigmine might have beneficial effects on postoperative pain status and inflammatory responses. This study was conducted in a randomized, double-blind fashion. Thirty women with American Society of Anesthesiologists physical status I undergoing abdominal surgery were randomly divided into three groups : a control group (group C), a neostigmine bolus group (group N), and a continuous neostigmine infusion group (group CN). All patients received 10-ml epidural bolus of 1% mepivacaine followed by continuous epidural infusion of 0.25% bupivacaine at 4 ml/hour. In addition, patients in groups N and CN received an epidural bolus of 0.3 mg neostigmine, and patients in group CN received continuous epidural infusion of neostigmine at 0.04 mg/hour. The patients' pain was assessed with a visual analogue scale (VAS) 2, 24, and 72 hours after surgery. The VAS scores in group N (2 hours : median, 0.5 [25^{th}-75^{th} percentile, 0-3.5] ; 24 hours : 1.3 [0-2.5]) and CN (2 hours : 1 [0-3] ; 24 hours : 2 [0-2] ; $n=10$) were significantly ($p<0.05$) lower than those in group C (2 hours : 7 [4.5-8] ; 24 hours : 4 [2-5]). The times for first rescue analgesics in group N (11.5 [2-24]) and CN (10 [2-24]) were also longer than that in group C (2 [2-2.5]) but did not differ significantly between groups N and CN. Bolus administration of epidural neostigmine produced postoperative analgesic effects, but continuous infusion of neostigmine provided no additional benefit. (Jikeikai Med J 2005 ; 52 : 7-13)

Key words : neostigmine, epidural, continuous infusion, postoperative pain, stress response

INTRODUCTION

Epidural neostigmine is a useful for treating perioperative pain. The antinociceptive effects of neostigmine result from its inhibition of the breakdown of spinally released acethylcholine (ACh). The accumulated ACh activates inhibitory interneurons in the spinal cord to modulate sensory input. One advantage of the epidural route of administration of neostigmine over the intrathecal route is the lower incidence of adverse events, such as nausea and vomiting[1,2]. Epidural neostigmine administered with lidocaine produces an analgesic effect and reduces postoperative rescue analgesic use in patients undergoing minor orthopedic procedures[3]. Analgesia lasts longer in patients who receive epidural neostigmine with bupivacaine than in patients who receive bupivacaine alone after abdominal hysterectomy[4]. We have also reported that preincisional administration of epidural neostigmine reduces postoperative pain scores and decreases plasma levels of cortisol early after surgery in patients undergoing lower abdominal surgery[5]. However, the effects of preincisional neostigmine are short-lived and insufficient and plasma levels of interleukin (IL)-6 are not effected. These findings suggest that the effects of neostig-

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mine would not last long enough to suppress the inflammatory responses following surgical incision.

The unsatisfactory results of our previous study led us to contemplate an alternative technique. Although its pharmacokinetics are not completely understood, epidural neostigmine is reported to relieve pain for 5 to 6 hours[2]. We hypothesized that the continuous epidural infusion of neostigmine would enhance the effects of preincisional neostigmine and decrease the inflammatory response. Therefore, we examined the effects of continuous epidural infusion of neostigmine on patients' pain scores by using a visual analogue scale (VAS) postoperatively. We also measured plasma concentrations of IL-6 and cortisol perioperatively.

Materials and Methods

After we obtained the approval of The Jikei University School of Medicine's Ethics Committee for Biomedical Research and written informed consent from each subject, 30 women undergoing lower abdominal surgery for benign gynecological diseases (abdominal total hysterectomy, myomectomy, salpingo-oophrectomy, or ovarian cystectomy) were randomly divided into three groups as follows: a control (group C), a neostigmine bolus group (group N), and a continuous neostigmine group (group CN). Exclusion criteria were age greater than 50 years; a history of corticosteroid use; hypersensitivity to mepivacaine, bupivacaine, or neostigmine; a history of sensory deficits; and surgical blood loss greater than 1,500 ml. All patients had American Society of Anesthesiologists physical status I. Patients received instructions on 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 randomized, double-blind fashion.

