Randomized Trial

The Effect of Speed of Normal Saline Injection on Optic Nerve Sheath Diameter in Thoracic Epidural Anesthesia

Ji Hee Hong, MD, PhD[1], Sung Won Jung, MD, PhD[2], and Ji Hoon Park, MD[1]

From: [1]Department of Anesthesiology and Pain Medicine, Keimyung University DongSan Hospital, Daegu, South Korea; [2]Department of Psychiatry, Keimyung University DongSan Hospital, Daegu, South Korea

Address Correspondence:
Ji Hee Hong, MD, PhD
Department of Anesthesiology and Pain Medicine, Keimyung University DongSan Hospital
56, Dal-Sung Ro, Jung gu
Daegu 700-712, South Korea
E-mail: swon13@daum.net

Disclaimer: This study was supported by Keimyung University Research Grant of 2018.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 08-19-2018
Revised manuscript received: 09-20-2018
Accepted for publication: 10-04-2018

Free full manuscript:
www.painphysicianjournal.com

Background: Intracranial pressure (ICP) is affected after epidural saline solution or local anesthetic injection. Both ICP and epidural pressures have been shown to reach peak pressure just after epidural injection and begin decline thereafter. Measuring the optic nerve sheath diameter (ONSD) through ultrasonography is one of the noninvasive methods used for ICP assessment.

Objectives: The purpose of this study was to investigate the effect of the speed of epidural saline injection on the ONSD under awake conditions.

Study Design: Prospective randomized trial.

Setting: An interventional pain management practice in South Korea.

Methods: This study included 40 patients receiving thoracic epidural catheterization for pain management after upper abdominal or thoracic surgery. Following successful epidural space confirmation, patients were randomized to receive epidural saline infusion with a speed of either 1 mL/second (slow speed, A group) or 3 mL/second (rapid speed, B group), respectively. For the measurement of ONSD, transorbital sonography was performed and ONSD was measured at 3 mm posterior to the optic nerve head.

Results: The A and B groups showed significant increases in ONSD according to time. Post hoc analysis of this result revealed that ONSD at T10 and T30 were significantly increased from baseline values (T0) ($*P < 0.05$ vs. T0; $+P < 0.001$ vs. T0). The mean values at any of the time points and degree of changes (T1-T0, T10-T0, and T30-T0) in ONSD between groups A and B did not show any significance.

Limitations: We could not confirm the time of normalization of ONSD after the end of epidural injection of normal saline.

Conclusions: Thoracic epidural injection of 10 mL of normal saline solution resulted in a significant increase of ONSD compared to baseline, however, the speed of injection did not affect the increase of ONSD.

Key words: Epidural, saline, optic nerve, diameter

Trial registry number: Clinical trial registry information service (NCT03362255).

Pain Physician 2019: 22:E325-E332

Thoracic epidural anesthesia is frequently used for postoperative analgesia of hepatobiliary, thoracic, or gastric surgery because of its favorable safety and efficacy (1,2).

Various factors contribute to the spread of epidural anesthesia. Among them, the influences of injection speed and epidural pressure remain controversial (3). In lumbar epidural anesthesia, the rapid speed of injection

group showed higher peak epidural pressure than the slow speed of injection group. The extent and regression time of the thermal block showed a consistent correlation with the epidural pressure (4). In contrast, the rapid injection of mepivacaine (8 mL/8 seconds vs. 8 mL/160 seconds) resulted in an equal number of sensory dermatomes blocked after 15 minutes as in the slow injection group. However, the onset of blockade was more rapid in the fast injection group (5).

Changes of pressure in the epidural space have been demonstrated to reflect real-time changes in intracranial pressure (ICP). Both ICP and epidural pressure have been shown to reach peak pressure just after epidural injection and begin decline thereafter (6-8).

