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Adenosine Facilitates Postoperative Analgesic Effect of Epidural Neostigmine after Open Lower Abdominal Surgery

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ABSTRACT

To examine whether epidural adenosine enhances the antinociceptive effect of neostigmine, we evaluated the effect of co-administration of epidural neostigmine and adenosine in patients undergoing lower open abdominal surgery for benign gynecological disease. The study was conducted in a randomized, double blind fashion. Forty ASA physical status I patients were randomly assigned into 4 groups to receive either the vehicle (control), 0.3 mg neostigmine, 2 mg adenosine or both with epidural 10 ml of 0.75% ropivacaine before the induction of general anesthesia. The patients' pain rating was assessed by using the visual analogue scale (VAS) at 2, 24, and 72 hr after surgery. The plasma levels of cortisol and interleukin-6 (IL-6) were also measured perioperatively. At 24 hr after surgery, the visual analogue scale for pain scores in patients who received the vehicle (4.5 (1-6.5), median (interquartile range)) were significantly ($p=0.0041$) decreased with epidural co-administration of neostigmine and adenosine (0 (0-1.5)). Epidural neostigmine alone also reduced the scores (2 (0-3.5)) and these were significantly ($p=0.023$) different from those in patients with the epidural adenosine alone (4.5 (2-5)). Epidural neostigmine and adenosine did not change plasma levels of cortisol and IL-6. Epidural adenosine facilitated analgesic effects of neostigmine and improved the postoperative pain status. Co-administration of epidural neostigmine and adenosine could be a useful treatment modality to alleviate postoperative pain.

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Key words : epidural analgesia, neostigmine, adenosine, postoperative pain

INTRODUCTION

Many treatment modalites including new analgesics have been employed to alleviate postoperative pain[1,2]. The neuraxial administration of neostigmine[3,4] and adenosine[5] has been reported to produce antinociceptive effects. In human studies, epidural neostigmine improved postoperative analgesia[3,6]. Intrathecal administration of adenosine produced long-lasting pain relief from chronic neuropathic pain[5].

This study was conducted to examine whether epidural adenosine enhances the effects of neostigmine. We measured the visual analogue scale (VAS), and plasma levels of cortisol and interleukin-6 (IL-6) following co-administration of epidural neostigmine and adenosine.

Epidural route of administration of neostigmine and adenosine was selected because in contrast to intrathecal injection, epidural injection is associated

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with fewer side effects such as nausea and vomiting[7]. Additionally, sites and mechanisms of action of both compounds seem to be different ; therefore, co-administration of neostigmine and adenosine should result in a greater effect than either drug alone.

MATERIALS AND METHODS

After obtaining the approval of the Jikei University School of Medicine Ethics Committee for Biomedical Research and individual written informed consent, 40 patients undergoing open lower abdominal surgery for benign gynecological disease (total abdominal hysterectomy, myomectomy or ovarian cystectomy) were randomly divided, *via* sealed envelope assignment, into 4 groups according to the epidural analgesics administered with ropivacaine (see below). Patients older than 50 years, those with history of steroid medication, those with known hypersensitivity to ropivacaine, neostigmine or adenosine and those with a history of sensory disturbance were excluded from the study. All patients were ASA physical status I and were instructed on the use of the VAS, which consisted of 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 zopiclone 7.5 mg (ultra-short benzodiazepine receptor acting agent), and ranitidine 150 mg was administered 90 min before arrival in the operating room. An epidural catheter was placed through a 17-gauge Tuohy needle using the loss-of-resistance technique at the L1-L2 interspace. Following a negative test dose consisting of 3 ml of 0.75% epidural ropivacaine, an additional 7 ml of 0.75% ropivacaine was administered with 0.3 mg neostigmine (group N), 2 mg adenosine (group A), both compounds (group NA), or vehicle/control (group C). The dermatomal analgesic level was evaluated by using an alcohol swab at 10 min after epidural administration. 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 and intermittent doses of vecuronium (1 to 2 mg) as clinically indicated. Upon early signs of intraoperative pain (i.e. ; increasing BP, HR, and pupil dilation etc.), additional epidural 0.75% ropivacaine (3 to 5 ml) was administered as judged by the anesthesiologist who was blind to the study design. Continuous epidural infusion was started with 0.2% ropivacaine at 4 ml/hr, 1 hr after the start of surgery and continued for 30 hr. Blood pressure was measured every 5 min, and electrocardiogram and percutaneous oxygen saturation were continuously monitored throughout surgery. A decrease in mean arterial blood pressure of more than 20% below preanesthetic baseline level was treated by intravenous increments of ephedrine and by intravenous fluid administration.