Patients received oral premedication consisting of 7.5 mg of zopiclone (ultrashort-acting benzodiazepine receptor agent) and 150 mg of ranitidine 90 minutes before arriving in the operating room. After the epidural space had been identified with the loss-of-resistance method, an epidural catheter was placed through a 17-gauge Tuohy needle at the L1-L2 interspace. After receiving a negative test dose consisting of 3 ml of 1% epidural mepivacaine, all patients received a bolus of 7 ml of 1% mepivacaine before the induction of general anesthesia, then received a continuous epidural infusion of 0.25% bupivacaine at 4 ml/hour for 30 hours starting 1 hour after the start of surgery. Patients in group N received an additional bolus dose of 0.3 mg neostigmine before the induction of general anesthesia, and patients in group CN received both an additional bolus dose of 0.3 mg neostigmine and an additional continuous infusion of neostigmine at 0.04 mg/hour (Fig. 1). The preincisional dose of 0.3 mg of neostigmine was chosen because of the unsatisfactory results of the previous study[5] and because of a desire to minimize side effects. The continuous infusion dosage of 0.04 mg/hour for 30 hours was selected on the basis of neostigmine's putative pharmacokinetics[3].

The dermatomal analgesic level was evaluated with an alcohol swab 10 minutes after the administration of epidural anesthesia. 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, 67% N_2O, intermittent doses of vecuronium (1 to 2 mg) as clinically indicated. Upon the earliest sign of pain (i.e.; increasing blood pressure, heart rate, and pupil size), additional epidural 1% mepivacaine (3 to 5 ml) was administered by an anesthesiologist blinded to the patient's group assignment.

For postoperative pain relief, drip infusion of 2 mg of butorphanol over 1 hour at an interval of at least 6 hours was ordered by the patient's gynecologist and given upon patient request. If patients still complained of pain, a 50-mg dicrofenac suppository was available.

