Intravenous infusion of dexmedetomidine amplifies thoracic epidural analgesic effect after open thoracotomy

A prospective, double-blind, randomized controlled trial

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Abstract

Background: The anesthetic-sparing effect of dexmedetomidine has led to its use as a general adjuvant. The present study aimed to determine intravenous infusion of dexmedetomidine to epidural analgesia after open thoracotomy.

Methods: Forty-four patients scheduled for admission to the intensive care unit after open thoracotomy were divided into 2 groups. An epidural catheter was placed at T4 to T7. Thirty minutes before the end of thoracotomy, group D was injected with 0.3 µg/kg/h of dexmedetomidine and group C received an equal dose of normal saline. For patient-controlled epidural analgesia (PCEA), 150 mL of levobupivacaine 300 mg was infused at a rate of 1 mL/h, plus a bolus dose of 3 mL with a lockout time of 30 minutes. The primary outcome evaluated was analgesic efficacy using a visual analog scale (VAS) 48 hours postoperatively. Other outcomes included additional analgesic use, total consumed local analgesia via PCEA, sedation score, blood pressure, heart rate, arterial blood gases, patient satisfaction, and adverse effects.

Results: The VAS scores in group D were significantly lower than that in group C immediately, 1, 4, 12, 36, and 48 hours after admission to the intensive care unit ($P = .016$, .009, .015, .002, .001, and .042, respectively). The total dose of additional analgesic was also significantly lower in group D ($P = .011$). Patient satisfaction was higher in group D ($P < .05$). There were no significant differences in the other outcomes between groups.

Conclusion: Intravenous infusion of dexmedetomidine amplifies thoracic epidural analgesic effect after open thoracotomy.

Abbreviations: MOAA/S = Modified Observer’s Assessment of Alertness/Sedation, OLV = one-lung ventilation, PCEA = patient-controlled epidural analgesia, POD = postoperative day, VAS = visual analog scale.

Keywords: dexmedetomidine, epidural analgesia, intensive care unit, sedation, thoracotomy

1. Introduction

Postoperative pain in patients who have undergone open thoracotomy for lung cancer or other lung surgeries is known to be very severe. Acute incisional pain after open thoracotomy promotes ventilation/perfusion mismatch, atelectasis, hypoxemia, and infection by changing chest wall mechanics and interfering with effective chest expansion, coughing, and removal of secretions.\textsuperscript{[1]} As a result, this pain alters spontaneous breathing, and delays postoperative recovery, and persists as chronic post-thoracotomy pain syndrome. Post-thoracotomy pain syndrome is relatively common and is seen in approximately 50\% of patients after thoracotomy. It is a chronic condition, and about 30\% of patients might still experience pain 4 to 5 years after surgery.\textsuperscript{[1,3]}

Thoracic epidural analgesia using a combination of opioid with a local anesthetic is the standard and most effective method of acute post-thoracotomy pain management.\textsuperscript{[4]} The benefits include inhibition of stress response by sympatholysis, stabilized hemodynamics with reduction in cardiac morbidity, decreased pulmonary complications due to active physiotherapy and early mobilization, reduced bleeding, and thromboembolic complications.\textsuperscript{[5]} Propofol, midazolam, or dexmedetomidine are used for sedation in patients admitted to the intensive care unit (ICU) after open thoracotomy. Dexmedetomidine is a selective $\alpha_{2}$-agonist possessing sedative, anxiolytic, and analgesic properties without the development of respiratory depression.\textsuperscript{[6]} Several studies have shown that dexmedetomidine has an anesthetic-sparing effect, which has led to its use as a general adjuvant for prolonging peripheral nerve block duration.\textsuperscript{[7,8]}

We hypothesized that the intravenous infusion of the sedative dexmedetomidine added to thoracic epidural analgesia would...
reduce postoperative pain in patients undergoing acute open thoracotomy. The aim of the present study, therefore, was to investigate the effectiveness of the analgesia achieved by combining thoracic epidural analgesia with intravenous dexmedetomidine infusion for postoperative acute pain management in patients admitted to the ICU after open thoracotomy.

