Dexmedetomidine attenuates the increase of ultrasonographic optic nerve sheath diameter as a surrogate for intracranial pressure in patients undergoing robot-assisted laparoscopic prostatectomy

A randomized double-blind controlled trial

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Abstract

Background: Pneumoperitoneum and steep Trendelenburg position during robot-assisted laparoscopic prostatectomy (RALP) can increase intracranial pressure (ICP). Dexmedetomidine, a highly selective alpha-2 adrenergic receptor agonist, can cause cerebral vasoconstriction and decrease cerebral blood flow by stimulating the postsynaptic alpha-2 adrenergic receptors on cerebral blood vessels. However, the effects of dexmedetomidine on ICP are controversial and have not been evaluated during RALP under the establishment of pneumoperitoneum in the steep Trendelenburg position. Therefore, we evaluated the effect of dexmedetomidine on optic nerve sheath diameter (ONSD) as a surrogate for assessing ICP during RALP.

Methods: Patients were randomly allocated to receive dexmedetomidine (\(n = 63\)) (loading dose, 1 \(\mu\)g/kg for 10 minutes and continuous infusion, 0.4 \(\mu\)g/kg/hr) or normal saline (\(n = 63\)). The ONSD was measured at 10 minutes after induction of anesthesia in the supine position (T1), 30 minutes (T2) and 60 minutes (T3) after establishment of pneumoperitoneum in the steep Trendelenburg position, and at closing the skin in the supine position (T4). Hemodynamic and respiratory variables were measured at every time point.

Results: ONSDs at T2, T3, and T4 were significantly smaller in the dexmedetomidine group than in the control group (5.26 ± 0.25 mm vs 5.71 ± 0.26 mm, 5.29 ± 0.24 mm vs 5.81 ± 0.23 mm, and 4.97 ± 0.24 mm vs 5.15 ± 0.28 mm, all \(P < .001\)). ONSDs at T2, T3, and T4 were significantly increased compared to T1 in both groups. Hemodynamic and respiratory variables, except heart rate, did not significantly differ between the 2 groups. The bradycardia and atropine administration were not significantly different between the 2 groups.

Conclusion: Dexmedetomidine attenuates the increase of ONSD during RALP, suggesting that intraoperative dexmedetomidine administration may effectively attenuate the ICP increase during pneumoperitoneum in the Trendelenburg position.

Abbreviations: ICP = intracranial pressure, ONSD = optic nerve sheath diameter, RALP = robot-assisted laparoscopic prostatectomy.

Keywords: dexmedetomidine, optic nerve sheath diameter, robot-assisted laparoscopic prostatectomy

1. Introduction

Robot-assisted laparoscopic prostatectomy (RALP) has advantages of easy access to the surgical site, less bleeding, less postoperative pain, and faster recovery of sexual function, compared with open prostatectomy.\textsuperscript{[1]} However, the conditions of pneumoperitoneum and steep Trendelenburg position needed to obtain better view of the surgical field during the RALP can affect respiratory, hemodynamic, and cerebral functions.\textsuperscript{[2,3]} Changes in respiratory function include increased airway pressure, decreased compliance, increased mismatch in ventilation/perfusion, and hypercapnia.\textsuperscript{[4]} Changes of hemodynamic function include decreased venous return and increased systemic vascular resistance.\textsuperscript{[2]} These conditions affect the physiology of the cerebral system and lead to increased intracranial pressure (ICP).\textsuperscript{[3]}

Dexmedetomidine is a potent alpha-2 adrenergic receptor agonist. Alpha-2 adrenergic receptors exist presynaptically and postsynaptically; the activation of the presynaptic alpha-2
adrenergic receptor reduces norepinephrine and epinephrine release, whereas the activation of the postsynaptic alpha-2 adrenergic receptor leads to hyperpolarization of the neuronal membrane. Therefore, the stimulation of the alpha-2 adrenergic receptor by dexmedetomidine can provide hemodynamic stability and effective sedation and analgesia.\[^{[5]}\] In addition, dexmedetomidine-induced stimulation of postsynaptic alpha-2 adrenergic receptor on the cerebral blood vessels can cause cerebral vasocostriction and decrease cerebral blood flow.\[^{[6]}\] However, the effects of dexmedetomidine on ICP are controver-
sial. Dexmedetomidine was reported to effectively reduce cerebral metabolism and ICP by decreasing cerebrospinal fluid pressure in patients with cerebral tumors or head injuries that require craniotomy.\[^{[7,8]}\] However, it was also reported to exhibit no effect on ICP.\[^{[9]}\] Furthermore, the effects of dexmedetomidine on ICP have not been evaluated during RALP under specific conditions, such as pneumoperitoneum and steep Trendelenburg position, which may increase ICP.

