

Prospective Trial

Comparison of Increase in the Optic Nerve Sheath Diameter between Epidural Saline and Contrast Medium Injections

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Background: Normal saline or contrast medium is one of the widely used injection materials during fluoroscopic guided injections. Optic nerve sheath diameter (ONSD) measurement is a reliable and noninvasive method for intracranial pressure evaluation.

Objectives: The purpose of this study was to compare the increase in ONSD and cerebral oxygen saturation (rSO₂) between normal saline and contrast medium when they were injected into the epidural space.

Study Design: Prospective randomized trial.

Setting: An interventional pain management clinic in South Korea.

Methods: This study included 42 patients who were scheduled to receive thoracic epidural catheterization for postoperative pain control. Patients were randomly allocated to receive 5 mL normal saline or contrast medium following successful thoracic epidural entry. The ONSD was measured using transorbital sonography at baseline (T0), 10 min (T10), 20 min (T20), and 40 min (T40) after epidural normal saline or contrast medium injection.

Results: Both groups demonstrated significant increases in ONSD from T10 to T40 when compared with the baseline. Although both groups showed a significant increase in ONSD compared with the baseline, group saline showed a higher increase in ONSD than group contrast. A significantly higher increase in ONSD in group saline than in group contrast was maintained from T10 to T40 ($P = 0.015$).

Limitations: We could not determine the returning point of the normalized ONSD value.

Conclusion: Thoracic epidural injection of 5 mL normal saline or contrast medium resulted in a significant increase of ONSD compared to baseline; however, the degree of ONSD increase was more attenuated in the contrast group than the saline group.

Key words: Optic nerve sheath diameter, normal saline, contrast medium, cerebral oxygen saturation

Trial Registry Number: Clinical trial registry information service (NCT04826042).

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For proper intraoperative and postoperative pain control, thoracic epidural analgesia has been the gold standard method following major thoracic and upper abdominal surgery (1,2). Intracranial

pressure (ICP) increases after epidural injection (3). Direct measurement of ICP requires measuring the pressure in the ventricle or brain parenchyma. Due to the invasiveness of ICP measurement, predicting ICP by

measuring optic nerve sheath diameter (ONSD) using ocular ultrasonography has been advocated. Previous studies have shown that ONSD correlates well with the degree of ICP changes (4-7).

Recent study has shown that higher injection volumes of local anesthetics during caudal epidural anesthesia demonstrated a significant increase in ONSD compared with lower injection volumes (8). In contrast to the injection volume, posture and injection speed did not affect the increase in ONSD (9,10). Although diverse ONSD studies comparing different injection volumes (8), injection speeds (10), and postures (9) have been conducted, no study has shown that injection material, which has different nature, could affect the increase in ONSD.

During fluoroscopic guided injection, contrast medium is always used to determine successful epidural distribution and other nerve blockade. Depending on the therapeutic procedure, the volume of an injected contrast medium varies.

Contrast medium shows distinct characteristics since it has unique osmolality and viscosity. Currently available contrast medium can be divided into high-osmolar, iso-osmolar, and low-osmolar contrast medium. The contents of iodine are variable ranging from 140 mg/mL to 480 mg/mL. It is widely accepted that since higher osmolality is a main contributor to the development of nephrotoxicity, using a low-osmolar contrast medium is more desirable (11). Another property of contrast medium is its viscosity. The viscosity of contrast medium is temperature dependent and higher at lower temperatures (11).

Contrast medium is one of the routinely used materials in every pain intervention procedure; however, there has been no study showing contrast medium has any influence on the increase in ONSD.

The primary endpoint of this study is to compare the increase in ONSD and cerebral oxygen saturation (rSO_2) between normal saline and contrast medium when they were injected into the epidural space.

METHODS

Our Institutional Review Board (IRB #2021-01-041) approved this prospective and randomized study. Before enrollment of patients to this study, the benefits and risks of this study were fully explained and every patient who agreed to participate provided informed consent. This study was registered before enrollment of patients at clinicaltrials.gov (NCT04826042).