2. Methods

2.1. Enrollment

After approval from the Institutional Review Board of Pusan National University Yangsan Hospital (IRB number: 05-2016-072), a prospective randomized, double-blinded trial was performed. This study was registered in the Clinical Research Information Service (trial registry number: KCT0002787). Informed written consent for participation in the trial was obtained from each patient. Forty-four patients older than 19 years with an American Society of Anesthesiologists physical status I–III were scheduled to undergo open thoracotomy for lung cancer or other lung diseases, and to receive postoperative sedation in the ICU. Patients with neurological or intellectual disability, spinal deformities, drug abuse, allergic reaction to anesthetics in the PCEA infusion system was also recorded. When the VAS was >6 and the patient wanted analgesics during postoperative period, pethidine 25 to 50mg was injected as rescue analgesics. The total dose of additional analgesics was documented and registered by the blinded researcher. Sedation assessments used the responsiveness scores of the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scales (Table 1).[9] Hemodynamic parameters, such as blood pressure and heart rate, were evaluated. Adverse events, including postoperative nausea and vomiting, pruritus, hypotension, urinary retention, and bradycardia, were also evaluated. Changes in the partial pressure of carbon dioxide (PaCO2), partial pressure of oxygen (PaO2), and O2 saturation were also evaluated during one-lung ventilation (OLV), and postoperative day (POD) 1 and 2. After removal of the PCEA, patient satisfaction and the total amount of local anesthetics consumed from the PCEA were recorded. Patient satisfaction was assessed using a 4-point scale,[10] with 4 = very satisfied, 3 = somewhat satisfied, 2 = somewhat dissatisfied, and 1 = very dissatisfied.

2.2. Randomization

At the preanesthetic visit, all subjects were fully informed of how to use a patient-controlled analgesic device, the randomization protocol, and pain assessment using the visual analog scale (VAS), and were accepted into the study. A list of random numbers generated using Excel (Microsoft Corporation, Redmond, WA) was used to randomly assign patients into 2 groups (D and C). Group D were continuously infused with dexmedetomidine 0.3 µg/kg/h, and group C received the same dose of normal saline for 12 hours. A co-investigator, who did not participate in subsequent aspects of the study, prepared dexmedetomidine and the same dose of normal saline the morning of the operation.

2.3. Analgesic technique

An epidural catheter was placed at the level of thoracic (T) T4 to T7 for continuous epidural analgesia, before general anesthesia. A test dose with lidocaine 60mg (0.2% lidocaine 3 mL) + epinephrine 15 µg was injected through the catheter to confirm no hemodynamic or neurological changes. When the hemodynamic state stabilized after endotracheal intubation, a loading dose of fentanyl 50 µg + 0.2% levobupivacaine 7.5 mL was injected via the preplaced epidural catheter. For open thoracic surgery, general anesthesia was maintained with 2 vol% of sevoflurane, and rocuronium 0.2 mg/kg was administered intraoperatively at 40- to 60-minute intervals to maintain muscle relaxation.

Thirty minutes before the end of surgery, patients in group D were continuously infused with dexmedetomidine 0.3 µg/kg/h, and group C received the same dose of normal saline for 12 hours. The drug and placebo were recorded separately so that they were known only to the co-investigator, and kept in a private laboratory until study completion. For patient-controlled epidural analgesia (PCEA), a total volume of 150 mL (levobupivacaine 300 mg + fentanyl 500 µg) was infused through the epidural catheter via an infusion system (Gemstar, Hospira, Lake Forest, IL) in the ICU. Both groups received a continuous infusion of 0.2% levobupivacaine at a rate of 1 mL/h plus a bolus dose of 3 mL, with a lockout time of 30 minutes through the epidural catheter.