Therefore, we evaluated the effect of dexmedetomidine on optic nerve sheath diameter (ONSĐ), a useful non-invasive surrogate for assessing ICP\[^{[10]}\] in patients undergoing RALP. We hypothesized that patients receiving intraoperative dexmedetomidine (dexmedetomidine group) would manifest an attenuation of ONSĐ increase when compared to those receiving normal saline (control group).

2. Methods

2.1. Study design

We performed a randomized, double-blind, controlled trial at Asan Medical Center from May through August in 2018. The protocol of this study was approved by the institutional review board of Asan Medical Center (approval no. 2018-0523) and was registered at ClinicalTrials.gov (NCT03529643). All patients provided written informed consent.

2.2. Patients

We included prostate cancer patients who underwent RALP using the da Vinci\[^{TM}\] robot system (Intuitive Surgical, Inc., Sunnyvale, CA). We excluded patients with cerebrovascular disease, glauco-
ma, hepatic failure, renal failure, history of anaphylactic reaction to dexmedetomidine, and those younger than 20 or older than 79 years. Patients did not receive the allocated intervention if the surgery was unexpectedly canceled, the procedure was converted to open abdominal surgery, they became hemodynamically unstable during surgery, or the ONSĐ was not measured.

2.3. Randomization

Patients were randomized into 2 groups by using Random Allocation Software, a web-based randomization software (version 1.0, Isfahan University of Medical Sciences, Isfahan, Iran). For block randomization, an allocation ratio of 1:1 and a block size of 4 were used. The envelopes labeled with sequential study numbers were kept sealed in possession of 1 investigator, who opened them just before anesthesia induction and prepared either dexmedetomidine or normal saline with concealed syringes. A second investigator performed anesthesia without knowing the group allocation. A third investigator who was blinded to group allocation collected the hemodynamic and respiratory data and measured the ONSĐ at each time point. Before data analysis, the group allocations were hidden from all investigators except for the investigator who prepared the medications. All participants were also blinded to the group allocation.

2.4. Anesthetic and surgical techniques

Monitoring of all patients included 3 lead electrocardiography, bispectral index (Aspect Medical Systems, Inc., Newton, MA), pulse oximetry, non-invasive blood pressure, and regional cerebral oxygen saturation using near-infrared spectroscopy (IVOS 5100\[^{TM}\], Somanetics Corp., Troy, MI). To perform preoxygenation, we used a facial mask to administer 8L/min of oxygen prior to anesthesia induction. Anesthesia was induced using propofol (1.5 mg/kg), which was maintained with remi-
ftenantil (1.0–3.0 ng/mL) and sevoflurane (1–2 vol%). A target-
controlled infusion system was used for continuous infusion of remifentanil.\[^{[11]}\] After loss of consciousness, 0.6 mg/kg of rocuronium was given for muscle relaxation. In the dexmedeto-
midine group, 10 minutes after induction of anesthesia, 1 μg/kg of dexmedetomidine was loaded for 10 minutes and administered at a rate of 0.4 μg/kg/hr continuously until skin closure. In the control group, 10 minutes after induction of anesthesia, 0.9% normal saline was administered at the same rate. An arterial line was inserted in the radial artery for continuous arterial blood pressure monitoring. During surgery, sevoflurane (1–2 vol%) and remifentanil (1.0–3.0 ng/mL) were adjusted to maintain arterial blood pressure and heart rate within 20% of the baseline and the depth of anesthesia was maintained at a bispectral index score of 40 to 60. Oxygen at 50% was supplied with medical air. The volume control mode was used for mechanical ventilation. We adjusted the respiratory rate and tidal volume in order to maintain peak airway pressure at <30 mmHg and end-tidal carbon dioxide concentration within 30 to 35 mmHg. We did not apply positive end-expiratory pressure. Crystalloid fluid with Plasma Solution A (CJ Pharmaceutical, Seoul, Korea) was administered at a rate of 2 to 4 mL/kg/hr. An esophageal probe for measuring body temperature was inserted in the lower portion of esophagus. Body temperature was maintained at 36 to 37°C. Intraoperative hypotension was defined as a systolic blood pressure of <80 mmHg for >5 minutes. Intraoperative brady-
cardia was defined as a heart rate of <60 beats/min for >5 minutes. If a systolic blood pressure of <80 mmHg or a heart rate of <40 beats/min occurred, ephedrine (5 mg) or atropine (0.5 mg) was administered, respectively.