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

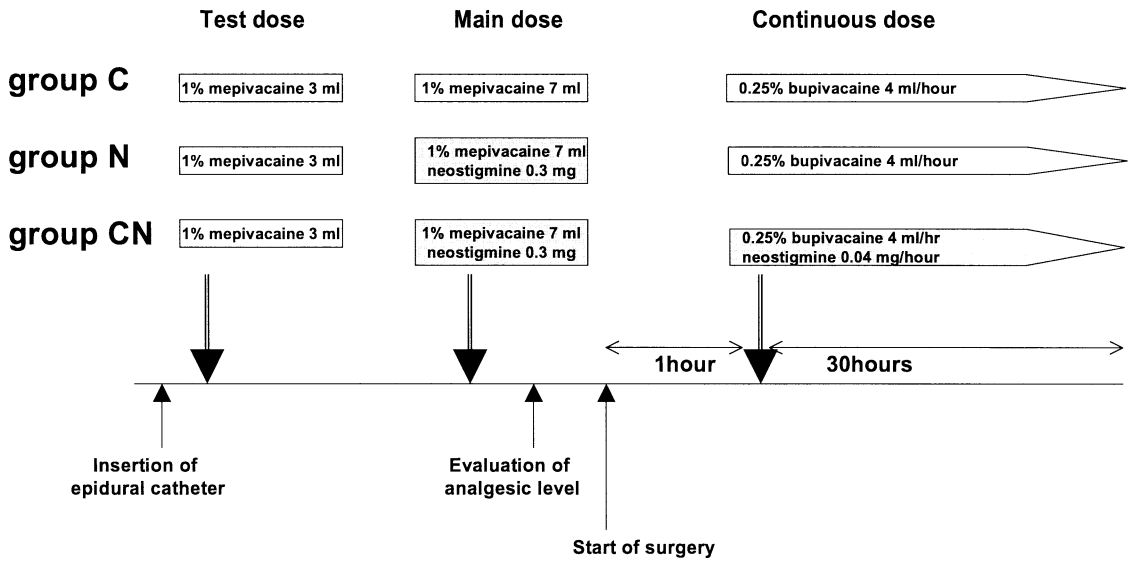

Fig. 1. Design of the study in each group

Blood samples were obtained to measure plasma levels of IL-6 and cortisol upon arrival at the operating room, 30 minutes after the start of surgery, upon admission to the postanesthesia care unit, and 24 hours after the conclusion 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 level of IL-6 and cortisol were determined with an enzyme-linked immunosorbent assay kit (Amersham Pharmacia Biotech Inc, Piscataway, NJ, USA) and an enzyme immunoassay kit (Diagnostic Systems Laboratories, Inc, Webster, TX, USA), respectively.

A sample size of 10 patients in each group was calculated with the STATA statistical software program (version 8.0 ; Stata Corp., College Station, TX, USA) to have at least 80% power with α value of 0.017 to detect reduction of pain scores from 5.9±2.5 to 1.8±1.3 (mean±SD) between groups. These numbers were selected with the assumption that neostigmine had the same effects as in our previous study[5]. This assumption would require five patients in each group. To further increase the power, we studied 10 patients in each group. The data were analyzed using repeated-measure analysis of variance, with subsequent intragroup comparisons made with Scheffe's F-test. The VAS scores and the time for first rescue analgesics were analyzed with the Mann-Whitney U-test. A p value<0.05 was considered to indicate significance.

Results

Patient characteristics, duration of operation, the total amount of 1% mepivacaine used, and dermatomal analgesic level did not differ between groups (Table 1).

The types of surgical procedures performed during the study are shown in Table 2.

Additional mepivacaine in the first 30 minutes after surgical incision was administered to 6, 9, and 7 patients in groups C, N, and CN, respectively. No patient required further epidural administration of

Table 1. Summary of treatment groups

group	group C	group N	group CN
Age (years)	38±7	37±9	40±9
Body weight (kg)	55±7	53±9	48±6
Height (cm)	161±7	158±6	159±7
Surgery duration (minute)	85±19	78±19	84±38
Total amount of mepivacain (ml)	15.0±4.3	16.4±3.8	14.0±2.9
Dermatomal analgesic level (range)	7.4±0.7 (Th7-9)	7.1±0.9 (Th6-9)	7.2±0.9 (Th6-9)

Data are expressed mean±SD (n=10)
There were no differences between groups

Table 2. Operative Procedures Performed

group	group C	group N	group CN
Total abdominal hysterectomy	4	1	5
Salpingo-oophorectomy	1	2	0
Myomectomy	4	5	3
Ovarian cystectomy	1	2	2

mepivacaine after the start of continuous epidural infusion of bupivacaine.

The VAS pain scores 2 and 24 hours after the completion of surgery were significantly lower in groups N and CN than in group C (Table 3). However, the addition of continuous infusion of neostigmine (group CN) did result in pain scores lower than those achieved with preincisional neostigmine (group N). Although bolus administration of epidural neostigmine (groups N and CN) increased the time before first rescue analgesics, continuous infusion of neostigmine (group CN) had no effect.

Use of the analgesic butorphanol during the first 24 hours postoperatively did not differ among the groups (3.8±1.9, 2.4±2.4, and 2.8±2.6 mg in groups C, N, and CN, respectively. $n=10$, mean±SD). However, two patients in group C required only additional diclofenac.

Levels of IL-6 increased during and after the operation; however, IL-6 levels did not differ among the groups (Fig. 2).

Although cortisol levels increased after surgery in group C, the increases in cortisol levels 30 minutes after the start of surgery were not observed in group N and CN (Fig. 3). Levels of cortisol were significantly lower in group N and CN than group C.

Nausea and vomiting, were observed in 1, 0, and 1 patient in groups C, N, and CN, respectively, and either required no treatment or were easily treated with 10 mg metoclopramide (0, 0, and 1 patient). The patients complained of no other side effects.