In this study, patients with abdominal aortic aneu-

rysm, donors for liver transplantation, and those stomach, lung, and liver cancers were included. The aforementioned patients were planned to receive thoracic epidural analgesia prior to surgery for postoperative pain control. Five patients refused to participate in this study. Overall, we enrolled 42 patients aged between 20 and 76 years from March to August in 2021.

Patients at risk of increased ICP due to a history of brain trauma or surgery and cerebrovascular disorder were excluded. Also, patients with infection, spine surgery at thoracic level, coagulopathy and ophthalmic disease were excluded.

Group Allocation

The focus of this study is to measure the changes in ONSD following injections of normal saline or contrast medium; therefore, the patients were randomly assigned to be in one of the 2 groups receiving different injection materials. The 2 groups receiving 5 mL normal saline (group saline) or 5 mL contrast medium (group contrast) were determined by a computer-generated randomization table.

Procedure of Thoracic Epidural Entry

A pain physician with more than 10 years experience in fluoroscopic guided interventions performed all procedures. The back of the patient from T7 to L1 was disinfected using a povidone-iodine solution. A paramedian approach was used for thoracic epidural entry. The interlaminar space of the eighth to the ninth thoracic vertebra was targeted using a 17 G Touhy needle. The Touhy needle was advanced slowly until it approached an area near the spinolaminar line in a lateral fluoroscopic view. Once it was determined that the Touhy needle was near the spinolaminar line, the loss of resistance with air was used to confirm the epidural space. Final confirmation of thoracic epidural space was determined under fluoroscopic views of anteroposterior and lateral views using 2 mL contrast medium (Bonorex, 300 mg I/ mL). In cases of successful epidural entry, group saline and group contrast were injected with 5 mL normal saline and 5 mL contrast medium via the Touhy needle, respectively. After the completion of the injection of normal saline or contrast medium, an epidural catheter was inserted slowly and was advanced from the sixth to the seventh thoracic spine.

In our institution, we routinely use low-osmolar (nonionic, iodine content [300 mg I/mL]) contrast medium for fluoroscopic guided injection.

Measurement of ONSD

ONSD was measured before the procedure of thoracic epidural entry and after the completion of epidural entry with allocated material injection at the following time points: before (baseline, T0), 10 min (T10), 20 min (T20), and 40 min (T40) following injection of 5 mL normal saline (group saline) or 5 mL contrast medium (group contrast).

This measurement was performed on the right and left sides of the eyeball, twice at each time point, to obtain a more accurate ONSD value. The representative value of each time point was obtained by calculating the mean of 4 ONSD values. We assumed that if the measured ONSD value was more than 5.5 mm, such patients were considered to have increased ICP (7).

Sonographic ONSD measurement was performed by a single experienced physician, who had handled more than 250 cases of ONSD measurement and had prior experiences with similar studies (9,10). This physician was blinded to the group assignment. All patients were evaluated in a relaxed position lying in a bed.

ONSD was measured by transorbital sonography using a hockey-stick probe (GE Healthcare, Logiq S8, Milwaukee, USA). We minimized the risk of ultrasound-induced orbital injury by reducing the power output (mechanical index, 0.2; thermal index, 0). The hockey stick probe was placed gently on the closed upper eyelid following appliance of ultrasound gel and adjusted to a suitable angle by tilting a probe from the anterior to the posterior direction to capture the clearest axial image of the optic nerve entry. An axial image of the optic nerve entry was obtained with the depth of 3.0-4.0 cm (Fig. 1). According to the recommendations of previous studies, ONSD was measured at a depth of 3 mm behind the eye globe (8-10,12).

Before the patients were sent back to their admission room following the completion of ONSD measurements, the presence of complications of increased ICP including headache, blurred vision, nausea, vomiting, and dizziness was checked.

