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Long-term Postoperative Analgesic Effects of Continuous Epidural Co-administration of Neostigmine and Adenosine

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ABSTRACT

Neuraxial administration of neostigmine and adenosine produces antinociceptive effects. We have hypothesized that the continuous epidural co-administration of neostigmine and adenosine might allow better postoperative pain control. This study was conducted in a randomized, double-blind fashion. Thirty patients with American Society of Anesthesiologists physical status I undergoing abdominal surgery were randomly assigned to three groups : a control group (group C), a bolus neostigmine and adenosine group (group NA), and a continuous neostigmine and adenosine group (group CNA). In group C, patients received 10 ml of 0.75% epidural ropivacaine followed by continuous infusion of 0.2% ropivacaine at 4 mL/hour. The same amount of 0.75% ropivacaine along with 0.3 mg of neostigmine and 2 mg of adenosine was administered to both group NA and group CNA. In addition, neostigmine (0.04 mg/hour) and adenosine (0.27 mg/hour) were added to the continuous infusion of 0.2% ropivacaine in group CNA. The patients' pain was assessed with a visual analogue scale (VAS) 2, 24, and 72 hours after surgery. The VAS scores at 24 hours in group NA (0.6 ± 1.1, mean$\pm$SD, $n=10$) and group CNA (0.6 ± 1.4) were significantly ($p<0.05$) lower than those in group C (4.0 ± 2.7). Furthermore, at 72 hours the VAS score was significantly lower in group CNA (0.1 ± 0.4) than in group C (1.8 ± 1.2) or group NA (1.1 ± 0.9). The bolus epidural co-administration of neostigmine and adenosine improved postoperative pain status, and the continuous co-administration of both agents prolong the analgesic effect.

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Key words : neostigmine, adenosine, epidural, continuous infusion, postoperative pain

INTRODUCTION

The neuraxial administration of neostigmine and adenosine has been reported to be a useful technique for improving perioperative pain management[1,2]. The antinociceptive effects of neostigmine result from its inhibition of the breakdown of spinally released acetylcholine. The accumulated acetylcholine activates inhibitory interneurons in the spinal cord to modulate sensory input[3]. In contrast, adenosine inhibits excitatory glutamatergic neurotransmission through presynaptic and postsynaptic mechanisms[4]. The duration of analgesia is greater in patients who receive epidural neostigmine after abdominal hysterectomy[1], and intrathecal adenosine produces long-lasting relief from chronic neuropathic pain[2]. An advantage of the epidural route over the intrathecal route for the administration of neostigmine and adenosine is the lower incidence of adverse effects, such as nausea and vomiting[5,6]. We have previously

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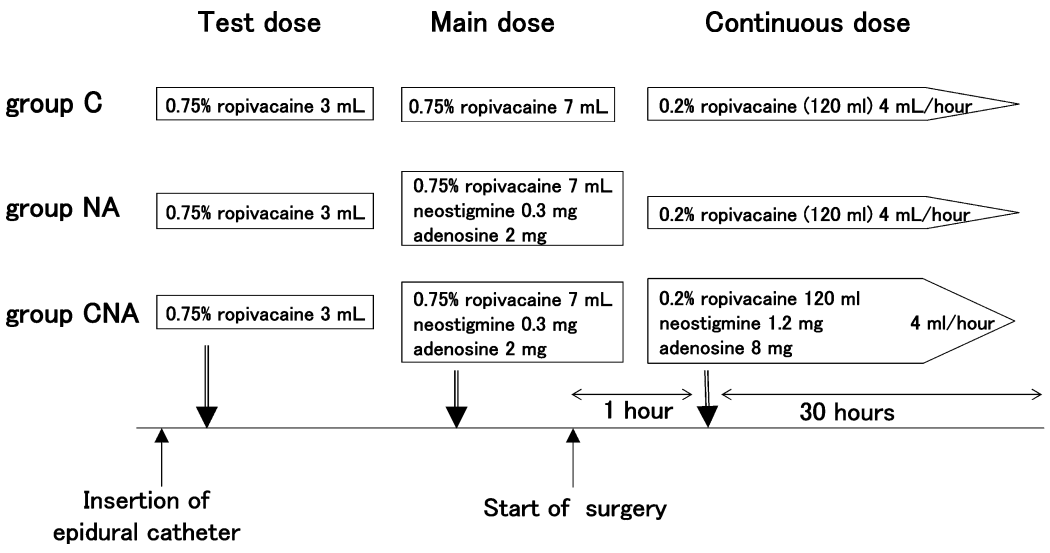

Fig. 1. Study design for each group.

reported that bolus epidural administration of neostigmine reduces postoperative pain scores of patients undergoing lower abdominal surgery[7,8] and that these effects are enhanced by co-injection of adenosine[9]. However, the effects of bolus epidural co-administration of neostigmine and adenosine are transient and insufficient.