The RALP procedures were performed according to our standard protocols using the da Vinci\[^{TM}\] robot system by 5 highly experienced surgeons. Carbon dioxide pneumoperitoneum was established with intra-abdominal pressure of 15 mmHg and 6 trocars were inserted. The patient was placed in the steep Trendelenburg position (45-degree). To access into the space of Retzius, bladder mobilization was performed. A transperitoneal antegrade approach was used to dissect the prostate and nerve sparing was carried out on all patients on sides that were not suspected for extension of cancer. Pelvis lymph node dissection was performed in intermediate- to high-risk groups as designated by the D’Amico criteria.\[^{[12]}\] Vesicourethral anastomosis was performed with a continuous suture.

2.5. Measurements

Hemodynamic variables included systolic blood pressure, heart rate, and regional cerebral oxygen saturation. The hemodynamic
variables were evaluated as the average value for 1 minute. Respiratory variables included peak inspiratory pressure and partial pressures of arterial carbon dioxide (PaCO\textsubscript{2}) and arterial oxygen (PaO\textsubscript{2}). The measurement time points were as follows: 10 minutes after induction of anesthesia in the supine position (T1), 30 minutes after establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position (T2), 60 minutes after establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position (T3), and at the end of surgery following pneumoperitoneum desufflation in the supine position (T4). Measurement of the ONSD was performed using a 7.5 MHz linear probe (Fig. 1); thus, a total of 4 measurements were taken by trained investigators\textsuperscript{[13,14]}. The average of the measured values was used in the analysis. And, 2 investigators measured a random sample of about 25\% of the ONSD twice to determine inter-observer variability. One investigator measured the ONSD twice to determine intra-observer variability. The inter- and intra-observer variabilities were calculated as the mean absolute difference between the 2 measured values divided by their mean and expressed as a percentage.

2.6. Primary and secondary outcomes

Our primary outcome was the ONSD at 60 minutes after the establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position (T3). The secondary outcomes were ONSDs at 30 minutes after establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position (T2) and at the end of surgery after desufflation of pneumoperitoneum in the supine position (T4). Postoperative neurologic and cardiac complications were evaluated. The postoperative neurologic complications included the occurrence of transient ischemic attack, stroke, confusion, or delirium. The postoperative cardiac complications included the occurrence of acute myocardial infarction, congestive cardiac failure, atrial fibrillation, or major arrhythmia. The duration of hospital stay, which was defined as the time from the day of operation to the day of discharge, was also evaluated.

2.7. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and categorical variables are expressed as the number of patients (%). A student t test, Mann–Whitney U test, chi-square test, or Fisher exact test was performed to compare between the 2 groups, as appropriate. To compare ONSD and other variables within and between the groups, we performed 2-way repeated measures analysis of variance with Bonferroni post-testing. P values <.05 were considered statistically significant. For all statistical analyses, SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY) was used.

The sample size was calculated based on our experience and previous study\textsuperscript{[15]}. The mean ± standard deviation of ONSD at 60 minutes after establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position under sevoflurane anesthesia was 5.6 ± 0.43 mm. We assumed that the ONSD decreased by 5\% in the dexmedetomidine group with power 90\% and a = 0.05 would be clinically significant. Considered the dropout rate of 20\%, a total of 128 subjects were studied.