Measurement of rSO_2

At the same time point of ONSD measurement from T0 to T40, an rSO_2 was evaluated. Before the procedure of thoracic epidural entry, we attached cerebral oximeter sensors 2 cm above each eyebrow on the left and right sides of the forehead bilaterally. The rSO_2 values were continuously monitored using O_3 regional oximetry (Root, Masimo Corp., Irvine, CA, USA).

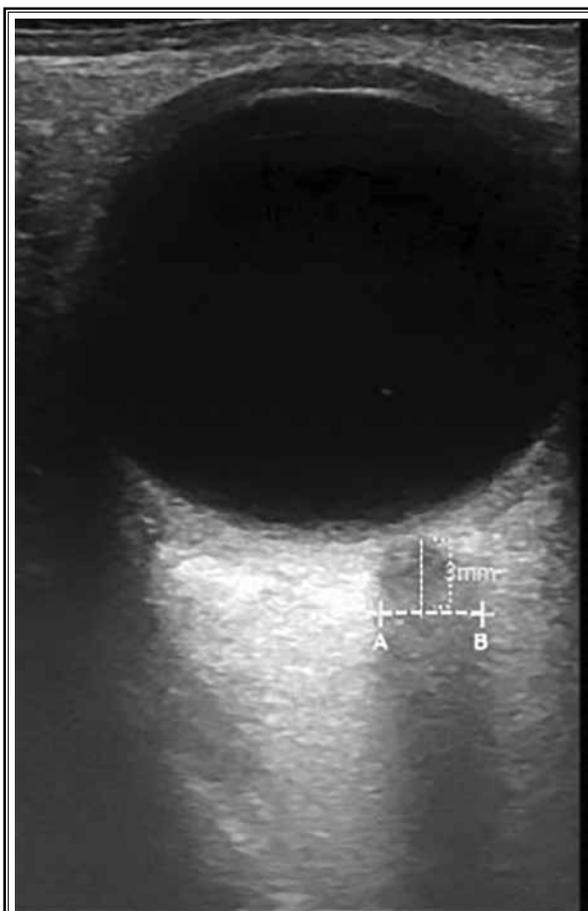


Fig. 1. Optic nerve sheath diameter (ONSD) measurement by ultrasonography. ONSD was measured 3 mm posterior to the optic nerve head (A-B) in the axial image of the orbit in the plane of optic nerve.

Statistical Analysis

A study has demonstrated that a difference in ONSD of more than 0.5 mm (10% of mean ONSD in asymptomatic normal adults [mean ONSD 4.9 mm]) would be clinically relevant (7). Twenty patients were required in each group using a 2-sided t-test, with a significance level of 5%, a power of 80%, and a drop-out rate of 15%.

Continuous variables are presented as mean \pm SD or median (interquartile range). Categorical variables are presented as number (percentile). Demographic data were compared using the chi square test, unpaired t-test, or Fisher's exact test. ONSD was repeatedly measured to evaluate the differences between the 2 groups using repeated measures analysis of variance. Intergroup comparisons of the changes in ONSD over time were

performed through group-by-time interaction. Post-hoc analyses for ONSD with Bonferroni correction were performed. All statistical values were 2-tailed, and P -values < 0.05 were used to denote statistical significance. Statistical evaluations were performed using Statistical Package for the Social Sciences (v. 22.0 IBM, Corp., NY, USA).

RESULTS

Among the 47 patients for the possible inclusion of this study, 5 patients refused to participate in this study; therefore, the remaining 42 patients completed this study without dropouts (Fig. 2). Patients with stomach, lung, and liver cancers, donors for liver transplantation, and abdominal aortic aneurysm were included. Gender distribution, age, and body mass index were similar between the 2 groups (Table 1).