Twelve cases of visual impairment following epiduroscopy or epidural spinal injection with variable volume (20-120 mL) have been reported (9-11). Evidently, retinal hemorrhage subsequent to epidural injection or epiduroscopy is owing to an increase in cerebrospinal fluid pressure proportional to the speed and the amount of fluid injected. A sudden increase in epidural pressure is transmitted to the subarachnoid space to the optic nerve sheath, causing a compression of the optic nerve and its vasculature (10-12). Caudal block with a high volume of local anesthetics showed reduced cerebral flow with decreased regional oxygenation caused by increased ICP (13). Therefore, high amount of volume and rapid speed of epidural injection raise the safety issues.

ICP can be measured directly in the ventricle or the brain parenchyma; however, such direct measurement is invasive. Optic nerve sheath diameter (ONSD) measurement by ultrasonography is one of the noninvasive methods for ICP assessment. Increasing evidence suggests that ONSD correlates well with the degree of ICP and can detect intracranial hypertension (14-16). A previous study suggested that the optimal cut-off point for identifying increased ICP was 5.5 mm (17).

A high volume compared to a low volume of epidural injection resulted in relevant increase of ONSD (13,18). However, the previous studies on this subject were performed under general anesthesia, which potentially affects the increase of ICP because of volatile anesthetics (13,18,19). Our study was designed to investigate the effect of speed of epidural injection to the ONSD under awake conditions without general anesthesia.

The primary endpoint of this study was to measure the ONSD using ultrasonography in 2 groups with different speeds of epidural saline injection.

Methods

Patients

This prospective and randomized study was approved by the institutional review board (IRB #08-017) of our institution. All patients were provided with written and verbal information about the trial and of the potential benefits and risks before they provided informed consent. This trial was registered prior to patient enrollment at www.clinicaltrials.gov (NCT03362255, Date of registration: November 28, 2017).

Among patients undergoing hepatobiliary, gastric, and thoracic surgery due to cancer, 40 patients aged between 20 and 80 years who were scheduled to received thoracic epidural catheterization for postoperative pain control were enrolled (November 2017 through May 2018). Patients with the following conditions were excluded: coagulopathy, infection, previous history of thoracic spine surgery, ophthalmic diseases, and a history of increased ICP.

Thoracic Epidural Catheterization

All thoracic epidural catheterization was performed by one pain physician with > 13 years of experience in fluoroscopy-guided interventions one day before the elective surgery at the pain management clinic. Patients in both groups were asked to lie down in a prone position on a fluoroscopy table and were draped in sterile fashion. An 18-gauge Tuohy needle was advanced slowly, targeting the interlaminar space of the eighth to ninth thoracic vertebra using the midline approach. When the needle approached near the targeted spinolaminar line using a lateral view, a loss of resistance with air was used to confirm the epidural space. Once the loss of resistance was felt, 2 mL of contrast medium was injected to confirm the thoracic epidural space in the anteroposterior (AP) and lateral views. After confirming the successful epidural injection, AP and lateral fluoroscopic images were saved to the hard disk of the C-arm.

An equal number of patients were randomly assigned to receive 0.9% normal saline solution with an injection speed of either 1mL/second (slow speed, A group) or 3 mL/seconds (rapid speed, B group) using a computer-generated randomization table. The administration of the normal saline solution at the predefined speed was performed with a syringe pump (Injectomat Agilia®, Brezins, France) with the infusion line connected from the Tuohy needle to the syringe pump. Injection of epidural saline solution was performed before insertion of the epidural catheter.

After completing the injection of 0.9% normal saline solution, an epidural catheter was inserted through the Touhy needle and advanced until the seventh thoracic vertebrae. The catheter was sutured with nylon 3-0 around the skin and fixed with an adhesive plaster. Once a patient had finished all processes of normal saline infusion and catheter insertion, they were sent to the observation room to be measured for ONSD.