3. Results

A total of 132 patients were assessed for eligibility preoperatively. Four patients were excluded and 128 patients were randomized (Fig. 2). One patient in the dexmedetomidine group and 1 patient in the control group did not receive the allocated intervention. A total of 126 patients (63 patients per group) were finally analyzed.

The clinical characteristics and intraoperative data of both groups of patients who underwent RALP are summarized in Tables 1 and 2. The 2 groups did not show significant differences in terms of the duration of anesthesia and surgery and the amount of crystalloid administered. However, the amount of intraoperative remifentanil administration was significantly lower in the dexmedetomidine group than in the control group (Table 2). In addition, patients in both groups did not receive neoadjuvant chemotherapy.

Compared with the control group, the dexmedetomidine group showed significantly smaller values of ONSDs at T2, T3, and T4 [5.26 ± 0.25 mm vs. 5.71 ± 0.26 mm, 5.29 ± 0.24 mm vs. 5.81 ± 0.23 mm, 4.97 ± 0.24 mm vs. 5.15 ± 0.28 mm, all P < .001] (Fig. 3). However, there was no significant difference in ONSD between the dexmedetomidine group and control group at T1 [4.66 ± 0.26 mm vs. 4.64 ± 0.24 mm, P = .679]. The ONSDs at T2, T3, and T4 were significantly increased compared to T1 in both groups. The intra- and inter-observer variabilities of the ONSD measurement were 2.0\% and 3.2\%.

Aside from heart rate, the hemodynamic and respiratory variables of the 2 groups did not show significant differences (Fig. 4). Heart rate was significantly lower in the dexmedetomidine group at T2 and T3. However, the incidence of bradycardia and number of patients of atropine administration did not show significant difference between the dexmedetomidine...
group and control group [56 (88.9%) vs 40 (63.5%), \( P = .142 \); 1 (1.6%) vs 2 (3.2%), \( P = .559 \)]. In addition, the number of patients of ephedrine administration was not significantly different between the dexmedetomidine group and control group [20 (31.7%) vs 19 (30.2%), \( P = .847 \)] (Table 2). Bispectral index scores were not significantly different between the 2 groups at T1, T2, T3, and T4. [49.7 vs 49.2, \( P = .675 \); 47.1 vs 48.0, \( P = .416 \); 49.3 vs 48.8, \( P = .676 \); 51.0 vs 51.2, \( P = .814 \)].

Postoperative neurologic and cardiac complications during hospital stay did not occur in either group. The duration of hospital stay was not significantly different between the dexmedetomidine group and control group [5.2 ± 1.1 days vs 5.4 ± 1.2 days, \( P = .306 \)].

4. Discussion
Our randomized, double-blind, controlled trial is the first to evaluate the effect of dexmedetomidine on ONSD, a non-invasive

### Table 1
Clinical characteristics of the patients.

|                     | Dexmedetomidine group (n = 63) | Control group (n = 63) |
|---------------------|--------------------------------|------------------------|
| Age, yr             | 65.5 ± 8.0                     | 66.8 ± 6.2             |
| Weight, kg          | 69.7 ± 8.2                     | 68.3 ± 9.6             |
| Height, cm          | 166.7 ± 5.4                    | 166.4 ± 6.4            |
| Body mass index, kg/m² | 25.0 ± 2.4                    | 24.6 ± 2.9             |
| Hypertension        | 24 (38.1)                      | 30 (47.6)              |
| Diabetes mellitus   | 11 (17.5)                      | 10 (15.9)              |
| Coronary artery disease | 4 (6.3)                      | 5 (7.9)                |
| Preoperative pulmonary function test |                   |
| FEV1, L             | 2.8 ± 0.6                      | 2.9 ± 0.5              |
| FVC, L              | 3.9 ± 0.7                      | 3.8 ± 0.6              |
| FEV1/FVC, %         | 72.3 ± 7.8                     | 74.7 ± 7.2             |
| Preoperative echocardiography |                      |
| Cardiac output, L/min | 4.2 ± 0.9                      | 4.0 ± 1.2              |
| Left ventricle ejection fraction, % | 62.8 ± 4.3                      | 61.7 ± 8.9             |
| Preoperative laboratory values |                   |
| Hematocrit, %       | 42.9 ± 3.6                     | 42.4 ± 3.5             |
| Albumin, g/dL       | 3.96 ± 2.94                    | 3.97 ± 2.90            |
| Creatinine, g/dL    | 0.93 ± 0.14                    | 0.94 ± 0.19            |

Data are expressed as mean ± standard deviation or number of patients (%). FEV1 = forced expired volume in 1 second, FVC = forced vital capacity.

