原　著

ネオスチグミン硬膜外投与とデクスメデトミジン全身投与併用による
術後早期鎮痛効果の検討

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Co-administration of systemic dexmedetomidine and epidural neostigmine
improves early postoperative pain status

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Abstract : BACKGROUND : Dexmedetomidine has analgesic and anesthetic sparing effects. Accumulating evidence indicates that intrathecal and epidural neostigmine results in antinociceptive effects postoperatively.　The purpose of this study is to investigate whether co-administration of intraoperative systemic dexmedetomidine and epidural neostigmine produces the postoperative analgesic effects.
METHODS : 60 patients undergoing lower abdominal surgery were randomly divided into four groups as follows ; control (group C), neostigmine (group N), dexmedetomidine (group D), and both neostigmine and dexmedetomidine (group ND).　In group C and group D, 10 ml of 0.375% ropivacaine was administered epidurally, while 0.3 mg neostigmine was added to the 0.375% ropivacaine in group N and group ND.　When the general anesthesia was induced, in group D and group ND, dexmedetomidine was started and continued at $0.4 \mu g/kg/hr$ until the end of surgery.　The pain status of patients was assessed by using Visual Analog Scale (VAS) at 2, 4, 6, 24 and 72 h postoperatively.
RESULTS : The co-administration of systemic dexmedetomidine and epidural neostigmine significantly decreased the VAS scores at 2 h after the surgery, although the intraoperative systemic infusion of dexmedetomidine alone did not reduce the postoperative VAS scores.
CONCLUSIONS : The co-administration of systemic dexmedetomidine and epidural neostigmine produced the analgesic effects, however, these effects were very short-lasting and insufficient. These results suggest that alternative approaches such as the higher doses of co-administration of dexmedetomidine and neostigmine may improve postoperative pain status.

Key words : dexmedetomidine, neostigmine, Visual Analog Scale (VAS)

INTRODUCTION

Dexmedetomidine, a specific α_2-receptor agonist, has both sedative and analgesic-sparing properties[1,2]. Analgesic effects of dexmedetomidine were reported when using a computer-controlled thermode to deliver painful heat stimuli in human volunteer studies[3].　Intraoperative infusion of dexmedetomidine was found to reduce postoperative morphine requirement after major inpatient surgery[4] and total abdominal hysterectomy[5].

The peripheral nerve injury and consequent inflammatory responses produced by surgical procedures result in a complicated pain response[6] which 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[7], tricyclic antidepressants[8] and neostigmine[9,10].

We previously demonstrated that co-administration of systemic dexmedetomidine and epidural neostigmine resulted in transient analgesic effects only in late postoperative periods under basal epidural administration of ropivacaine at relatively high dose (0.75%)[11]. Our previous unsatisfactory results prompted us to seek an alternative approach. We speculate that lowering the local anesthetic concentration used for basal epidural anesthesia might emphasize the effects of co-administration of systemic dexmedetomidine and epidural neostigmine. Therefore, we investigated here whether co-administration of intraoperative systemic dexmedetomidine and epidural neostigmine produces postoperative analgesic effects in early periods as well as those in late periods under basal epidural administration of ropivacaine at relatively low doses (0.375%). In patients undergoing lower abdominal surgery, we evaluated their postoperative pain scores using the visual analogue scale (VAS).

METHODS

After obtaining approval from our institutional human ethics committee and individual written informed consent, 60 patients undergoing open lower abdominal surgery *via* infra-unbilical low transverse incision for benign gynecological disease (total abdominal hysterectomy, myomectomy, or ovarian cystectomy) were randomly divided *via* sealed envelope assignment into four groups based on the allocation to receive epidural neostigmine and/or systemic dexmedetomidine as follows : control (group C), epidural neostigmine (group N), systemic dexmedetomidine (group D), and co-administered neostigmine and dexmedetomidine (group ND). Exclusion criteria were age over 50 years, known hypersensitivity to ropivacaine or neostigmine, patients taking analgesics preoperatively and pre-existing neurological deficit. All patients were ASA physical status I or II and were instructed on the use of the VAS, comprising a 10-cm line ranging from 0 "no pain at all" to 10 "the worst possible pain". Patients completed this pain assessment preoperatively and postoperatively. The study was conducted in a prospective, randomized, double-blind, placebo-controlled fashion.