2.4. Outcome measurements

A blinded investigator, who was not involved in the preparation or administration of medications, recorded and monitored several items immediately at admission, and at 1, 4, 12, 24, 36, and 48 hours after admission to the ICU. Postoperative pain was assessed using a VAS. The total consumed dose of local anesthetics in the PCEA infusion system was also recorded. When the VAS was >6 and the patient wanted analgesics during postoperative period, pethidine 25 to 50mg was injected as rescue analgesics. The total dose of additional analgesics was documented and registered by the blinded researcher. Sedation assessments used the responsiveness scores of the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scales (Table 1).[9] Hemodynamic parameters, such as blood pressure and heart rate, were evaluated. Adverse events, including postoperative nausea and vomiting, pruritus, hypotension, urinary retention, and bradycardia, were also evaluated. Changes in the partial pressure of carbon dioxide (PaCO2), partial pressure of oxygen (PaO2), and O2 saturation were also evaluated during one-lung ventilation (OLV), and postoperative day (POD) 1 and 2. After removal of the PCEA, patient satisfaction and the total amount of local anesthetics consumed from the PCEA were recorded. Patient satisfaction was assessed using a 4-point scale,[10] with 4 = very satisfied, 3 = somewhat satisfied, 2 = somewhat dissatisfied, and 1 = very dissatisfied.

2.5. Sample size

Postoperative pain assessed according to the VAS was the primary outcome variable, and on which the sample size estimation was based. A previous study reported a mean [±standard deviation (SD)] VAS score of 2.31 ± 1.6 in a group of patients who were administered dexmedetomidine.[8] A clinically significant minimum increase in the VAS after the operation was assumed to be 1.5 (e=1.5). The sample size calculation for the present study yielded 18 patients per group when type I (α) error = 0.05, type II (β) error = 0.20, SD (σ) = 1.6 were considered. A predicted dropout rate of 10% was projected, and 2 patients per group were added to increase the power of the test. There were 22 patients per group. The sample size was calculated according to the following equation:

\[ n = \frac{2(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{(e - |\mu_C - \mu_D|)^2} \]

Table 1

| Response | Score level |
|----------|-------------|
| Responds readily to name spoken in normal tone | 5 (Alert) |
| Lethargic response to name spoken in normal tone | 4 |
| Responds only after name is called loudly or repeatedly | 3 |
| Responds only after mild prodding or shaking | 2 |
| Does not respond to mild prodding or shaking | 1 |
| Does not respond to noxious stimulus | 0 |
In which $\sigma$ (standard deviation) = 1.6, $e$ (clinically significant minimum increase in the VAS at 24 h after the operation) = 1.5, and $\mu_C - \mu_D$ (the difference in VAS score between the means of the 2 groups) = 0.

2.6. Statistical analysis

Statistical analysis was performed using PASW Statistics version 18 (SPSS, Chicago, IL) for Windows (Microsoft Corporation, Redmond, WA). The Student $t$ test was used to compare VAS, MOAA/S scales, total consumed local anesthetics of PCEA, blood pressure, and heart rate. The incidences of adverse events were compared using the chi-squared test or Fisher exact test. The changes in PaCO$_2$, PaO$_2$, and O$_2$ saturation during OLV, and postoperatively were compared within the groups using a repeated-measures analysis of variance, and between the groups using the Student $t$ test. The chi-squared test was used to analyze other categorical data; $P < .05$ was considered to be statistically significant.

3. Results

Forty-four of the enrolled patients completed the study (Fig. 1). There were no statistical differences in sex, American Society of Anesthesiologists physical status, age, height, weight, and anesthesia time between the 2 groups (Table 2).

The mean differences (95% confidence interval [CI]) of the postoperative VAS immediately, and at 1, 4, 12, 24, 36, and 48 hours after admission to the ICU were 1.64 (0.32–2.96), 1.36 (0.36–2.37), 1.14 (0.23–2.04), 1.50 (0.58–2.42), 0.64 (–0.32–1.59), 1.64 (0.74–2.53), and 0.77 (0.03–1.51), respectively. The VAS scores in group D were significantly lower than in group C immediately, 1, 4, 12, 36, and 48 hours after admission to the ICU ($P = .016$, .009, .015, .002, .001, and .042, respectively) (Fig. 2). During the postoperative period, the total dose of pethidine administered to groups D and C was 20.2±21.8 and 48.9±44.0 mg, respectively. The total dose of additional analgesic was also significantly lower in group D ($P = .011$). There was no difference in the total consumed dose of local anesthetics from the PCEA infusion system between the groups (Fig. 3).

