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東北大歯誌 28: 43-48, 2009
(Tohoku Univ. Dent. J.)

原 著

Postoperative pain status after intraoperative administration of dexmedetomidine as a general anesthetic adjuvant

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Abstract : **BACKGROUND** : Dexmedetomidine has analgesic effects and provides excellent hemodynamic stability during the stressful extubation period. Dexmedetomidine may be useful in anesthetic management requiring smooth emergence from anesthesia. The purpose of this study is to determine the intraoperative systemic administration of dexmedetomidine on the postoperative pain staus.
METHODS : Sixty patients undergoing lower abdominal surgery were randomly divided into four groups according to the anesthetic to be administered, namely, sevoflurane (group S), propofol (group P), both sevoflurane and dexmedetomidine (group SD), and both propofol and dexmedetomidine (group PD) as maintenance general anesthetics. After induction, anesthesia was maintained with sevoflurane (0.5-1.5%) in group S, propofol (2-5 mg/kg/h) in group P, sevoflurane and dexmedetomidine (1 μg/kg over 10 min followed by 0.4 μg/kg/h until the end of surgery) in group SD, and propofol and dexmedetomidine in group PD with continuous epidural block. The pain status were evaluated using Visual Analog Scale (VAS).
RESULTS : Dexmedetomidine did not improve postoperative pain status under either sevoflurane or propofol anesthesia. The VAS scores at all corresponding times were similar among the groups throughout the observation period.
CONCLUSIONS : The intraoperative systemic administration of dexmedetomidine at doses causing sedation does not results in postoperative analgesic effects under both sevoflurane and propofol anesthesia. These results suggest that other interventions would be necessary for improvement of postoperative pain status when dexmedetomidine is used as a general anesthetic adjuvant.

Key words : Dexmedetomidine, Postoperative pain, Lower abdominal surgery, General anesthesia

INTRODUCTION

Dexmedetomidine, a specific α_2-receptor agonist, has both anesthetic and analgesic-sparing properties[1,2]. In addition, it provides excellent hemodynamic stability without inducing significant respiratory depression during the stressful extubation period[3]. Because of these properties, dexmedetomidine may be useful in anesthetic management requiring smooth emergence from anesthesia such as that in craniotomy and surgery in patients with cardiovascular disease.

While significant antinociceptive effects of systemic and intrathecal administration of dexmedetomidine have been demonstrated in animal models[4,5], studies examining the analgesic effects of systemic administration of dexmedetomidine at doses causing sedation in human volunteers and postoperative patients report conflicting results[6-9].

The purpose of this study is to examine the postoperative analgesic effects of dexmedetomidine, and to evaluate whether this drug is useful for general anesthetic adjuvant. We therefore assessed postoperative pain scores using the visual analogue scale (VAS) as well as recorded intraoperative hemodynamic values and side effects related to the use of dexmedetomidine the first 24 h after surgery.

METHODS

After obtaining the approval of our institutional human ethics committee and individual written informed consent, 60 patients undergoing open lower abdominal surgery for benign gynecological disease (total abdominal hysterectomy, myomectomy, salpingo-oophorectomy or ovarian cystectomy) were randomly divided, *via* sealed envelope assignment, into four groups according to the anesthetic to be administered, namely, sevoflurane (group S), propofol (group P), both sevoflurane and dexmedetomidine (group SD), and both propofol and dexmedetomidine (group PD) as maintenance general anesthetics. Patients older than 50 years, and those with a history of mental illness, use of psychotropic medicine, pain medications prior to surgery, and impaired sensation were excluded from the study. Patients were also excluded when the epidural technique failed (failure to properly place the epidural tube or unable to obtain the analgesic level up to Th 9 after the initial administration of ropivacaine). All patients were ASA physical status I or II.

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, 7 ml of the drug was administered epidurally before the induction of general anesthesia. The dermatomal analgesic level was evaluated using an alcohol swab 10 min after ropivacaine epidural administration. General anesthesia was induced with propofol (2 mg/kg), and vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation. Upon general anesthesia induction, in groups SD and PD, dexmedetomidine at a loading dose of 1 μ/kg for over 10 min was administered followed by continuous infusion at 0.4 μ/kg/h until the end of surgery. These doses were the recommended doses for sedation in an intensive care unit described in the product information and were selected for patient safety. 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 sevoflurane in group S, propofol in group P, both sevoflurane and dexmedetomidine in group SD, and both propofol and dexmedetomidine in group PD in 33% O_2 and 67% N_2O (1 L/min of O_2 and 2 L/min N_2O) with intermittent doses of vecuronium (1 to 2 mg) and continuous epidural block. Upon early signs of intraoperative pain (e.g., increase in blood pressure (BP) and heart rate (HR), pupil dilation etc.), additional epidural ropivacaine (0.375%, 3 to 5 ml) was administered, as judged by the anesthesiologist who was blinded to the administration of dexmedetomidine. BP was measured every 5 min, and electrocardiogram, end-tidal CO_2 ($EtCO_2$), end-tidal concentration of sevoflurane and hemoglobin oxygen saturation were continuously monitored throughout the surgery. Continuous epidural infusion with 0.2% ropivacaine at 4 ml/h was carried out 30 min after the start of surgery for 25 h. A decrease in mean arterial pressure of more than 20% below the preanesthetic baseline level was corrected by intravenous increments of ephedrine (4-8 mg in each time) and intravenous fluid administration.