Premedication was achieved with 7.5 mg zopiclone (ultra-short benzodiazepine receptor acting agent), and 150 mg ranitidine orally, prescribed 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. After a negative test dose with 3 ml of 0.375% ropivacaine, group C and group D were administered 7 ml of 0.375% ropivacaine epidurally before the induction of general anesthesia, while group N and group ND were administered 0.3 mg neostigmine added to 7 ml of 0.375% ropivacaine. 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. After general anesthesia was induced, in group D and group ND, a loading dose of dexmedetomidine at 1 μg/kg i.v. over 10 min was started and followed by a continuous infusion at 0.4 μg/kg/h until the end of surgery. Dexmedetomidine (200 μg/2 ml) was diluted with 48 ml of normal saline, and 50 ml of normal saline without dexmedetomidine was used for placebo. Anesthesia was maintained with 0.7 to 1.5% sevoflurane in 33% O_2, 67% N_2O (O_2 : 1 L/min and N_2O : 2 L/min) to maintain the bispectral index values within 45 ± 5 and intermittent doses of vecuronium (1 to 2 mg) as clinically indicated. Continuous epidural infusion with 0.2% ropivacaine at 4 ml/h was started at 30 min after the start of surgery for 25 h. Upon early signs of intraoperative pain (increasing blood pressure, heart rate, pupil dilation, etc.), additional epidural 0.375% ropivacaine (3 to 5 ml) was administered, as judged by the anesthesiologist who was blinded to the study protocol. Blood pressure was measured every 5 min, and electrocardiogram and hemoglobin oxygen saturation were continuously monitored throughout surgery. A decrease in mean arterial pressure of more than 20% below the preanesthetic baseline value was treated by intravenous increments of ephedrine (4-8 mg) and by intravenous fluid administration.

For postoperative pain relief, conventional analgesic (drip infusion of 2 mg butorphanol over 1 h at a minimum 6 h interval) ordered by the gynecologist was given according to patient request for 24 h in addition to the continuous epidural infusion. After the 24 h, 50 mg dicrofenac suppository was available at a minimum

4 hours interval.

　　The postoperative pain status of patients was assessed at rest using VAS scores at 2, 4, 6, 24 and 72 h postoperatively.　Time for first rescue of analgesics and side effects such as nausea, vomiting and pruritus were assessed and recorded during the first 24 h after surgery.　Nausea and vomiting were treated with 10 mg intravenous metoclopramide upon patient request.

　　A sample size of 15 patients in each group was calculated using STATA^{tm} (version 8.0 ; Stata Corporation, College Station, Tx) to have at least 80% power with 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$\pm$SD) between the two groups.　Those pain scores were chosen because the reduction of pain scores from 4.0 to 2.0 is considered clinically significant.　The data were analyzed using repeated measure analysis of variance.　The VAS scores were analyzed using Kruskal-Wallis test with subsequent intergroup comparisons made by Mann-Whitney U test with Bonferroni correction.　A P value < 0.05 was considered significant.

RESULTS

　　Patient details, operative duration, total usage amount of 0.375% ropivacaine, dermatomal analgesic level and time for first rescue analgesic are summarized in Table 1.　Additional bolus 0.375% ropivacaine to control earliest sign of pain after surgical incision was administered to 2, 2, 1 and 3 patients in group C, N, D and ND, respectively.　No patient required further epidural administration of bolus 0.375% ropivacaine after the start of continuous epidural infusion of 0.2% ropivacaine.　There were no significant differences among the groups. The types of surgical procedure performed during the study are shown in Table 2.

　　Neither intraoperative systemic infusion of dexmedetomidine alone nor epidural neostigmine alone as analgesic adjuncts to a continuous epidural infusion of ropivacaine reduced the postoperative VAS pain scores. However, the co-administration of systemic dexmedetomidine and epidural neostigmine significantly decreased the VAS scores at 2 h postoperatively (Figure 1).　Of note, these postoperative analgesic effects were not observed in the late postoperative period (4-72 h).　The VAS scores at all other corresponding times were similar among the groups throughout the observation period.