The failure of bolus epidural co-injection of neostigmine and adenosine to produce long-term reductions in postoperative pain scores prompted us to seek an alternative technique. Although the exact pharmacokinetics of epidural neostigmine and adenosine are unknown, epidural neostigmine and intrathecal adenosine relieve pain for 5 to 6 hours[6] and for 24 hours[10], respectively. We hypothesized that the continuous epidural co-administration of neostigmine and adenosine would prolong the analgesic effects of bolus co-administration of neostigmine and adenosine. Therefore, we examined the effects of the continuous epidural co-injection of neostigmine and adenosine on the pain scores of patients by using a visual analogue scale (VAS) postoperatively. We also measured the plasma concentration of interleukin (IL)-6 and cortisol perioperatively.

METHODS

After obtaining the approval of The Jikei University School of Medicine Ethics Committee for Biomedical Research and individual written informed consent, 30 patients undergoing lower abdominal surgery for benign gynecological conditions (total abdominal hysterectomy, myomectomy, salpingo-oophorectomy, or ovarian cystectomy) were randomly divided into 3 groups as follows; a control group (group C), a bolus neostigmine and adenosine group (group NA), and a continuous neostigmine and adenosine (group CNA). Patients were excluded if they were older than 50 years, had a history of corticosteroid use, had known hypersensitivity to ropivacaine, neostigmine, or adenosine, or had a history of sensory deficits. All patients were American Society of Anesthesiologists physical status I and were instructed before surgery 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. The study was conducted in a randomized, double-blind 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 patient's arrival in the operating room. The epidural space was identified with 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% epidural ropivacaine, patients received a bolus dose of 7 mL of 0.75% ropivacaine before the induction of general anesthesia. Continuous epidural infusion of 0.2% ropivacaine at rate of 4 mL/hour was started 1 hour after the start of surgery for 30 hours in group C. Seven milliliters of 0.75% ropivacaine, 0.3 mg of neostigmine, and 2 mg of adenosine were administered as a bolus to patients in group NA and group CNA. Furthermore, neostigmine (0.04 mg/hour) and adenosine (0.27 mg/hour) were added to the continuous infusion of ropivacaine in group CNA (Fig. 1).

The dermatomal analgesic level was evaluated with an alcohol swab 10 minutes after 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 and 67% N_2O, intermittent doses of vecuronium (1 to 2 mg), and epidural 0.75% ropivacaine (3 to 5 mL) as clinically indicated. Upon the earliest signs of pain (e.g., increasing blood pressure, heart rate, and pupil size), additional epidural 0.75% ropivacaine (3 to 5 mL) was administered by an anesthesiologist who was blinded to the study protocol.

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

For postoperative pain relief, a conventional analgesic (drip infusion of 2 mg of butorphanol over 1 hour after an interval of at least 6 hours) was prescribed by the gynecologist if requested by the patient.

Blood samples were obtained to measure plasma levels of cortisol and IL-6 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 completion 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 a commercially available 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 a statistical analysis software program (STATA version 8.0; Stata Corporation, College Station, TX. USA) to have at least 80% power with an α value of 0.017 to detect reduction of pain scores from 5.9±2.5 to 1.8±1.3 (mean±SD) between the groups. These numbers were selected with the assumption that neostigmine has the same effects as demonstrated in a previous study[7]. To validate this assumption, at least 5 patients were required for 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 Scheffé's F-test.

Results

Patient details, total doses of bolus 0.75%

Table 1. Summary of Treatment Groups

	group C	group NA	group CNA
Age (years)	38±8	39±5	40±8
Body weight (kg)	54±8	53±5	55±8
Height (cm)	157±6	157±7	158±5
Total amount of ropivacaine (mL)	10.4±1.4	10.8±1.7	10.0±0
Analgesic level	Th7 (6-8)	Th7 (7-8)	Th7 (7-8)
[range]	[Th6-9]	[Th6-9]	[Th6-9]

Data are expressed as mean±SD or median (interquartile range), $n=10$

Table 2 Operative Procedures Performed

	group C	group NA	group CNA
Total abdominal hysterectomy	4	1	3
Salpingo-oophorectomy	0	0	0
Myomectomy	5	8	5
Ovarian cystectomy	1	1	2