The MOAA/S scale for group D was lower than group C immediately on admission to the ICU ($P < .05$). Other MOAA/S scales were not different between the groups (Fig. 4).

Blood pressure and heart rate at all times were not significantly different between the groups (Fig. 5). Adverse events, including postoperative nausea and vomiting, pruritus, hypotension, urinary retention, and bradycardia, were not different between the groups (Table 3). Changes in PaCO$_2$, PaO$_2$, and O$_2$ saturation during OLV, and POD 1, and POD 2 were not different (Fig. 6). In comparison of patient satisfaction, group D was statistically higher “somewhat satisfied” response ($P = .005$) and lower “very dissatisfied” response than group C ($P = .048$) (Table 4).

4. Discussion

This randomized, double-blinded, comparative study was undertaken to investigate the effectiveness of analgesia resulting from combining thoracic epidural analgesia with intravenous dexmedetomidine infusion for acute pain management in patients admitted to the ICU after thoracotomy. Our principal finding was that intravenous dexmedetomidine administration amplified thoracic epidural analgesia after thoracotomy in the ICU. The VAS scores and total dose of additional opioid analgesics were decreased with dexmedetomidine administration. Although dexmedetomidine administration prolonged the time to return of consciousness from general anesthesia, hemodynamic stability, respiratory depression, and adverse events were not increased. Patient satisfaction was also higher in the dexmedetomidine-administration group.

Dexmedetomidine is a highly selective $\alpha_2$-adrenergic receptor agonist. The use of dexmedetomidine has evolved for various

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Table 2

| Characteristic          | Group D (n=22) | Group C (n=22) | $P$ |
|-------------------------|---------------|---------------|-----|
| Sex (M/F)               | 15/7          | 16/6          | .741 |
| ASA physical status (I/II/III) | 6/14/2      | 3/15/4        | .427 |
| Age, y                  | 65.8±10.1     | 67.2±8.4      | .628 |
| Height, cm              | 165.1±8.4     | 162.6±8.3     | .343 |
| Weight, kg              | 63.7±12.1     | 62.3±8.5      | .670 |
| Anesthesia time, h      | 5.1±2.1       | 4.7±1.7       | .463 |

All measured values are presented as mean±standard deviation or number of patients. ASA = American Society of Anesthesiologists.
applications in perioperative and critical care settings. Its stable hemodynamics and decreased oxygen demand due to improved sympathoadrenal stability have the advantage as a very useful adjuvant. It is commonly used to sedate patients without tracheal intubation. It does not cause respiratory depression, but in rare cases, it can cause hypotension, bradycardia, and serious complications.\(^{[11-13]}\)

Because of its effective sedative properties, dexmedetomidine infusion for sedation of ICU patients is particularly recommended to achieve adequate levels of continuous sedation. Its use in pain management has also been studied because of its analgesic sparing effects.\(^{[14]}\) It modulates antinociception by inhibiting peripheral norepinephrine release, thus terminating the propagation of pain signals. At the same time, post-synaptic activation of \(\alpha_2\)-adrenergic receptor in the central nervous system inhibits sympathetic activity and may result in hypotension and bradycardia. In this study, a lower MOAA/S scale score immediately after admission to the ICU was observed in the dexmedetomidine group. However, the sedation score was not different from baseline and comparable with the control group at most times. A study reported that the use of a large bolus dose or rapid loading infusion of dexmedetomidine (1.0–2.5 \(\mu\)g/kg/h) resulted in a transient increase in blood pressure and reflex decrease in heart rate, followed by decreased blood pressure without reflex tachycardia.\(^{[15]}\) The present study infused a low dose (0.3 \(\mu\)g/kg/h) of dexmedetomidine for 12 hours; therefore, our results reflected proper sedation and analgesia. Moreover, mean blood pressure and heart rate were not significantly different between the 2 groups. Adverse events, including hypotension and bradycardia, were not different between the groups. Only 2 (9.0\%) cases of hypotension, and 1 (4.5\%) case of bradycardia occurred in the dexmedetomidine group.