### Table 2
Intraoperative data.

|                     | Dexmedetomidine group (n = 63) | Control group (n = 63) | \( P \) value |
|---------------------|--------------------------------|------------------------|--------------|
| Duration of anesthesia, min | 164.8 ± 29.0                  | 162.2 ± 19.8           | .547         |
| Duration of surgery, min    | 127.0 ± 26.5                   | 125.2 ± 17.0           | .646         |
| Crystalloid amount, mL      | 1005.6 ± 271.5                 | 956.6 ± 274.0          | .178         |
| Remifentanil amount, mg     | 0.71 ± 0.26                    | 1.05 ± 0.34            | <.001        |
| Hypotension                 | 0 (0)                          | 0 (0)                  | 1.000        |
| Bradycardia                 | 56 (88.9)                      | 40 (63.5)              | .142         |

Values are presented as mean ± standard deviation or number of patients (%). Intraoperative hypotension was defined as a systolic blood pressure of < 80 mmHg for > 5 minutes. Intraoperative bradycardia was defined as a heart rate of < 60 beats/min for > 5 minutes.
Intraoperative dexmedetomidine administration increases with age,[16] and older patients have a higher incidence of prostate cancer patients. The incidence of prostate cancer effects of dexmedetomidine on ICP are controversial.[7,9,21] In the present study, intraoperative dexmedetomidine administration may provide an additional advantage of opioid sparing during RALP.

In a previous study, propofol anesthesia during RALP significantly decreased ONSD after pneumoperitoneum and steep Trendelenburg position, compared to that of sevoflurane anesthesia, suggesting that propofol might help minimize ICP changes in robotic prostatectomy patients.[15] In another study, the effects of desflurane and total intravenous anesthesia with propofol and remifentanil during RALP on ONSD were compared. Total intravenous anesthesia with propofol and remifentanil was shown to be a more suitable anesthetic option for patients undergoing RALP.[13] Therefore, dexmedetomidine or propofol administration could help minimize the increase in ICP during RALP.

**Figure 3.** Comparisons of ONSDs during robot-assisted laparoscopic prostatectomy. T1 indicates 10 minutes after anesthetic induction in the supine position. T2 indicates 30 minutes after establishing carbon dioxide pneumoperitoneum and steep Trendelenburg position. T3 indicates 60 minutes after establishing carbon dioxide pneumoperitoneum and steep Trendelenburg position. T4 indicates at the end of surgery after desufflation of pneumoperitoneum in the supine position. Control group (blue circle) comprised patients who received normal saline. Dexmedetomidine group (red square) comprised patients who received dexmedetomidine. ONSD = optic nerve sheath diameter. *indicates P < .05 between the 2 groups.

surrogate index used for assessing ICP, in patients undergoing RALP. Among the participating patients with prostate cancer who underwent RALP under carbon dioxide pneumoperitoneum in the steep Trendelenburg position, the ultrasonographic ONSDs were significantly smaller in the dexmedetomidine group than in the control group. Hemodynamic and respiratory variables, except heart rate, were not significantly different between the 2 groups. There was no significant difference in the incidence of bradycardia and number of patients of atropine use between the 2 groups.

Compared to open prostatectomy, RALP has the advantages of good visualization of the surgical field, less perioperative bleeding, and shorter hospital stay.[11] Therefore, RALP has been more commonly performed than open prostatectomy in prostate cancer patients. The incidence of prostate cancer increases with age,[15] and older patients have a higher incidence of cerebrovascular disease and are vulnerable to increased ICP.[17] These patients are at increased risk for complications of RALP associated with establishing pneumoperitoneum and steep Trendelenburg position. Previous studies have shown that ONSD, a non-invasive surrogate for ICP, is significantly increased in patients undergoing RALP.[15,18] Therefore, active interventions to attenuate the ICP increase may be needed for patients with prostate cancer who undergo RALP under pneumoperitoneum in the steep Trendelenburg position.