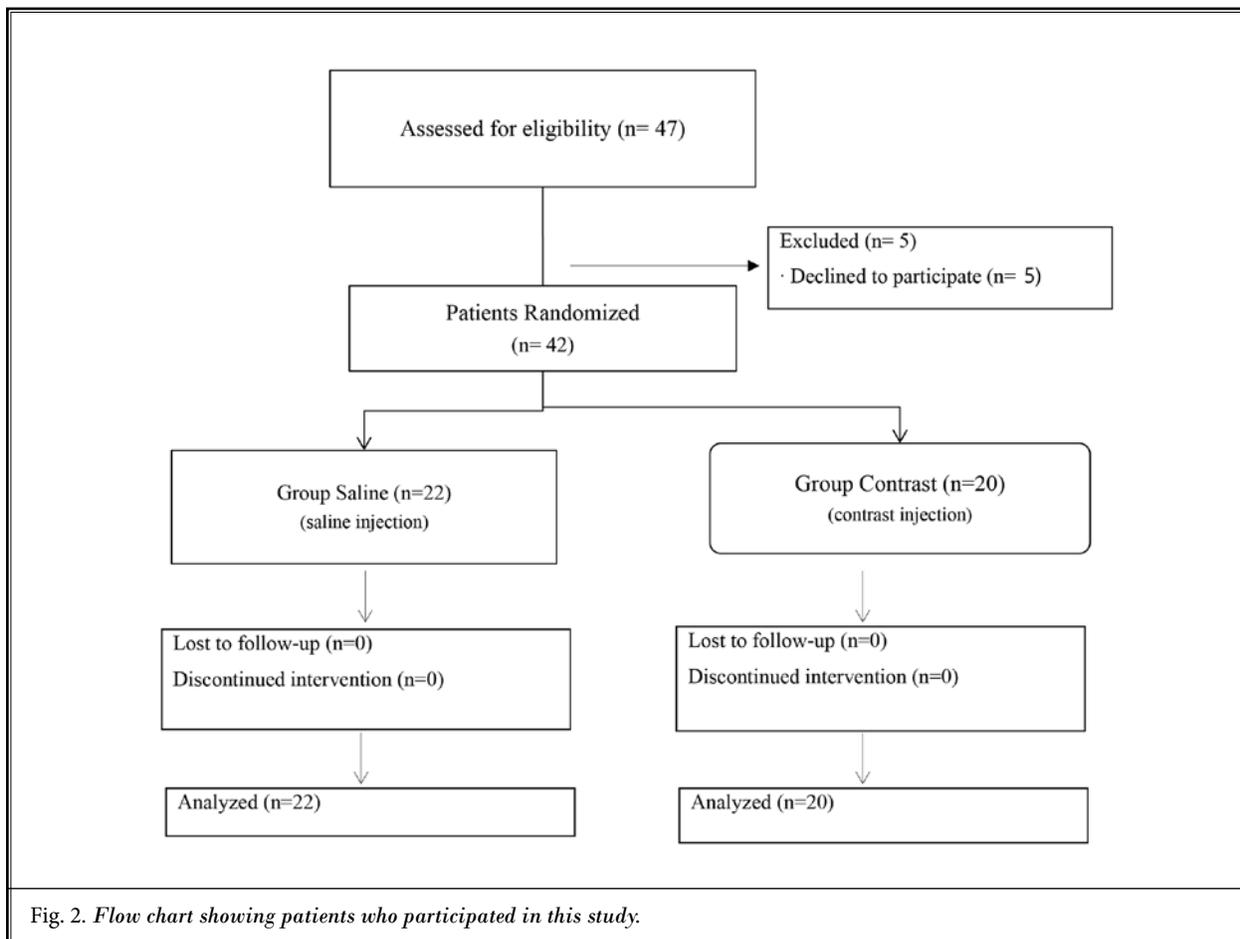
Both groups demonstrated significant increases in ONSD from T10 to T40 compared with those at baseline. Although both groups showed significant increases in

ONSD compared with those at baseline, group saline showed a higher increase of ONSD than group contrast. A significantly higher increase in ONSD in group saline than in group contrast was maintained from T10 to T40 ($P = 0.015$, Table 2, Fig. 3).