For postoperative pain relief, the conventional analgesic (drip infusion of 2 mg butorphanol over 1 hr with a minimum 6 hr interval) ordered by the gynecologist was administered according to the patient request. If pain persisted, 50 mg diclofenac suppository was given with a minimum 4 hr interval.

Blood samples were drawn for measurement of plasma cortisol and IL-6 levels before anesthesia, at 30 min after the start of surgery, upon arrival to the post-anesthesia care unit, and at 24 hr following surgery. The collected blood specimens were subjected to centrifugation at 1,600×g for 15 min and the separated plasma samples were stored at −80°C until analysis. Plasma level of cortisol and IL-6 were determined using commercially available enzyme immunoassay (Diagnostic Systems Laboratories, Inc, Webster, TX) and Enzyme-Linked Immunosorvent Assay (ELISA) kit (Amersham Pharmacia Biotech Inc, Piscataway, NJ), respectively.

The postoperative pain was assessed at rest using VAS at 2, 24 and 72 hr following surgery. Analgesic demand and side effects such as nausea, vomiting, pruritus etc. were assessed and recorded during the first 24 hr after surgery. Nausea and vomiting were treated with 10 mg intravenous metoclopramide upon patient request.

A sample size of 10 patients in each group was calculated using STATA^{tm} (version 8.0 ; Stata Corporation, College Station, Tx) to have a minimum of

80% power with an α value of 0.0083 (two-sided) in order to detect reduction of pain scores from 4.0±1.6 to 2.0±0.8 (mean±SD) between the 2 groups. These numbers are selected with assumption for neostigmine to have the same effect as revealed in a preliminary study. The data were analyzed using repeated measures analysis of variance with subsequent intergroup comparisons made by Bonferroni. The VAS scores were analyzed with the Mann-Whitney U-test. A P value of 0.05 was considered significant.

Results

Patient details, duration of operation, total dose of 0.75% ropivacaine, analgesic level, and the time to first rescue dose of analgesics are summarized in Table 1.

There were no significant differences among the groups. Additional ropivacaine in the first 30 min after surgical incision was required by 1 patient each in groups C and N and 2 patients each in groups A and NA. The types of surgical procedures performed during the study are shown in Table 2.

The VAS scores at 2 and 72 hr after completion of surgery were not significantly different among the groups. However, at 24 hr, the co-administration of epidural neostigmine and adenosine significantly ($p=0.0041$) suppressed the pain scores. The epidural administration of neostigmine also decreased the pain scores, and these were significantly ($p=0.023$) different from those of the epidural administration of adenosine (Table 3).

The plasma cortisol levels are shown in Fig. 1. Epidural neostigmine, adenosine and the co-administration of both compounds did not significantly alter the cortisol levels perioperatively.

Table 1. Summary of Treatment Groups

	group C	group N	group A	group NA
Age (yr)	38±8	36±4	36±5	39±5
Body Weight (kg)	54±8	56±14	54±7	53±5
Height (cm)	157±6	159±6	155±5	157±7
Duration of surgery (min)	86±33	93±61	99±44	99±44
Total amount of ropivacaine (ml)	10.4±1.4	10.6±2.0	10.8±1.8	10.8±1.7
Analgesic level (range)	Th7.3±0.3 (Th6-9)	Th7.4±0.2 (Th6-8)	Th7.3±0.3 (Th6-9)	Th7.4±0.3 (Th6-9)
Time to first rescue dose of analgesics (hr)	8.1±6.7	11.7±5.8	11.9±7.6	12.9±9.0

Data are expressed mean±SD ($n=10$)

Table 2. Operative Procedures Performed

	group C	group N	group A	group NA
Total abdominal hysterectomy	4	3	1	1
Myomectomy	5	4	4	8
Ovarian cystectomy	1	3	5	1

Table 3. Post Operative Pain Scores (VAS)

	group C	group N	group A	group NA
2 hr	0 (0-1 [0-2])	0 (0-0.5 [0-2])	0 (0-0.5 [0-1.5])	0 (0-0.5 [0-3])
24 hr	4.5 (1-6.5 [0-8])	2 (0-3.5 [0-4])†	4.5 (2-5 [1-7])	0 (0-1.5 [0-3])*§
72 hr	2 (0.5-3 [0-3])	0 (0-1 [0-4])	1.5 (0-2.5 [0-3])	1 (0-2 [0-2])

Median (interquartile range [range]),
*$p=0.0041$ (vs group C), †$p=0.023$, §$p=0.001$ vs group A