Measurement of ONSD

One investigator with experience in over 150 cases of ultrasonographic ONSD measurement, who was blinded to the group assignment, measured the ONSD. For the measurement of ONSD, transorbital sonography was performed using a hockey stick probe (GE Healthcare, Logiq S8, Milwaukee, MI) with the power output reduced (mechanical index, 0.2; thermal index, 0) to minimize the possibility of ultrasound-induced eye injury. Patients were asked to close their eyes and a sterile gel was applied on each closed upper eyelid. The probe was placed smoothly to minimize the exerted pressure. The probe was tilted slightly in the cephalad or caudal direction to obtain the best axial image of the orbit in the plane of the optic nerve. The ONSD was measured 3 mm posterior to the optic nerve head (Fig. 1) (16,18). All axial images of orbit were obtained within a depth parameter of 3.0-4.0 cm. Each ONSD was measured in each eye at the following time points: before (baseline, T0), immediately after (T1), 10 minutes (T10) and 30 minutes (T30) after injection of normal saline solution. The mean value of the 4 measurements was considered the ONSD at each time point. Patients were considered having increased ICP if the measured ONSD was > 5.5 mm, which was the cut-off point of the previous study (17).

After completing the ONSD measurement, patients were asked about the presence of headache, nausea, vomiting, dizziness, or blurred vision. If patients showed no complications related to increased ICP or the procedure of thoracic epidural catheterization, they were sent to their admission room.

Statistical Analysis

This study was designed to identify whether there would be any differences in ONSD according to the speed of normal saline injection. According to the results of a previous study (17), a difference in ONSD > 0.5 mm (10% of mean ONSD in asymptomatic normal adults [mean ONSD 4.9 mm]) was considered clinically relevant. Twenty patients were required in each group considering a significance level of 5%, a power of 80%, and a dropout rate of 15%.

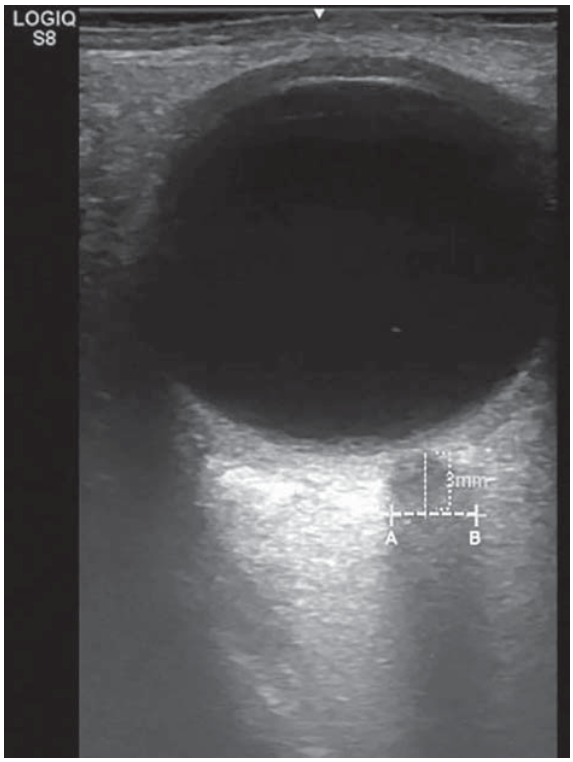

Fig. 1. *ONSD measurement by ultrasonography. ONSD was measured 3 mm posterior to the optic nerve head (A-B) in the axial image of the obit in the plane of optic nerve.*

Continuous variables are presented as mean (SD), and categorical variables are presented as number (percentile). Demographic data were compared by the unpaired t test, the Chi-square test or the Fisher exact test. The repeated measurement of ONSD was performed to investigate the differences between the 2 groups. Intergroup comparison of the changes in ONSD over time was performed through group-by-time interaction. If significant differences were identified in the repeated measure analysis, post hoc analyses for ONSD with Bonferroni correction were performed. All statistical values were 2-tailed, and *P* values < 0.05 were considered statistically significant. Statistical evaluations were performed using SPSS Version 22.0 (IBM Corporation, Armonk, NY).

Results

Forty-seven patients were assessed for eligibility and 40 of these patients completed the study (November 2017 through May 2018) without dropout (Fig. 2). There were no significant differences in patient characteristics or the type of disease requiring thoracic epidural catheterization between the 2 groups (Table 1). Type of surgeries that the patients underwent included laparoscopic gastrectomy, lung lobectomy, liver lobectomy, esophagectomy, and Whipple procedure.