Changes in the ONSD increase (T10-T0, T20-T0, and T40-T0) between the 2 groups showed significant differences (Table 3). The degree of ONSD increase was most pronounced at T10 in both groups; however, the degree of increase was more attenuated in group contrast than that in group saline.

From T10 to T40, there was a significant difference in the number of patients showing an increase in ONSD beyond 5.5 mm. A much higher number of patients in group saline showed an increase in ONSD beyond 5.5 mm (Table 4) than in group contrast. Both groups showed an rSO_2 to be distributed between 60~70% without any statistical differences (Fig. 4).

Complications of increased ICP, such as headache,



blurred vision, dizziness, nausea, and vomiting, were not found.

DISCUSSION

This study investigated whether different injection materials have any influence on the degree of ONSD increase when injected into epidural space with an equivalent volume. Thoracic epidural injection with normal saline or contrast medium resulted in a significant increase in ONSD compared with that at baseline, which did not return to baseline level even 40 min after injection. However, when normal saline was injected into the epidural space, a higher increase in ONSD was observed than what was observed when contrast medium was injected. Group contrast showed a more attenuated increase in ONSD than group saline, such a trend of attenuated increase was maintained during the entire study period. Furthermore, the number of patients who showed an increase in ONSD beyond 5.5 mm was higher in group saline than in group contrast.

When normal saline or local anesthetics are injected into the epidural space, the important phenomenon elevating ICP is thought to be the movement of CSF from the spinal subarachnoid space to the cranial cavity. Such a movement of CSF toward the intracranial space occurs due to a pressure difference between the spinal and intracranial spaces when normal saline or local anesthetics are injected into the epidural space (13). A powerful effect of thecal sac compression should be performed previously by epidural injection of either normal saline or contrast medium to generate any pressure difference and CSF movement to cranial direction (9,10,13).

Table 1. Demographic data and type of disease required for thoracic epidural catheterization.

	Group Saline (n = 22)	Group Contrast (n = 20)	P value
Gender (men/women)	13 (59.1)/9 (40.9)	10 (50)/10 (50)	0.554
Age (years)	59.0 ± 9.9	57.5 ± 13.8	0.686
Body mass index (kg/m ²)	24.6 ± 2.9	24.9 ± 2.9	0.754
Type of disease			0.752
Stomach cancer	14 (63.6)	13 (65.0)	
Lung cancer	4 (18.2)	3 (15.0)	
Hepatoma	1 (4.5)	2 (10.0)	
Donor for liver transplantation	1 (4.5)	2 (10.0)	
Abdominal aortic aneurysm	2 (9.1)	0 (0)	

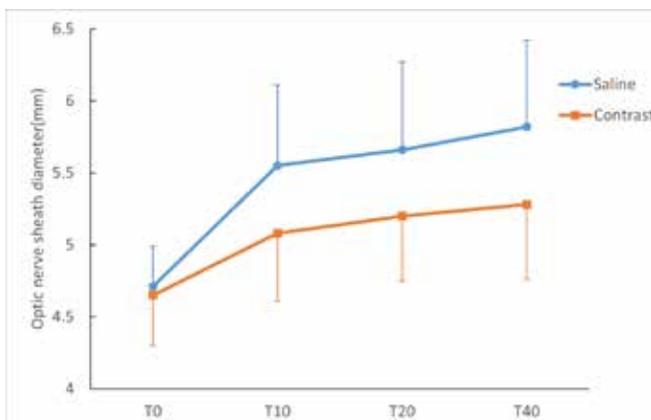
Values are presented as mean ± SD for quantitative variables and N (%) for qualitative variables.

Table 2. Mean values of optic nerve sheath diameter (ONSD) at each time points.