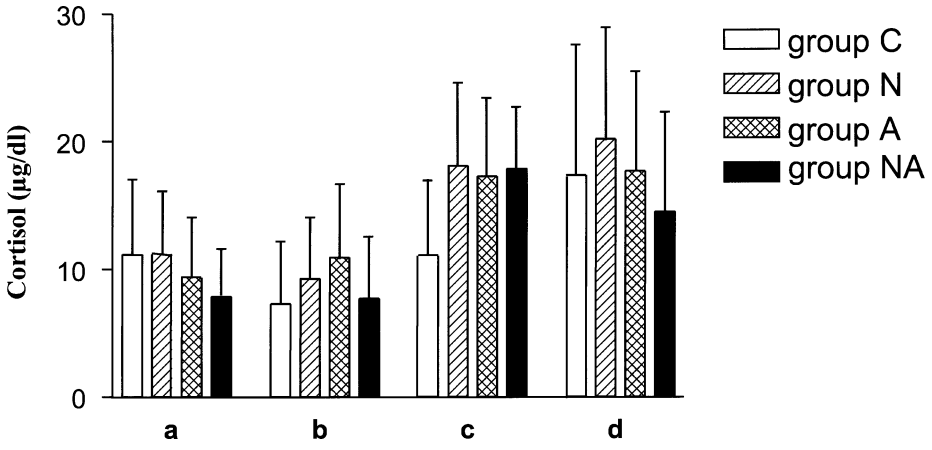

Fig. 1. Plasma levels of cortisol. Blood sampling was performed a ; before induction of general anesthesia, b ; at 30 min after the start of surgery, c ; at the time of entering the postanesthesia care unit, d ; at 24 hr following surgery. Plasma levels of cortisol were determined by enzyme immunoassay.
Data are expressed as mean SD ($n=10$).

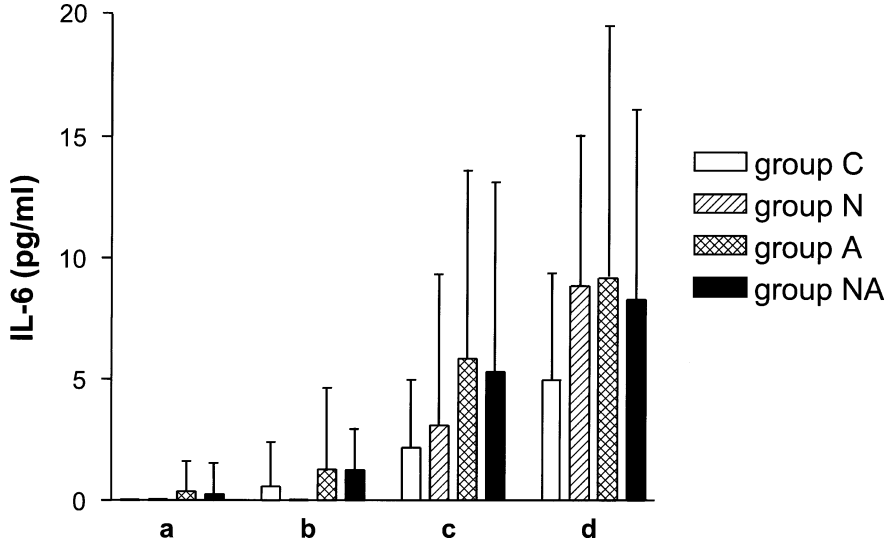

Fig. 2. Plasma levels of IL-6. Blood sampling was performed a ; before induction of general anesthesia, b ; at 30 min after the start of surgery, c ; at the time of entering the postanesthesia care unit, d ; at 24 hr following surgery. Plasma levels of IL-6 were determined by ELISA.
Data are expressed as mean SD ($n=10$).

The plasma IL-6 levels were increased during and following surgery, however, there were no significant differences among the groups (Fig. 2).

Nausea and vomiting, assessed by only the complaint of the patients without using a nausea scale, were observed in 1 patient each in groups C and N, 2 patients in group A and 3 patients in group NA. The patient in group C and N required no treatment while 2 patients in groups A and NA were easily treated with 10 mg metoclopramide. The patients complained of no other side effects. Analgesic (butorphanol) consumption during the first 24 hr postoperatively was not statistically different among the groups (2.8 ± 1.9, 1.8 ± 1.5, 2.3 ± 1.7, and 2.0 ± 1.7 mg in group C, N, A and NA, respectively. $n=10$, mean$\pm$SD). Additional diclofenac administration was required by 1 patient each in groups N and A.

Discussion

The main finding of this study is that co-administration of epidural neostigmine and adenosine improves postoperative pain relief in patients undergoing open lower abdominal surgery for gynecological disease, although adenosine alone does not affect the pain status. These results might indicate that both compounds act together and reduce pain responses that are generated by surgery.