The A and B groups showed significant increases in ONSD according to time (Fig. 3). Post hoc analysis of this result revealed that ONSD at T10 and T30 were significantly increased from the baseline value (T0) (corrected for age and body mass index, $*P < 0.05$ vs. T0; $+P < 0.001$ vs. T0; Table 2). Both groups showed peak values of ONSD at T30. The mean values at any of the time points and degree of changes (T1-T0, T10-T0, and T30-T0) in ONSD between groups A and B did not show any significant changes (Tables 2 and 3). From T10, more than half of patients in both groups started to demonstrate ONSD of > 5.5 mm (Table 4).

Symptoms related to increased ICP such as headache, nausea, vomiting, dizziness, and blurred vision were not found in either group. Complications related to thoracic epidural catheterization included mild sore-

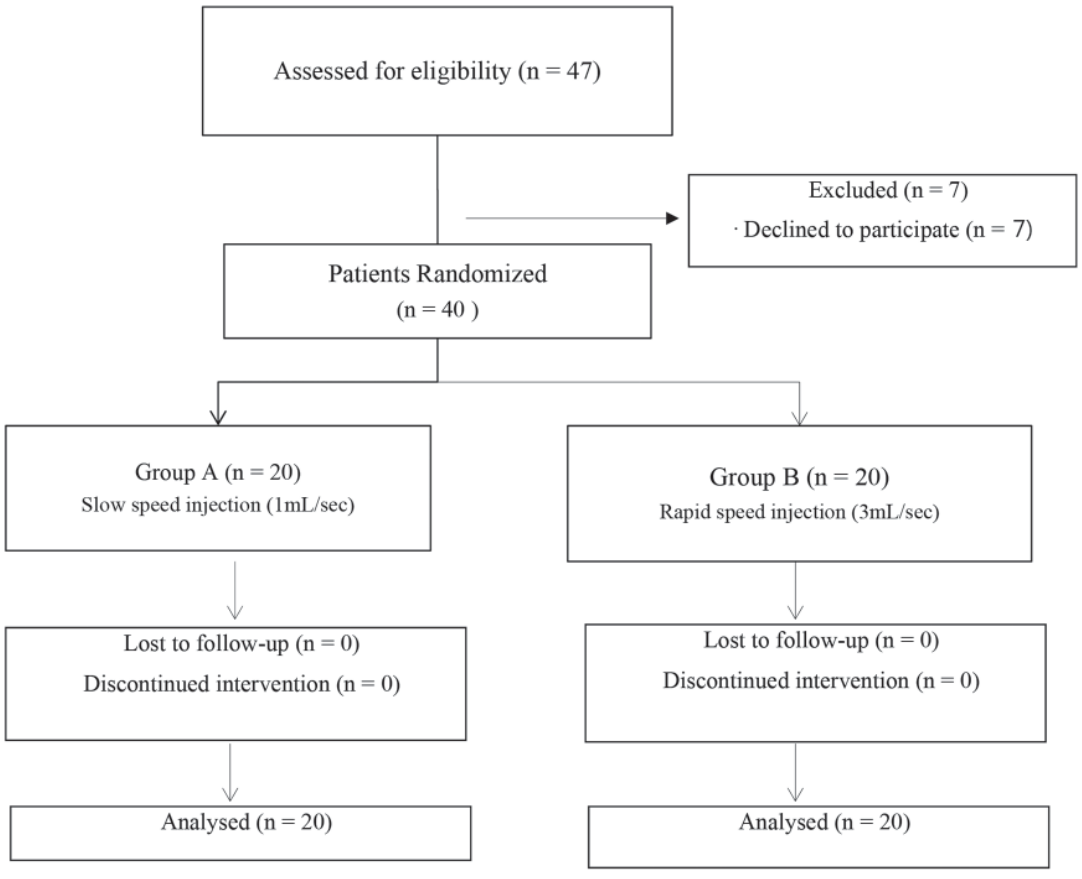

Fig. 2. *Flow chart showing patients who participated in this study.*

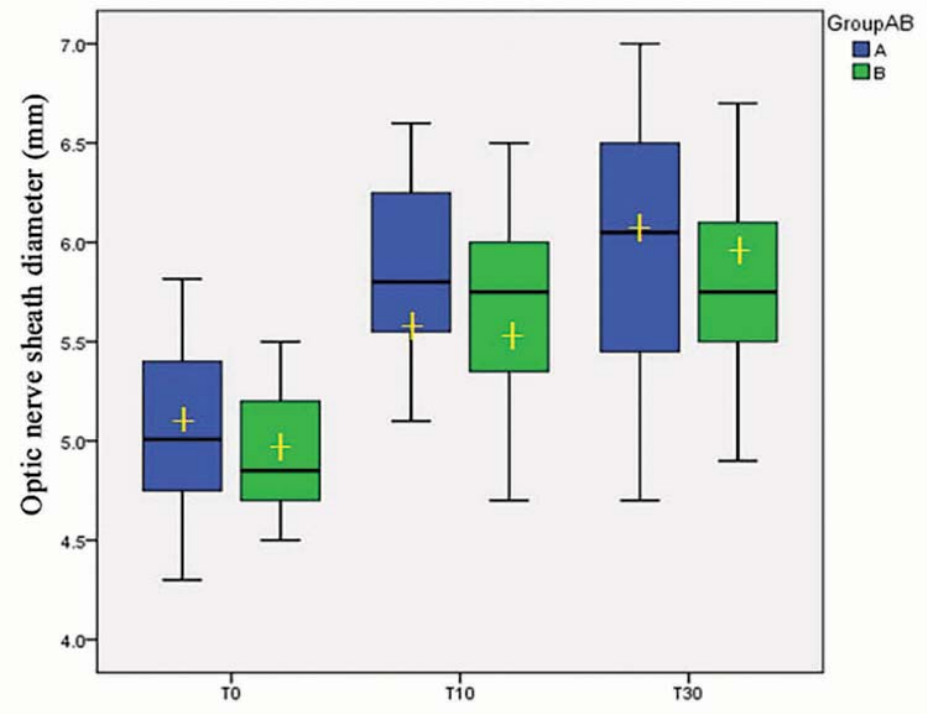

Fig. 3. *Changes in ONSD according to time. Values are mean (cross in the box), median (bar in the box), 25 and 75 percentiles (boxes), and the range (whiskers). T0, baseline; T10, 10 minutes after epidural normal saline injection; T30, 30 minutes after epidural normal saline injection.*

ness around catheter insertion area that were resolved spontaneously several hours later.

Discussion

We investigated the effect of normal saline injection on ICP by measuring ONSD in upper abdominal or thoracic surgery patients requiring thoracic epidural catheterization for pain control. Thoracic epidural injection of 10 mL of normal saline solution with either a slow or fast speed (1 mL/second or 3 mL/seconds) resulted in relevant increase in ONSD.

Both 1 mL/second and 3 mL/seconds epidural injection speeds resulted in similar increases in ONSD. Although there was a tendency of the slow speed of injection (group A, 1 mL/second) showing higher increase of ONSD, this trend was not statistically significant between the 2 groups. A previous study of caudal epidural injection of different volumes (1.0 mL/kg or 1.5 mL/kg) and ONSD measurement showed that a higher volume resulted in significantly greater increases of ONSD from baseline to 10 minutes and 30 minutes after caudal block (18). In contrast to the effect of volume on ONSD,