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

	group C	group N	group CN
2 hours	7[4.5-8]	0.5[0-3.5]*	1[0-3]*
24 hours	4[2-5]	1.3[0-2.5]*	2[0-2]*
72 hours	1[0-2.5]	0[0-0.5]	0[0-0.5]
Time for first rescue analgesics (hours)	2[2-2.5]	11.5[2-24]*	10[2-24]*

Data are expressed median [25th-75th percentile] ($n=10$)
*$p<0.05$ vs group C

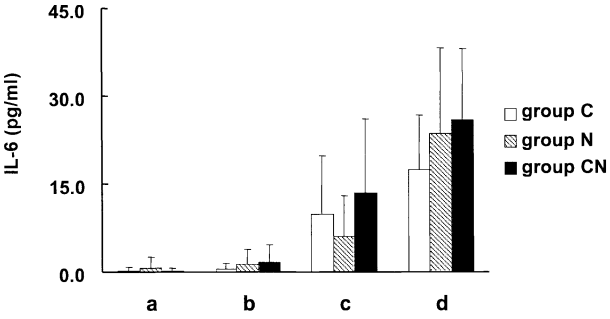

Fig. 2. Plasma levels of IL-6. Blood samples were obtained: **a**, upon arrival at the operating room; **b**, 30 minutes after the start of surgery; **c**, upon entering the postanesthesia care unit; and **d**, 24 hours after the conclusion of surgery. Plasma levels of IL-6 were determined with using enzyme-linked immunosorbent assay. Data are expressed as mean±SD ($n=10$). There were no differences between groups.

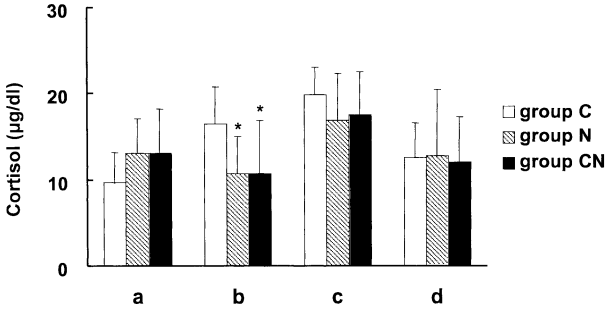

Fig. 3. Plasma levels of cortisol. Blood samples were obtained: **a**, upon arrival at the operating room; **b**, 30 minutes after the start of surgery; **c**, upon entering the postanesthesia care unit; and **d**, 24 hours after the conclusion of surgery. Data are expressed as mean±SD ($n=10$). *$p<0.05$ vs group C

DISCUSSION

The findings of the present study were similar to those of our previous study[5]: preincisional epidural neostigmine decreased postoperative pain scores but did not affect IL-6 levels. In addition, contrary to our hypothesis, the continuous epidural infusion of neostigmine did not enhance the analgesic effects of preincisional epidural administration of neostigmine

and did not decrease inflammatory responses, as assessed with levels of IL-6. Therefore, continuous infusion of neostigmine does not enhance the effects of preincisional neostigmine.

There are several possible explanations why continuous epidural infusion of neostigmine did not lead to further improvements in postoperative pain status and inflammatory and stress responses. First, two types of nociceptive inputs are produced after a surgical procedure. Inputs from incisional injury are followed by inputs from inflammatory responses[6]. These inputs result in complicated pain responses, such as spontaneous pain, hyperalgesia, and allodynia, which are extremely difficult to treat with conventional analgesics[7,8]. Therefore, both types of input must be controlled to improve the analgesic status of patients postoperatively. The effectiveness of neostigmine for treating acute incisional pain has been demonstrated by several studies, including ours[2,5,9]. We attempted to use continuous epidural infusion of neostigmine to control nociceptive responses produced by both incisional injury and inflammatory responses. However, this treatment did not improve the postoperative pain status, suggesting that the nociceptive input from inflammatory responses cannot be controlled with epidural neostigmine.