At the end of surgery, nitrous oxide, dexmedetomidine, and sevoflurane or propofol were discontinued abruptly without tapering and the patient's lung was ventilated with 100% oxygen at a flow rate of 6 L/min until extubation. After the confirmation of eye opening, neuromuscular blockade was reversed with intravenous administration of neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). Just before neuromuscular reversal, BP and HR were measured and recorded to assess hemodynamic values before the extubation.

The postoperative pain status of patients was assessed at rest using a visual analog scale (VAS) at 2, 4, 6, 24, and 72 h after the completion of surgery. The patients were instructed on the use of the VAS, which consisted of a 10-cm line with 0 indicating "no pain at all" and 10 indicating "the worst possible pain", for pain assessment preoperatively. Initially, postoperative pain was controlled by continuous epidural infusion of 0.2% ropivacaine. If patients still complained of pain, a conventional analgesic (drip infusion of butorphanol (2 mg) over 1 h at a minimum of 6-h intervals) prescribed by a gynecologist was administered upon patient request in addition to the continuous epidural infusion of ropivacaine.

Hemodynamic events induced by the intraoperative infusion of dexmedetomidine such as hypertension, hypotension and bradycardia, and side effects such as nausea, vomiting, and pruritus were assessed and recorded during the first 24 h after surgery. Nausea, vomiting and pruritus were assessed based on the

complaint of patients alone. Nausea and vomiting were treated with intravenous metoclopramide (10 mg) 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 SD) between group S and SD. Those pain scores were chosen because the pain score in control group in our preliminary study was around 4 and the reduction of pain scores by 2 is considered clinically significant. The data were analyzed using repeated measures analysis of variance with subsequent intergroup comparisons using Shéffe's F test. The VAS scores were analyzed using the Kruskal-Wallis test with subsequent intergroup comparisons made using the Mann-Whitney U test with Bonferroni correction. A P value<0.05 was considered significant.

RESULTS

Patient details and the duration of operation are summarized in Table 1. There were no significant differences among the groups. The surgical procedures performed in this study are shown in Table 2.

Dexmedetomidine did not improve postoperative pain status under continuous epidural infusion. The VAS scores at all corresponding times were similar among the groups throughout the observation period (Figure 1). The dermatomal analgesic level (Table 1), the times for the first rescue (data not shown) and consumption of analgesics (Table 3) during the first 24 h postoperatively were not significantly different among the groups.

At the infusion of dexmedetomidine at its loading dose, systolic blood pressure increased to approximately 180 mmHg in one patient in group PD. However, this elevation was transient and required no treatment. Severe hypotension and bradycardia requiring intervention were not observed. HR decreased by about 75% in groups SD and PD (approximately 55±10), and mean arterial pressure (MAP) remained at similar levels (70±10) in all groups during anesthesia. Dexmedetomidine induced less change in hemodynamic values before the extubation. MAP and HR in groups S and P increased before extubation compared with the preanesthetic values, whereas those in groups SD and PD did not (Table 4). Nausea and vomiting, assessed only from the complaint of patients without using a nausea scale, were observed in one patient in each group, and were successfully treated with metoclopramide (10 mg). The patients complained of no other side effects such as

Table 1. Summary of treatment groups

	group S	group SD	group P	group PD
Height (cm)	158±5	158±5	157±5	158±6
Weight (kg)	57±12	52±7	59±11	56±8
Age (years)	40±6	39±8	41±6	39±9
Duration of surgery (minutes)	89±35	108±34	88±25	97±40
Analgesic level	Th7 (6-8 [6-9])	Th7 (7-8 [6-8])	Th7 (7-8 [6-9])	Th7 (7-8 [6-9])

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

Table 2. The types of surgical procedure

	group S	group SD	group P	group PD
abdominal total hysterectomy	7	7	8	8
myomectomy	1	3	3	2
salpingo-oophrectomy	5	1	1	2
cystectomy	2	4	3	3

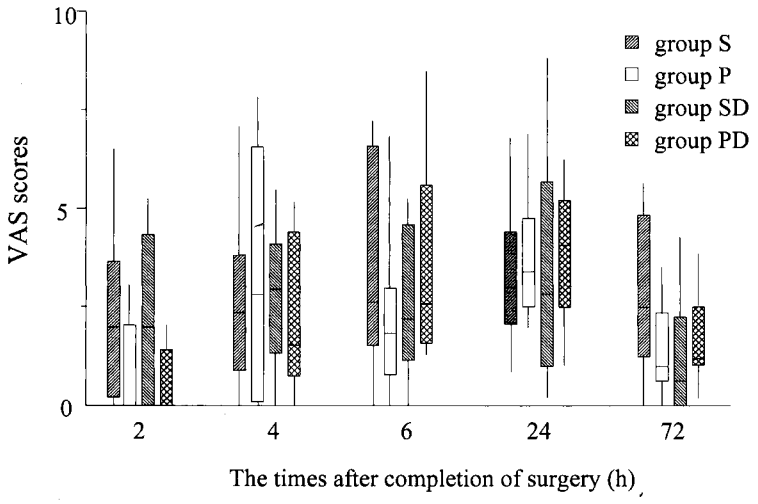

Figure 1. Postoperative VAS pain scores. Postoperative pain status of patients at rest was assessed using VAS at 2, 4, 6, 24 and 72 h after the end of surgery. Box represents the 25th-75th percentiles, and the solid horizontal line represents the median. Extended bars (whisker) represent the 10th-90th percentiles ($n=15$). There were no significant differences among the groups.