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

	Group A (n = 20)	Group B (n = 20)	*P* Value
Gender (male/female)	16/4	12/8	0.168
Age (yrs)	63.3 ± 12.8	62.2 ± 13	0.789
Height (cm)	162.5 ± 8	162.1 ± 7.2	0.852
Weight (kg)	61.9 ± 11.8	64.7 ± 9.9	0.428
Body mass index (kg/m^2)	23 ± 2	24.1 ± 3.2	0.235
Type of disease			
Gastric cancer	6 (30)	6 (30)	
Esophageal cancer	4 (20)	0 (0)	
Lung cancer	7 (35)	8 (40)	0.369
Hepatobiliary cancer	1 (5)	3 (15)	
Pancreas cancer	1 (5)	2 (10)	
Donor for liver transplantation	1 (5)	1 (5)	

Values are presented as mean ± SD for quantitative variables and n (%) for qualitative variables. There were no significant differences between Groups A and B. Group A: slow injection of normal saline solution (1 mL/second). Group B: rapid injection of normal saline solution (3 mL/second).

Table 2. *Values of ONSD at each time point.*

	Group A (n = 20)	Group B (n = 20)	Adjusted *P* Value
ONSD (mm)			
T0	5.13 (0.47)	4.92 (0.30)	0.392
T1	5.49 (0.56)*	5.23 (0.42)*	0.436
T10	5.55 (0.44)+	5.45 (0.57)+	0.436
T30	6.01 (0.64)+	5.81 (0.46)+	> 0.999

Values are presented as mean (SD). Adjusted *P* value indicates the Bonferroni-corrected P value. *$P < 0.05$ versus T0. +$P < 0.001$ versus T0 in each group. Post hoc analysis was corrected for age and body mass index. T0, baseline; T1, immediately after epidural normal saline injection; T10, 10 minutes after epidural normal saline injection; T30, 30 minutes after epidural normal saline injection.

Table 3. *Degree of changes in ONSD between time points.*

	Group A (n = 20)	Group B (n = 20)	Adjusted *P* Value
Changes in ONSD (mm)			
T1-T0	0.36 (0.44)	0.31 (0.36)	> 0.999
T10-T0	0.42 (0.54)	0.53 (0.56)	> 0.999
T30-T0	0.88 (0.52)	0.89 (0.52)	> 0.999

Values are presented as mean (SD). Adjusted *P* value indicates the Bonferroni-corrected *P* value. T0, baseline; T1, immediately after epidural normal saline injection; T10, 10 minutes after epidural normal saline injection; T30, 30 minutes after epidural normal saline injection.

Table 4. *Number of patients (%) who showed ONSD > 5.5 mm.*

	Group A (n = 20)	Group B (n = 20)
ONSD > 5.5 mm		
T0	0 (0 %)	0 (0%)
T1	8 (40%)	7 (35%)
T10	16 (80%)	13 (65%)
T30	15 (75%)	15 (75%)

T0, baseline; T1, immediately after epidural normal saline injection; T10, 10 minutes after epidural normal saline injection; T30, 30 minutes after epidural normal saline injection.

the speed of injection did not show any significant effect.

Local anesthetic injection into the epidural space results in a subsequent increase of epidural pressure. Epidural pressure and ICP demonstrated a very close relationship. Epidural pressure monitoring has been reported to reflect real-time changes of ICP, and both ICP and epidural pressures have been shown to reach peak pressure just after epidural injection and begin to decline thereafter (6-8). The curve of epidural pressure is composed of 3 parts, including the peak, the descent, and the residual parts. The peak part of the epidural pressure curve is obtained from dilatation of the epidural space induced by the injection of local anesthetics. The increase of peak epidural pressure is very immediate and of short duration. If the injection speed is higher, the peak pressure is higher as well (4,5). The descent is related to compliance and resistance of epidural space and children of high compliance and low resistance show a rapid descent despite the higher injection speed. Importantly, the peak epidural pressure is directly correlated with the injection speed (4,5,19). However, the residual pressure obtained just following the end of the local anesthetic injection has been shown to be similar between the slow speed and rapid speed injection groups (4). Similarly, different speed of injection of the local anesthetics during caudal block did not affect the cranial spread assessed by ultrasound. They suggested that the final extent of the block is influenced by the residual epidural pressure (19). We presume that the final increase of ONSD is influenced by the residual pressure, not by the peak pressure.