A second possible explanation is that long-term exposure to ACh due to continuous infusion of neostigmine can desensitize the ACh receptor. The activation of both muscarinic and nicotinic receptors are intimately involved in the mechanism of antinociception in the spinal cord[10,11]. Agonist-induced desensitization occurs with both types of receptor[12,13]. Although the implications for desensitization in physiological, pathological, and pharmacological states are diverse[14-16], desensitization leads to loss of response during periods of repetitive stimulation[17]. The desensitization of ACh receptors in the spinal cord might contribute to the unsuccessful attempts to enhance analgesia with continuous infusion of epidural neostigmine.

A third possible explanation for the lack of further improvement with continuous epidural infusion of neostigmine is that the dosage might have been insufficient. In our previous study[5], we examined the effect of preincisional epidural neostigmine at doses as high as 0.15 mg. For the present study we chose a higher preincisional dose of 0.3 mg because of the unsatisfactory results and no significant side effects of the previous study. Contrary to our expectations, increasing the dose of preincisional neostigmine did not enhance its antinociceptive effects, suggesting the analgesic effects reach a plateau ; therefore, the dose of preincisional neostigmine is sufficient. However, we have not examined the dose-dependence of continuously infused neostigmine. The continuous infusion dosage of 0.04 mg/hr for 30 hours was selected on the basis of neostigmine's putative pharmacokinetics[3]. Increasing the dosage for continuous infusion of neostigmine may lead to better analgesic effects.

In this study, epidural neostigmine, even when continuously infused, did not affect plasma levels of IL-6. This finding supports the notion that nociceptive inputs from the inflammatory response by the surgical incision could not be controlled with epidural neostigmine, as mentioned above. The elevation of IL-6 after abdominal hysterectomy can be successfully suppressed by preoperative administration of oral clonidine[18] and preemptive epidural analgesia with bupivacaine and fentanyl[19]. However, Moor et al. have reported that blockade of painful stimuli with extradural analgesia does not regulate the production of IL-6[20]. Whether blocking pain helps decrease the production of proinflammatory cytokines or whether reduced production of proinflammatory cytokines results in less severe pain being experienced is difficult to determine[19]. However, the control of IL-6 production is an important consideration because IL-6 is involved in the mechanisms of allodynia and postoperative neuropathic pain[21,22]. An alternative technique, such as co-administration of neostigmine and anti-inflammatory agents, may suppress IL-6 production after surgery. Indeed, an antinociceptive synergistic interaction between neostigmine and anti-inflammatory agents has been reported in mice[23].

Milder and less frequent side effects could be an advantage of administering neostigmine via the epidural route rather than the intrathecal route. In the present study only two patients complained of

nausea and one patient was given metoclopramide. We did not observe any other side effects, such as hemodynamic instability, even in group CN. The severe gastrointestinal side effects of neostigmine after intrathecal injection limit its routine clinical use[2]. Because neostigmine is hydrophilic[3], the dura mater and the arachnoid help slow its entry into the cerebrospinal fluid and spinal cord and minimize side effects.

Additional epidural injection of mepivacaine was needed in 73% of patients (22 of 30 patients) in the present study. The cortisol level in group C was also increased 30 minutes after the start of surgery. These results indicate that basal epidural anesthesia with 10 ml of mepivacaine is not sufficient to block nociceptive inputs from incisions for lower abdominal gynecologic surgery. Preincisional administration of epidural neostigmine resulted in postoperative analgesia under these conditions. However, whether epidural neostigmine has further antinociceptive effects when administered with local anesthetics in surgical concentrations is uncertain. Additional studies are necessary to evaluate the effects of epidural neostigmine on perioperative analgesia.

In summary, epidural neostigmine had postoperative analgesic effects but had no effect on the inflammatory and stress responses. The continuous infusion of neostigmine during and after surgery failed to enhance the preincisional effects of neostigmine. Alternative techniques, such as co-administration of other types of drug, may increase the clinical usefulness of epidural neostigmine.

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