Table 1.　Summary of Treatment Groups

	group C	group N	group D	group ND
Age (yr)	38±8	36±4	41±7	39±7
Body Weight (kg)	54±9	56±13	51±9	59±9
Height (cm)	157±6	159±6	159±5	160±7
Duration of surgery (min)	86±32	93±51	101±40	99±44
Total amount of ropivacaine (ml)	10.4±1.3	10.6±1.8	10.2±1.1	11±1.9
Dermatomal Analgesic level	Th7 (6.5-8 [6-9])	Th7.5 (7-8 [6-8])	Th7 (7-8 [6-9])	Th7 (7-8 [6-9])
Time to first rescue analgesics (h)	7 (3-24 [2-24])	10 (6-12 [5-24])	7 (4-19 [2-24])	8 (3-24 [2-24])
Analgesic (butorphanol) consumption (mg)	3.0±1.7	2.1±1.6	2.4±1.5	1.7±2.5

Data are expressed as mean±SD or median (interquartile range [range]), $n=15$ There was no significant difference among the groups.

Table 2.　Operative Procedures Performed

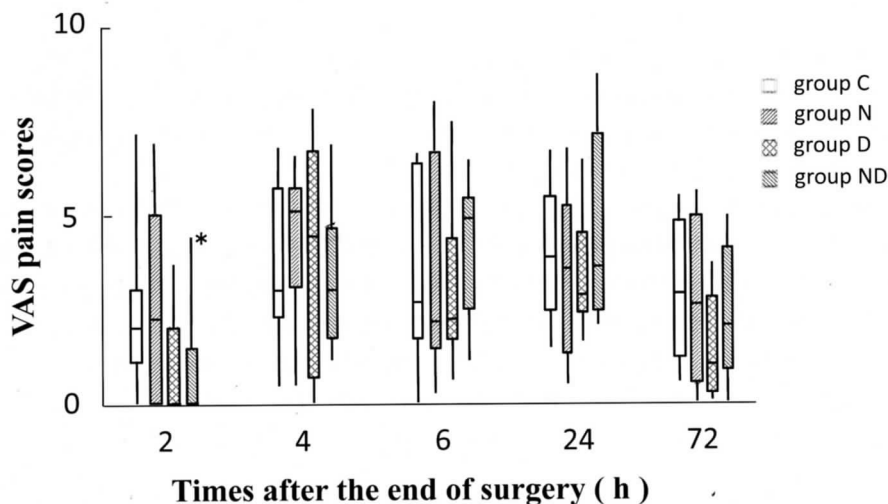|	group C	group N	group D	group ND
Total abdominal hysterectomy	6	7	2	3
Myomectomy	5	4	6	8
Ovarian cystectomy	4	4	7	4

Figure 1. Postoperative VAS scores. The postoperative pain status of patients at rest was assessed using the VAS at 2, 4, 6, 24 and 72 h after the end of surgery. Box represents the 25th-75th percentiles, and solid line represents the median. Extended bars represent the 10th-90th percentiles, $n=15$. VAS scores were significantly lower in group ND compared with group C (*$P<0.05$).

Time to first rescue analgesic did not differ among the groups, and analgesic (butorphanol) consumption during the first 24 h postoperatively was not significantly different among the groups (Table 1). Additional diclofenac was required by 0, 1, 1 and 0 patient in each group, respectively.

Side effects caused by the administration of dexmedetomidine and neostigmine were minimal. Nausea and vomiting, assessed only by patient complaint without use of a nausea scale, were observed in 1 patient in group C, 2 in group N, 0 in group D and 1 in group ND. They either required no treatment, or were easily treated with 10 mg metoclopramide (1 patient in group N and 1 in group ND). Patients complained of no other side effects.

DISCUSSION

The main findings of this study are that co-administration of systemic dexmedetomidine and epidural neostigmine resulted in temporary analgesia postoperatively although intraoperative systemic dexmedetomidine and epidural neostigmine alone did not change postoperative pain score. No serious side effects caused by the administration of dexmedetomidine and neostigmine such as hemodynamic changes was observed in any patients. A few patients complained nausea and vomiting which required no treatment, or were easily treated. These results suggest that the co-administration of both intraoperative systemic dexmedetomidine and epidural neostigmine may be useful for postoperative pain control of patients undergoing lower abdominal surgery under basal epidural administration of ropivacaine at relatively low doses (0.375%) because of lack of serious side effects.