The optic nerve is a structure encircled by the expansible subarachnoid space (20). An increase of ICP can displace cerebrospinal fluid into the perineural space from the intracranial cavity, causing an increase in ONSD. Several previous studies have demonstrated that the ultrasonographic measurement of ONSD is closely related to ICP and is a valuable method for detecting increases in ICP (14-16). In addition, a recent study showed that ONSD measurement by ultrasonography correlated well with ICP measured by invasive methods (21). Therefore, our results indicate that 10 mL of normal saline solution resulted in a significant increase of ICP, although the speed of injection did not affect the increase of ICP.

Normal saline solution is frequently used during spinal epiduroscopy for the purpose of irrigation or opening the epidural space to obtain a proper visual field. Considering the increasing rate of spinal interventions due to chronic pain, use of a high amount of normal saline solution raises the safety issues, especially in patients with risk factors associated with increased ICP. The patients enrolled in this study did not show any symptoms related to increased ICP. However, previous studies have reported the occurrence of visual impairment following epidural injection or spinal endoscopy (9-12). During epiduroscopy or epidural injection, the injected amount of saline solution varied from 20-120

mL, and most patients showed visual impairment due to retinal hemorrhage. Abrupt increase in ICP subsequent to epidural saline injection is presumed to be the main cause of retinal vessel damage (12). This study examined the occurrence of complications related to increased ICP after final measurement of ONSD at 30 minutes. However, 30 minutes after epidural saline injection might not be enough time interval to observe such complication.

A previous ONSD study showed that the optimal cut-off point of 5.5 mm yielded a sensitivity of 98.77% and a specificity of 85.19% for detecting increased ICP in Korean patients (17). Our study showed that approximately 10 minutes were required to show the increase of ONSD (≥ 5.5 mm) after acute increase of ICP. A recent study showed that caudal epidural block increased ICP and epidural pressure simultaneously, however, because of the pressure difference of the cranial and spinal compartment, CSF movement occurred from the spinal subarachnoid space and then into the intracranium, which ultimately increased the ONSD (22). This phenomenon explains the delayed appearance of increased ONSD.

Limitations

The measurement of ONSD was performed for 30 minutes and T30 showed the highest value of ONSD. Therefore, we could not confirm the time of normalization of ONSD after the end of epidural injection of normal saline solution. Further study on the measurement of ONSD that includes the time of complete normalization is required.

Conclusions

Thoracic epidural injection of 10 mL of normal saline solution resulted in a significant increase of ONSD compared to baseline, however, the speed of injection did not affect the increase of ONSD.