Table 3. Total doses of intraoperative 0.375% ropivacaine and postoperative butorphanol

	group S	group SD	group P	group PD
0.375% ropivacaine (ml)	13.2±2.7	10.7±1.7	11.9±2.9	11.3±2.3
butorphanol (mg)	3.3±1.8	2.8±2.0	3.2±2.7	2.9±2.1

Data are expressed mean±SD, ($n=15$)
There was no significant difference among the groups

Table 4. Change in hemodynamic values before extubation

	group S	group P	group SD	group PD
MAP (mmHg)				
pre-anesthetic values	80±13	88±5	85±12	87±15
before extubation	93±12	97±12	85±10*	87±15
(% of pre-anesthetic values)	(118±23)	(111±17)	(102±18**)	(102±11)
HR (bpm)				
pre-anesthetic values	72±5	71±6	70±14	68±8
before extubation	92±15	85±14	69±12†	61±14†
(% of preanesthetic values)	(131±27)	(120±20)	(100±12†)	(89±16†)

MAP=mean arterial pressure, HR=heart rate. Data are expressed mean±SD ($n=15$)
**$p<0.001$, *$p=0.043$ vs group S, †$p<0.001$ vs group S, group P, respectively

pruritus.

DISCUSSION

The main finding of this study is that dexmedetomidine does not improve postoperative pain status with continuous epidural infusion under either sevoflurane or propofol anesthesia. These results suggest that other interventions such as higher doses of dexmedetomidine and/or continuous intra- and postoperative infusion would be necessary for postoperative pain control.

While significant antinociceptive effects of dexmedetomidine have been demonstrated in humans at high

doses[2] and in animal models[4], the analgesic effects of systemic dexmedetomidine at doses causing sedation remain controversial in human studies. In human volunteer studies, the systemic administration of dexmedetomidine at doses causing mild to severe sedation lacked analgesic effcacy for heat and electrical pain[6], whereas the intraoperative infusion of dexmedetomidine was found to reduce postoperative morphine requirement in patients undergoing abdominal hysterectomy[9]. Dexmedetomidine did not reduce postoperative pain score in molar surgery under local anesthesia[11,12]. The dose of dexmedetomidine used in the present study was the recommended dose for sedation in an intensive care unit described in the product information for patient safety, and we administered dexmedetomidine only intraoperatively and not postoperatively. Furthermore, the continuous epidural infusion technique was employed for postoperative pain control in the present study. This technique can mask postoperative analgesic effects of intraoperative infusion of dexmedetomidine. Although further studies are necessary, higher doses of dexmedetomidine and/or continuous intraoperative and postoperative infusions may represent different characteristics under both sevoflurane and propofol anesthesia even in patients for dental surgery.

Since the increases in MAP and HR before the extubation were suppressed by co-administration of dexmedetomidine (Table 4) as previously reported[3,10], dexmedetomidine could be useful in anesthetic management requiring smooth emergence from anesthesia. No patients needed intervention for bradycardia or hypotension. The patients were administered atropine (1 mg) as premedication before surgery to prevent dexmedetomidine-induced bradycardia requiring intervention. Except for a few patients showing nausea and vomiting that were easily treatable, no other severe adverse effects were observed. These findings confirm the safety of co-administration of dexmedetomidine under sevoflurane or propofol anesthesia.

One of the limitations of the present study was a sample size calculation. A sample size in each group was calculated by the assumption that dexmedetomidine alone reduces pain score from 4 to 2. Those pain scores were chosen because the pain score in control group in our preliminary study was around 4 and the reduction of pain scores by 2 is considered clinically significant. However, this assumption seemed to be unrealistic, because it has been demonstrated that dexmedetomidine did not affected pain score but changed opioid demand in several previous studies[9]. If we selected the number that could detect small pain differences, the results would have been different.

In conclusion, the intraoperative systemic infusion of dexmedetomidine at doses causing sedation did not have postoperative analgesic effects in patients undergoing gynecological surgery under continuous epidural infusion with ropivacaine for postoperative pain control. Because dexmedetomidine provided less hemodynamic change before extubation, this drug could be useful for general anesthetic adjuvant. However, other interventions such as higher doses of dexmedetomidine and/or continuous intra- and postoperative infusion would be necessary for postoperative pain control.

Financial Support : This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan to M.Y. (No. 21791429) and N.O. (No. 21791429).

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