The analgesic effects produced by co-administration of systemic dexmedetomidine and epidural neostigmine were observed in only early postoperative periods but not late postoperative periods despite our expectation. The dose of dexmedetomidine used in this study is recommended dose for sedation in the intensive care unit as mentioned in the prescribed information. The half lives of dexmedetomidine at these doses are reported to be around 2 h while the exact pharmacokinetics epidural neostigmine has not been clarified. The concentration of dexmedetomidine was too low to show analgesic interaction with epidural neostigmine after 4 h postoperatively.

The co-administration of systemic dexmedetomidine and epidural neostigmine produced temporary postoperative analgesic effects. The dexmedetomidine and neostigmine may interact with each other and have analgesic effects similar to those displayed by the co-administration of clonidine and neostigmine[12,13]. It may

be an additive or synergistic effect secondary to the different sites and mechanisms of action of dexmedetomidine and neostigmine. In the spinal cord, the α_2-receptor agonists produce antinociception by decreasing the release of glutamate from primary afferent nerve terminals[14], and by suppressing the noxiously evoked activity of wide dynamic range neurons[15]. On the other hand, neostigmine increases cerebrospinal ACh (acetylcholine) by inhibiting the breakdown of endogenous ACh in ACh-containing spinal neurons localized in the superficial laminae of the dorsal horn of the spinal cord[16]. The activation of interneurons with ACh-receptors would, in turn, lead to increased inhibitory input of the secondary sensory afferent neurons[17].

Several studies have reported that systemic dexmedetomidine at doses causing sedation produced postoperative analgesic effects, while intraoperative infusion of dexmedetomidine was reported not to change the VAS scores for postoperative pain. In molar surgery, the intraoperative infusion of dexmedetomidine at doses causing sedation did not result in reduction of pain score[18,19]. These results are consistent with our data in this study that dexmedetomidine alone did not decrease in postoperative VAS scores. Although the epidural technique cannot be applied for dental surgery, the use of analgesics which has same mechanisms of action of neostigmine in pain pathway in dento-oral area could improve postoperative pain status when co-administered with dexmedetomisine.

The continuous epidural technique was employed for perioperative analgesia in this study. We selected this approach because continuous epidural analgesia is a simple, efficient and conventional technique for open abdominal surgery. The epidural infusion could partially account for the insufficient postoperative analgesic effects of the dexmedetomidine and neostigmine at 4, 6, 24 h postoperatively. The basal epidural analgesaia with 0.375% ropivacaine followed by continuous infusion of 0.2% ropivacaine may block incisional and inflammatory stimulus to some extent, and masks antinociceptive effects of the dexmedetomidine and neostigmine. In addition, the residual analgesic effects of the 10 ml of 0.375% ropivacaine at the start of surgery and the diminished stimulus produced by surgical incision and followed inflammatory responses could explain the lower pain scores at 2 and 72 h postoperatively in all groups, respectively.

There are limitations to this study. We examined the effects of a single dose of dexmedetomidine, of neostigmine and of one combination. It has been demonstrated that higher doses of dexmedetomidine than those causing sedation result in analgesic effects[1], and high doses of dexmedetomidine have been used as total intravenous anesthesia (TIVA)[20]. The dose of 0.3 mg neostigmine was selected in consultation with the previous studies[10]. The doses of 0.5-0.7 mg of neostigmine demonstrated more satisfactory results[21,22]. In addition, in the present study we administered dexmedetomidine only intraoperatively and not postoperatively. The postoperative administration of dexmedetomidine after thoracic surgery was found to decrease VAS scores for pain in the early postoperative period and decrease the requirements for supplemental epidural fentanyl[23]. The lower dose was chosen due to fear for side effects. Alternative approaches such as higher doses of dexmedetomidine and neostigmine and/or continuous intra- and postoperative infusion may improve postoperative pain status.

In conclusion, the co-administration of systemic dexmedetomidine and epidural neostigmine resulted in temporary analgesia postoperatively under basal epidural administration of ropivacaine at relatively low doses (0.375%). Because of lack of serious side effects, this approach may be useful to improve postoperative pain although additional studies are necessary to evaluate the effectiveness of the co-administration of dexmedetomidine and neostigmine.

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