Peripheral nerve injury and consequent inflammatory responses produced by surgical procedures result in 3 different types of pain responses : spontaneous pain, hyperalgesia and allodynia[8]. These neuropathic pain symptoms are difficult to treat with conventional analgesics such as opioids and non-steroidal anti-inflammatory drugs, but may respond to other classes of analgesics such as α_2-adrenergic agonists[9] and tricyclic antidepressants[10]. Both neostigmine and adenosine are alternative analgesics. Postoperative and chronic neuropathic pains are reportedly well managed by the epidural and intrathecal administration of neostigmine[3] and adenosine[5], respectively. Previously, we also demonstrated that epidural neostigmine improved postoperative analgesia, however, these analgesic effects were too of short duration. Significant reduction in postoperative pain scores with co-administration of both neostigmine and adenosine suggests that these 2 compounds cooperate to inhibit the conduction of nociceptive responses.

In the present study, a significant difference in the postoperative pain scores was observed at only 24 hr. The duration of action of neuraxial neostigmine and adenosine are shown to be less than 24 hr[11], in addition, continuous epidural 0.2% ropivacaine was started one hour after the start of surgery and continued for 30 hr. However, the VAS score at 24 hr has been reported to reflect the patient's overall impression during the 24 hr period after the injection[12]. Furthermore, the preemptive analgesic effect of epidural neostigmine[13] and local anesthetics[14] are demonstrated. The epidural neostigmine before surgical stimuli produces analgesic effects at 24 hr following surgery[3,13]. The VAS scores were recorded up to 72 hr to evaluate the preemptive analgesic effects of neostigmine, adenosine and ropivacaine in the present study.

A number of corroborative data support the safety of co-administration of epidural neostigmine and adenosine. First, the safety of neuraxial administration of each compound has been confirmed in human studies. The side effects of epidural neostigmine with local anesthetics were minimal and no serious occurrences have been reported[3]. Head, back and leg ache of unknown etiology have been observed in healthy volunteers[15] and patients[16] after intrathecal injection of adenosine. However, these adverse effects were transient and unlikely to be due to neurotoxicity. Moreover, in peripheral nerve block application, the side effects of adenosine in combination with local anesthetics for brachial plexus block were negligible[17]. Second, there is no report describing the interaction between neostigmine (quaternary ammonium) and adenosine (nucleoside), to our knowledge. The precautions described in the prescribing information of both agents do not include drug interactions between neostigmine and adenosine. Finally, visual inspection of the mixed solution of three drugs (neostigmine, adenosine and ropivacaine) revealed no conspicuous reaction although we did not directly assess the stability of the mixed solution. The solution was clear with no precipitation, haziness or crystallization observed. Indeed, we did not observe any severe undesirable side effects after epidural administration of neostigmine and adenosine. There were no episodes of hemodynamic instability. One patient in group N, two in group A and three in group NA complained of mild nausea and/or vomiting, and were easily treated with 10 mg metoclopramide or required no medication. Furthermore, none of the patients who received both neostigmine and adenosine complained of any neurologic symptoms in the telephone interview performed 12 months after surgery.

The host immune competence is an important self-defense mechanism that is often compromised by surgical and anesthetic procedures. The plasma level of cortisol is elevated after surgical insults and several attempts including epidural anesthesia have been made to control this response[17,18]. In the present study, significant elevation of plasma level of cortisol

was not observed in all groups, suggesting that the basal epidural anesthesia with ropivacaine alone under 1.0–2.0% sevoflurane anesthesia may be sufficient to block neural input from surgical wound to stimulate stress responses. The epidural neostigmine and adenosine would not produce further reduction of plasma cortisol levels in these setting. Unlike the plasma level of cortisol, the level of IL-6 was increased after surgical procedures but not affected by epidural neostigmine and adenosine. These results indicate that the regulation of IL-6 production was not altered by adequate blockade of painful stimuli with epidural anesthesia as suggested by Moor et al[19]. Many factors contribute to the production of IL-6[20,21] and successful treatment approaches to control IL-6 level have been reported in patients undergoing surgery[18,22]. High levels of plasma IL-6 may be associated with undesirable outcomes including increased postoperative pain[23,24], therefore, additional techniques should be sought to regulate the production of IL-6.

In summary, epidural neostigmine and adenosine cooperate and improve postoperative analgesia in patients undergoing open abdominal surgeries, although neither compound alone altered the pain scores significantly. Co-administration of epidural neostigmine and adenosine may be a useful treatment modality for reduction of postoperative pain.

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