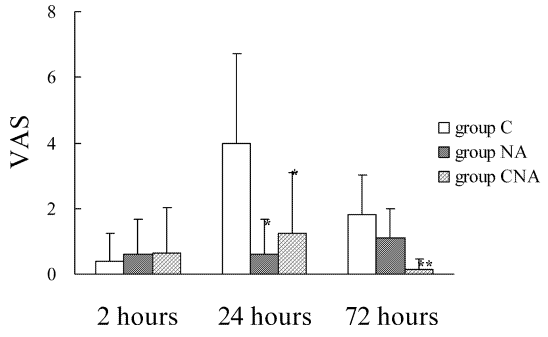

Fig. 2. Postoperative VAS scores. The postoperative pain status was assessed with a VAS 2, 24, and 72 hours after completion of surgery with the patients at rest. Data are expressed as mean±SD (n=10).
*P<0.05 vs group C, **P<0.05 vs groups C and NA

ropivacaine, and dermatomal analgesic levels did not differ between the groups (Table 1).

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

Additional bolus doses of 0.75% ropivacaine to control the earliest signs of pain after surgical incision were administered to 1, 2, and 0 patients in groups C, NA, and CNA, respectively. No patient required additional epidural doses of 0.75% ropivacaine after the start of continuous epidural infusion of 0.2% ropivacaine.

The VAS scores for pain status 2 hours after the completion of surgery did not differ among the groups. However, at 24 hours, the VAS scores in groups NA and CNA were significantly lower than those in group C. Furthermore, at 72 hours VAS scores were significantly lower in group CNA than in groups C and NA (Fig. 2).

Epidural neostigmine and adenosine did not significantly alter perioperative cortisol levels (Fig. 3). Levels of IL-6 increased during and after surgery but did not differ significantly between the groups (Fig. 4).

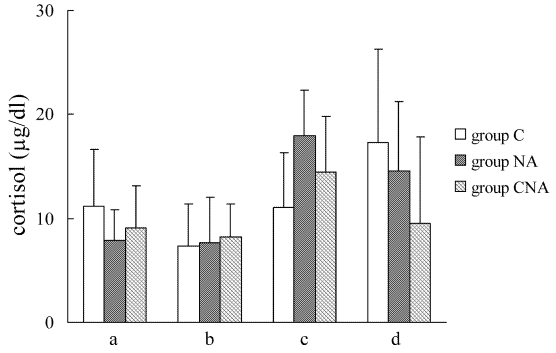

Fig. 3. Plasma levels of cortisol. Blood samples were drawn: a) upon entering the operating room, b) 30 minutes after the start of surgery, c) upon admission to the postanesthesia care unit, and d) 24 hours after the completion of surgery. Data are expressed as mean±SD (n=10). There were no differences between the groups.

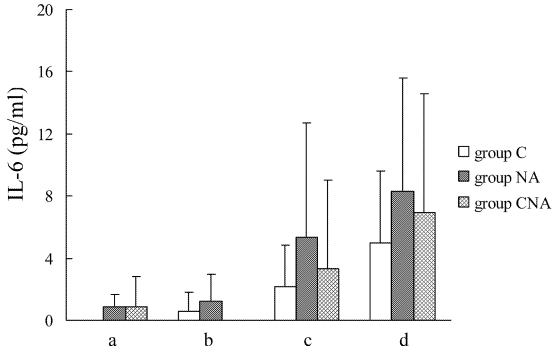

Fig. 4. Plasma levels of IL-6. Blood samples were drawn: a) upon entering the operating room, b) 30 minutes after the start of surgery, c) upon admission to the postanesthesia care unit, and d) 24 hours after the completion of surgery. Plasma levels of IL-6 were determined with an enzyme-linked immunosorbent assay kit.
Data are expressed as mean±SD (n=10). There were no differences between the groups.

Nausea and vomiting, which were assessed without a nausea scale only when patients complained, developed in 1, 4, and 2 patients in groups C, NA, and CNA, respectively, and were easily treated with 10 mg of metoclopramide. The patients complained of no other side effects. Consumption of the analgesic (butorphanol) during the first 24 hours after surgery did not differ significantly among the groups (2.8±1.9, 2.0±1.7, and 1.7±1.4 mg in groups C, NA, and CNA, respectively; n=10, mean±SD).