Dexmedetomidine exerts effects such as sedation, anxiolysis, analgesia, and neural protection.[19,20] However, the reported effects of dexmedetomidine on ICP are controversial.[7,9,21] In the present study, intraoperative dexmedetomidine administration reduced the ONSD during RALP. The mechanism by which dexmedetomidine attenuates ICP is not well understood, but it is known to act directly on the alpha 2-adrenergic receptor and reduce catecholamine surge. These mechanisms reduce oxygen consumption and cerebral metabolic rate, decreasing the ICP by reducing cerebrospinal fluid pressure without the risk of cerebral ischemia.[22,23] Therefore, we consider that intraoperative dexmedetomidine administration can attenuate the increase of ONSD during RALP.

In this study, we measured the ultrasonographic ONSD to estimate ICP. Ultrasonography has been used to measure the degree of change in ONSD.[24] The ONSD is known to be closely correlated with ICP.[10] Also, the ONSD can reflect the ICP in real-time during surgery.[25] Therefore, ONSD measurement is known as a useful method for early detection of an increase in ICP.[26] The subarachnoid space surrounds the retrobulbar segment of the optic nerve, and the sheath surrounding the optic nerve is distensible and the diameter increases with an increase in cerebrospinal fluid pressure. When the ONSD exceeds 5 to 5.2 mm, the ICP is reported to exceed 20 mmHg.[27] Intracranial hypertension is suspected when the ICP is greater than 20 mmHg.[28] In our current study, the ONSDs of the dexmedetomidine group and the control group were 5.29 ± 0.24 mm and 5.81 ± 0.23 mm, respectively, at 60 minutes after establishment of pneumoperitoneum in the steep Trendelenburg position. Therefore, frequent ultrasonographic measurement of ONSD needs to be performed to evaluate the ICP changes during RALP.

In our study, the dexmedetomidine group had significantly lower heart rate during RALP than did the control group. Dexmedetomidine stimulates alpha 2-adrenergic receptors dose-dependently, and then decreases the serum norepinephrine concentration and reduces arterial blood pressure and heart rate.[29] However, in the present study, with a loading dose of 1 μg/kg and continuous infusion dose of 0.4 μg/kg/hr, arterial blood pressure and heart rate were well maintained within 20% of the baseline. Also, the 2 groups did not show significant differences in bradycardia and atropine use. Therefore, dexmedetomidine might be safely used to reduce ICP during RALP without causing hemodynamic instability.

We also found that the dexmedetomidine group had significantly lower amount of remifentanil. As an adjuvant in general anesthesia, dexmedetomidine provides hemodynamic stability and reduced perioperative opioid administration during intubation and operation.[30,31] Dexmedetomidine is known to bind to central and peripheral alpha 2-adrenergic receptors, and has analgesic effects and reduces opioid usage.[32] Therefore, intraoperative dexmedetomidine administration may provide an additional advantage of opioid sparing during RALP.

Besides dexmedetomidine, a few studies evaluated the effects of different anesthetic methods used during RALP on ONSDs.[15,33] In a previous study, propofol anesthesia during RALP significantly decreased ONSD after pneumoperitoneum and steep Trendelenburg position, compared to that of sevoflurane anesthesia, with propofol and remifentanil during RALP on ONSD were compared. Total intravenous anesthesia with propofol and remifentanil was shown to be a more suitable anesthetic option for patients undergoing RALP.[13] Therefore, dexmedetomidine or propofol administration could help minimize the increase in ICP during RALP.
Our study is limited in that the ICP could not be directly measured. Because the methods of direct ICP assessment such as ventriculostomy are difficult and invasive, they pose an ethical problem. However, ONSD is known to correlate strongly with increase in ICP. Second, because this was a single-center study, our results may have limited generalizability.

In conclusion, dexmedetomidine attenuates the ONSD increase during RALP. This result suggests that intraoperative dexmedetomidine administration may effectively attenuate the ICP increase in patients with prostate cancer who undergo RALP with the establishment of carbon dioxide pneumoperitoneum in the steep Trendelenburg position.

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