The mechanism of prolonged block of local anesthetics may be an additive or synergistic effect secondary to the different mechanisms of action of local anesthetics. Dexmedetomidine acts by binding to the presynaptic C-fibers and postsynaptic dorsal horn neurons. It produces analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons. The complementary action of local anesthetics and dexmedetomidine accounts for the profound analgesic effects. The prolongation of block may be the result of dexmedetomidine binding to the neurons in the dorsal horn.\(^{[16]}\) Several studies have reported that dexmedetomidine infusion prolongs the duration of sensory and motor blockade.\(^{[17,18]}\) In these studies, the prolongation of thoracic epidural analgesia may be attributed to the continuous infusion of dexmedetomidine. The lower VAS score in the dexmedetomidine group may have been due to the prolongation of thoracic epidural analgesia. The dexmedetomidine group used less additional opioids than the placebo group with equal analgesia, which demonstrates the opioid-sparing properties of dexmedetomidine.

Some studies have shown dexmedetomidine mixed with local anesthetics and applied to regional or peripheral nerve blocks,\(^{[19,20]}\) there is little research on the effects of intravenous infusion. The use of dexmedetomidine as an adjuvant to local anesthetic for regional or peripheral nerve blocks has not been approved by the US Food and Drug Administration or by the European Medicines Agency. Because the use of dexmedetomidine is limited to intravenous infusion, we planned this study. In
our study, intravenous infusion of dexmedetomidine for sedation during ICU management amplified thoracic epidural analgesia. In the cases of regional or peripheral blocks, intravenous infusion of dexmedetomidine can be applied to the patient because it affects pain control and prolonged block period.

No adverse effects, such as respiratory depression, were noted in our study. Changes in PaCO₂, PaO₂, and O₂ saturation were maintained equally well in both groups. The other adverse event profiles of dexmedetomidine were quite favorable, which correlates very well with other studies. Patient satisfaction with postoperative pain control was found to be higher in the dexmedetomidine group, in which effective analgesia and sedation were achieved with minimal adverse effects compared with the control group.

Our study had several limitations, including its small sample size. The authors also struggled with the relatively small sample size. Since there are not many articles to refer to when calculating the sample size, it was calculated with reference [8]. Second, it did not account for the duration of the sensory and motor block. We limited our observations to postoperative pain scores because our primary aim was to investigate the effectiveness of analgesia resulting from combining thoracic epidural analgesia with intravenous dexmedetomidine infusion for acute pain management in patients admitted to the ICU after thoracotomy. Finally, we also did not evaluate postdischarge pain assessment because this study was not designed to evaluate the prevention of chronic postdischarge pain. The follow-up study about chronic pain assessment after discharge is also needed.

In conclusion, intravenous infusion of dexmedetomidine for sedation during ICU management amplified thoracic epidural

### Table 3

| Characteristic     | Group D (n=22) | Group C (n=22) | P    |
|-------------------|--------------|--------------|------|
| Nausea            | 1 (4.5)      | 2 (9.0)      | 1.000|
| Pruritus          | 2 (9.0)      | 2 (9.0)      | 1.000|
| Hypotension       | 2 (9.0)      | 0 (0.0)      | .488 |
| Urinary retention | 2 (9.0)      | 1 (4.5)      | 1.000|
| Bradycardia       | 1 (4.5)      | 0 (0.0)      | 1.000|

Values are the number of patients (%).
analgesia in patients undergoing open thoracotomy. Although its use did not reduce the requirement for PCEA, and prolonged the time to return to consciousness from general anesthesia, dexmedetomidine significantly reduced the requirement for supplemental analgesics, and achieved hemodynamic stability without adverse hypotension and bradycardia.

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