Discussion

The main findings of the present study were that bolus epidural co-administration of neostigmine and adenosine decreased the postoperative pain scores of patients and that continuous co-administration of both agents prolonged the analgesic effect. These results suggest that the continuous epidural co-administration of neostigmine and adenosine is effective for the long-term control of several types of nociceptive input generated by surgical procedures. Continuous epidural co-administration of neostigmine and adenosine would be a useful technique for reducing postoperative pain.

After the surgical procedure, the nociceptive input from the incisional injury is followed by that from inflammatory responses[11]. These inputs result in complicated pain responses, such as spontaneous pain, hyperalgesia, and allodynia, which are extremely difficult to treat with conventional analgesics[12,13]. Acute incisional pain is well managed with epidural neostigmine[6,7], and neuropathic pain responds to adenosine, as do hypersensitivity and allodynia[10,14]. Therefore, we have previously attempted to use bolus epidural co-administration of neostigmine and adenosine to alleviate postoperative pain[9]. However, the effects were transient and insufficient. In the present study, continuous epidural co-administration of neostigmine and adenosine prolonged the postoperative analgesic effects of bolus co-administration of both agents. This finding suggests that the nociceptive inputs generated by the surgical procedure continue after surgery and that the continuous administration of several kinds of analgesics is necessary to manage complicated postoperative pain.

Although epidural co-administration of neostigmine and adenosine improved the postoperative pain status, it did not affect plasma levels of cortisol and IL-6. The plasma cortisol level is elevated after surgical insults, and several attempts have been made to control this response with epidural anesthesia[15,16]. In the present study, plasma cortisol levels were within the normal range throughout the perioperative period in all groups. This finding suggests that basal epidural anesthesia with ropivacaine alone is sufficient to block neural input from surgical wounds that stimulate stress responses. In contrast, plasma IL-6 levels were elevated by the surgical procedure to similar levels in all groups. These results are consistent with the finding of Moor et al[16] that regulation of IL-6 production is not altered even with adequate blockade of painful stimuli by epidural anesthesia. It is difficult to determine whether blocking pain contributes to the reduced production of proinflammatory cytokines or whether reduced production of proinflammatory cytokines results in less severe pain[15]. However, the control of IL-6 production is an important issue because IL-6 is involved in both allodynia and postoperative neuropathic pain[17,18]. An alternative technique, such as the addition of other types of agent, may suppress IL-6 after a surgical procedure. Indeed, antinociceptive interactions including neostigmine and adenosine have been reported in mice[19] and rats[20].

The epidural route was chosen for neostigmine and adenosine because it is associated with fewer side effects[1] than is the intrathecal route. In the present study, 7 patients complained of nausea and vomiting, which were easily treated with metoclopramide. The main side effects after neuraxial administration of neostigmine and adenosine, respectively, are gastrointestinal symptoms[6] and aches of the head, back, and leg[10,21]. If the total dose of neostigmine were decreased, the incidence of nausea and vomiting might be lower than that in the present study. We did not observe any other side effects, such as hemodynamic instability.

Several pieces of evidence support the safety of epidural co-administration of neostigmine and adenosine. First, the safety of neuraxial administration of each compound has been confirmed in human studies[21,22]. Second, a study in rats has suggested that intrathecal co-administration of neostigmine and adenosine does not contribute to severe side effects[23]. Third, to our knowledge no interaction between neostigmine (a quaternary ammonium compound) and adenosine (a nucleoside) has been described. Information supplied by the manufacturers of both agents does not describe drug interactions between neostigmine and adenosine. Fourth, visual inspection of the

mixed solution of neostigmine, adenosine, and ropivacaine revealed no conspicuous reaction. Indeed, none of the patients who had received both neostigmine and adenosine complained of any neurologic symptoms during telephone interviews performed 12 months after surgery.

We did not examine the effects of different doses of neostigmine and adenosine on plasma levels of IL-6 and cortisol or on postoperative pain status. This limitation of the study design raises the question of whether the doses of neostigmine and adenosine were too low to affect plasma levels of IL-6 and cortisol. In addition, larger combined doses of neostigmine and adenosine might have produced greater antinociceptive effects. Additional studies with larger numbers of patients are needed to resolve this question. It is also important to note that the safety and stability of larger combined doses are unknown.

In summary, bolus epidural co-administration of neostigmine and adenosine improves postoperative pain status in patients undergoing open abdominal surgery and continuous co-administration of both agents prolongs the analgesic effect. Continuous epidural co-administration of neostigmine and adenosine may be a useful technique for reducing postoperative pain.

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