	Group Saline (n = 22)	Group Contrast (n = 20)	Adjusted P value
ONSD (mm)			
T0	4.71 ± 0.28	4.65 ± 0.35	>0.999
T10	5.55 ± 0.56‡	5.08 ± 0.47*	0.022
T20	5.66 ± 0.61‡	5.20 ± 0.45†	0.038
T40	5.82 ± 0.60‡	5.28 ± 0.52†	0.015

Values are presented as mean ± SD. Adjusted P-value indicates the Bonferroni-corrected P-value. T0, baseline; T10, 10 min after epidural normal saline or contrast medium injection; T20, 20 min after epidural normal saline or contrast medium injection; T40, 40 min after epidural normal saline or contrast medium injection. *P < 0.05 vs T0; †P < 0.01 vs T0; and ‡P < 0.001 vs T0 in each group

Fig. 3. Changes in optic nerve sheath diameter (ONSD) according to time. The two groups showed significant differences in changes in ONSD according to time in repeated measure of ANOVA (P_{group×time} = 0.015). Values are mean ± SD. T0, baseline; T10, 10 min after epidural normal saline or contrast medium injection; T20, 20 min after epidural normal saline or contrast medium injection; T40, 40 min after epidural normal saline or contrast medium injection.



The epidural space is a potential space, where a certain degree of thecal sac compression will be generated subsequent to injection of any material (14). With higher volumes of injection, the degree of thecal sac compression can be pronounced (8). In

contrast to normal saline, contrast medium is thought to have a weak effect of thecal sac compression, such a weak effect of thecal sac compression might have resulted in less movement of CSF and pressure difference compared to the injection of normal saline. Since an equivalent volume of normal saline or contrast medium was injected into the epidural space, a generation of different degrees of thecal sac compression could be resulted from the different nature of the 2 materials. When contrast medium is injected into the epidural space, it is thought that contrast medium adheres to adjacent tissues rapidly due to its higher viscosity, such a higher viscosity and rapid adherence to adjacent tissue in group contrast could result in a less pronounced effect of thecal sac compression compared to normal saline. This effect ultimately leads to a more attenuated increase in ONSD in group contrast than group saline. The effect of the viscosity of contrast medium was also influenced in the epidural distribution through the transforaminal injections. The contrast medium of higher viscosity demonstrated a more limited epidural distribution than lower viscosity of contrast medium (14). A wider distribution of normal saline in the epidural space than contrast medium might generate a more potent pressure effect on the thecal sac.

Table 3. Degree of changes in optic nerve sheath diameter (ONSD) between time points

	Group Saline (n = 22)	Group Contrast (n = 20)	Adjusted P value
Changes in ONSD (mm)			
T10-T0	0.85 ± 0.46	0.43 ± 0.46	0.019
T20-T0	0.95 ± 0.52	0.55 ± 0.57	0.070
T40-T0	1.11 ± 0.60	0.63 ± 0.59	0.037

Values are presented as mean ± SD. Adjusted P-value indicates the Bonferroni-corrected P-value. T0, baseline; T10, 10 min after epidural normal saline or contrast medium injection; T20, 20 min after epidural normal saline or contrast medium injection; T40, 40 min after epidural normal saline or contrast medium injection.

Table 4. Number of patients (%) who showed optic nerve sheath diameter more than 5.5 mm.

	Group Saline (n = 22)	Group Contrast (n = 20)	P value
ONSD ≥ 5.5 mm			
T0	0(0)	0(0)	>0.999
T10	13(59.1)	4(20.0)	0.010
T20	13(59.1)	4(20.0)	0.010
T40	14(63.6)	7(35.0)	0.064

T0, baseline; T10, 10 min after epidural normal saline or contrast medium injection; T20, 20 min after epidural normal saline or contrast medium injection; T40, 40 min after epidural normal saline or contrast medium injection.

Contrast medium presents diverse ranges of iodine content, osmolality, and viscosity. In this study, we used a contrast medium of nonionic, low-osmolality (300 mg I/ mL), and medium-grade viscosity. Further study is required to determine whether a contrast medium of different properties, such as high-osmolality and high-grade viscosity, could generate a more pronounced or attenuated effect of ONSD increase.