References

1. Koul A, Pant D, Rudravaram S, Sood J. Thoracic epidural analgesia in donor hepatectomy: An analysis. *Liver Transpl* 2018; 24:214-221.
2. Yassin HM, Abd Elmoneim AT, El Moutaz H. The analgesic efficiency of ultrasound-guided rectus sheath analgesia compared with low thoracic epidural analgesia after elective abdominal surgery with a midline incision: A prospective randomized controlled trial. *Anesth Pain Med* 2017; 7:e14244.
3. Visser WA, Lee RA, Gielen MJ. Factors affecting the distribution of neural blockade by local anesthetics in epidural anesthesia and a comparison of lumbar versus thoracic epidural anesthesia. *Anesth Analg* 2008; 107:708-721.
4. Cardoso MM, Carvalho JC. Epidural pressures and spread of 2% lidocaine in the epidural space: Influence of volume and speed of injection of the local anesthetic solution. *Reg Anesth Pain Med* 1998; 23:14-19.
5. Kanai A, Suzuki A, Hoka S. Rapid injection of epidural mepivacaine speeds the onset of nerve blockade. *Can J Anaesth* 2005; 52:281-284.
6. Eide PK, Sorteberg W. Simultaneous measurements of intracranial pressure parameters in the epidural space and in brain parenchyma in patients with hydrocephalus. *J Neurosurg* 2010; 113:1317-1325.
7. Grocott HP, Mutch WA. Epidural anesthesia and acutely increased intracranial pressure. Lumbar epidural space hydrodynamics in a porcine model. *Anesthesiology* 1996; 85:1086-1091.
8. Uldall M, Juhler M, Skjolding AD, Kruuse C, Jansen-Olesen I, Jensen R. A novel method for long-term monitoring of intracranial pressure in rats. *J Neurosci Methods* 2014; 227:1-9.
9. Williams RC, Doliner SJ, Lipton RM, Franz JA, Delaney RD. Retinal hemorrhage as a consequence of epidural steroid injection. *Arch Ophthalmol* 1996; 114:362-363.
10. Moschos MM, Rouvas A, Papaspirou A, Apostolopoulos M. Acute visual loss and intraocular hemorrhages associated with endoscopic spinal surgery. *Clin Ophthalmol* 2008; 2:937-939.
11. Amirikia A, Scott IU, Murray TG, Halperin LS. Acute bilateral visual loss associated with retinal hemorrhages following epiduroscopy. *Arch Ophthalmol* 2000; 118:287-289.
12. Gill JB, Heavner JE. Visual impairment following epidural fluid injections and epiduroscopy: A review. *Pain Med* 2005; 6:367-374.
13. Lundblad M, Forestier J, Marhofer D, Eksborg S, Winberg P, Lonnqvist PA. Reduction of cerebral mean blood flow velocity and oxygenation after high-volume (1.5 ml kg(-)(1)) caudal block in infants. *Br J Anaesth* 2014; 113:688-694.
14. Ohle R, McIsaac SM, Woo MY, Perry JJ. Sonography of the optic nerve sheath diameter for detection of raised intracranial pressure compared to computed tomography: A systematic review and meta-analysis. *J Ultrasound Med* 2015; 34:1285-1294.
15. Dubost C, Le Gouez A, Jouffroy V, Roger-Christoph S, Benhamou D, Mercier FJ, Geeraerts T. Optic nerve sheath diameter used as ultrasonographic assessment of the incidence of raised intracranial pressure in preeclampsia: A pilot study. *Anesthesiology* 2012; 116:1066-1071.
16. Moretti R, Pizzi B. Ultrasonography of the optic nerve in neurocritically ill patients. *Acta Anaesthesiol Scand* 2011; 55:644-652.
17. Lee SU, Jeon JP, Lee H, Han JH, Seo M, Byoun HS, Cho WS, Ryu HG, Kang HS, Kim JE, Kim HC, Jang KS. Optic nerve sheath diameter threshold by ocular ultrasonography for detection of increased intracranial pressure in Korean adult patients with brain lesions. *Medicine (Baltimore)* 2016; 95:e5061.

18. Lee B, Koo BN, Choi YS, Kil HK, Kim MS, Lee JH. Effect of caudal block using different volumes of local anaesthetic on optic nerve sheath diameter in children: A prospective, randomized trial. *Br J Anaesth* 2017; 118:781-787.
19. Triffterer L, Machata AM, Latzke D, Willschke H, Rebhandl W, Kimberger O, Marhofer P. Ultrasound assessment of cranial spread during caudal blockade in children: Effect of the speed of injection of local anaesthetics. *Br J Anaesth* 2012; 108:670-674.
20. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension II. Patient study. *Pediatr Radiol* 1996; 26:706-710.
21. Padayachy LC, Padayachy V, Galal U, Pollock T, Fieggen AG. The relationship between transorbital ultrasound measurement of the optic nerve sheath diameter (ONSD) and invasively measured ICP in children. Part II: Age-related ONSD cut-off values and patency of the anterior fontanelle. *Childs Nerv Syst* 2016; 32:1779-1785.
22. Klarica M, Rados M, Erceg G, Petosic A, Jurjevic I, Oreskovic D. The influence of body position on cerebrospinal fluid pressure gradient and movement in cats with normal and impaired craniospinal communication. *PLoS One* 2014; 9:e95229.