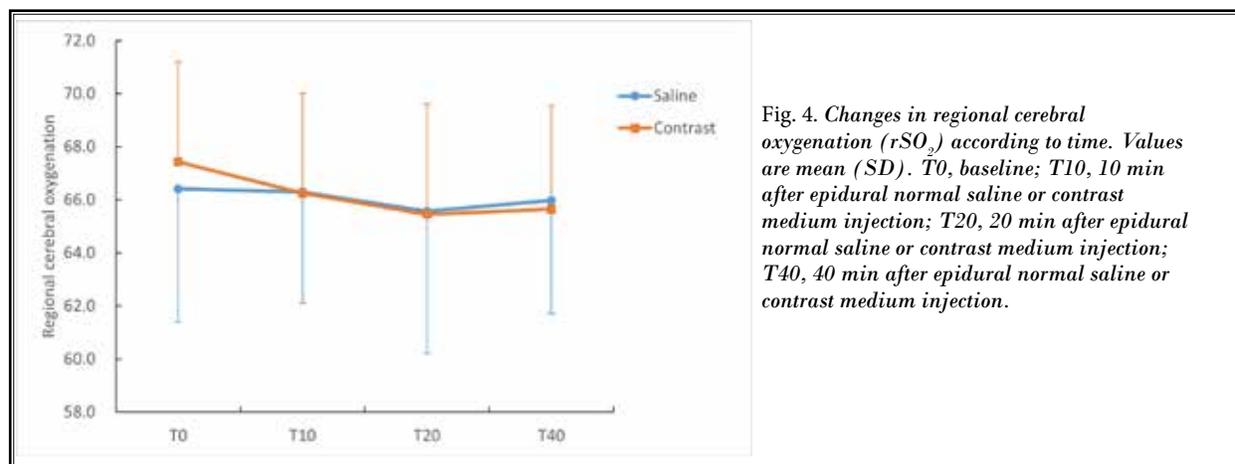


Fig. 4. Changes in regional cerebral oxygenation (rSO₂) according to time. Values are mean (SD). T0, baseline; T10, 10 min after epidural normal saline or contrast medium injection; T20, 20 min after epidural normal saline or contrast medium injection; T40, 40 min after epidural normal saline or contrast medium injection.

Cerebral oxygenation which is monitored using rSO_2 reflects the value of cerebral perfusion. The rSO_2 comprises 25% arterial and 75% venous blood according to the manufacturer. The rSO_2 represents oxygen saturation of the frontal lobe, but not the entire brain (15). During the entire study period, from T0 to T40, rSO_2 was maintained between 60% ~ 70% and did not show any significant increase or decrease of rSO_2 between the 2 groups.

The optic nerve is closely encircled by the subarachnoid space, therefore, an increase in ICP can cause movement of CSF into the perineural subarachnoid space. The subarachnoid space surrounding the optic nerve sheath has an elastic trabecular structure. It is most distensible 3 mm behind the papilla in the eye globe. Due to such a distensibility, the optic nerve sheath inflates within a few minutes of exposure to increased ICP (5,16); moreover, previous study has demonstrated that ONSD measured using ocular ultraso-

nography correlated with ICP measured using invasive methods (17,18).

This study includes several limitations. First, the ONSD values measured at T40 did not return to a baseline value. This study could not conclude the time point when the value of ONSD was normalized. Further study is required to confirm when the ONSD value is normalized. Second, it is recommended that patients should lie in bed with minimal positional changes for the stable measurement of rSO_2 ; however, patients had to move to fluoroscopic table for the subsequent thoracic epidural catheterization. This movement might have influenced the value of rSO_2 .

In conclusion, epidural injection of 5 mL normal saline or contrast medium resulted in significant increase in ONSD, compared with that at baseline; however, the degree of ONSD increase was more attenuated in group contrast than in group saline.

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