의학석사 학위논문

뇌병변을 가진 한국 성인의 뇌압상승을 진단하기 위한 안구 초음파를 통한 시신경초 직경의 역치에 대한 연구

2016년 02월

서울대학교 대학원

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ABSTRACT

Optic Nerve Sheath Diameter Threshold by Ocular Ultrasonography for Detection of Increased Intracranial Pressure in Korean Adult Patients with Brain Lesions

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Objective: Optic nerve sheath diameter (ONSD) seen on ocular US has been associated with increased intracranial pressure (IICP). However, most studies have analyzed normal range of ONSD and its optimal cut-off point for IICP in Caucasian populations. Considering ONSD differences according to ethnicity, previous results may not accurately reflect the association between IICP and ONSD in Koreans. Therefore, we conducted this study to investigate normal range of ONSD and its optimal threshold for detecting IICP in Korean patients.

Methods: This prospective multi-center study was performed for patients with suspected IICP. ONSD was measured 3 mm behind the globe using a 13-MHz US probe. IICP was defined as significant brain edema, midline shift, compression of ventricle or basal cistern, effacement of sulci, insufficient gray/white differentiation, and transfalcine herniation by radiologic tests. The results of the ONSD are described as the median (25th -75th percentile). The differences of ONSD according to disease entity were analyzed. A receiver operator characteristic (ROC) curve was generated to determine the optimal cut-off point for identifying IICP.

Results: A total of 134 patients were enrolled. The patients were divided into 3 groups as follows: patients with IICP, n=81 (60.5%); patients without IICP, n=27 (20.1%), and control group, n=26 (19.4%). ONSD in patients with IICP (5.9mm (5.8–6.2)) is significantly higher than those without IICP (5.2mm (4.8–5.4)) ($p < .01$) and normal control group (4.9mm (4.6–5.2)) ($p < .001$). Between patients without IICP and normal control group, the difference of ONSD did not reach statistical significance ($p = .31$). ONSD >5.5mm yielded a sensitivity of 98.77% (95% CI: 93.3% to 100%) and a specificity of 85.19% (95% CI: 66.3% to 95.8%).

Conclusion: The optimal cut-off point of ONSD for identifying IICP was 5.5mm. ONSD seen on ocular US can be a feasible method for detection and serial monitoring of ICP in Korean adult patients.

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Key words: increased intracranial pressure, optic nerve sheath diameter, optimal threshold, ultrasonography

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INTRODUCTION

Early detection of increased intracranial pressure (IICP) and prompt management is essential for patients with intracranial lesions. ICP can be accurately estimated using invasive monitoring probes, such as an intra-ventricular or intra-parenchymal catheter. However, clinical concerns include procedure-related complications, limited technical availability due to performance by only neurosurgeon, and unsuitable patients who have coagulopathy or vital sign instability (1).

Ultrasonography (US) has become widely used in the emergency department (ED) or intensive care unit (ICU) settings due to its non-invasive nature, real-time tracking at the bedside, and capability of repetitive examination without radiation exposure. Optic nerve sheath diameter (ONSD) seen on ocular US has been associated with increased ICP (1, 2, 3). However, most studies have analyzed normal range of ONSD and its optimal cut-off point for IICP in Caucasian populations (4). Considering ONSD differences according to ethnicity (5), results obtained from Caucasian may not accurately reflect the association between IICP and ONSD in Koreans. Therefore, we conducted this study to investigate normal range of ONSD and its optimal threshold for detecting IICP in Korean patients.

METHODS

This prospective multi-center study was performed in three institutions. Patients who visited the ED or ICU for suspected IICP from September 2013 to August 2015 were enrolled. Inclusion criteria were age>18 years; clinical signs of IICP that included headache, nausea, vomiting, or altered mentality; and radiologic tests like brain computed tomography (CT) or magnetic resonance imaging (MRI), and US within a 1-hour interval. In case of the patients who required mechanical ventilator and sedation, measurement of ONSD was performed before sedation. Patients who were younger than 18 years of age, or who had an orbital trauma or mass, or cavernous sinus arachnoid cysts were excluded (2).

Radiologic tests scans such as brain CT and MRI were interpreted independently by two neuroradiologists blinded to clinical information. IICP was defined as significant brain edema, midline shift, compression of ventricle or basal cistern, effacement of sulci, insufficient gray/white differentiation, and transfalcine herniation (2, 6, 7). Ocular US was performed using a ProSound Alpha 6 13-MHz US probe (Hitachi Medical Corp., Tokyo, Japan) according to a previously reported method (8). ONSD assessments were independently done by two trained investigators (JPJ and HNL). For each subject, the investigator performed two measurements on each eye. The resulting eight measurements performed by two investigators were then averaged to yield a mean ONSD to minimize intraobserver and interobserver variability. This study was approved by the Institutional Review Boards at the participating institutions (H-1309-004-515).

Statistical analyses

Categorical variables are presented as numbers and percentages. Continuous data are shown as the mean ± standard deviation (SD). The intraobserver and interobserver agreements were calculated using kappa statistics. Since the two measurements on each eye, the right and the left, were averaged to obtain a mean ONSD, paired t-test and intraclass correlation coefficient (ICC) analysis were conducted to determine the agreement between the measurements on each eye. An ICC > 0.80 showed concordance among the measurements. The results of the ONSD are described as the median (25th-75th percentile). A comparison of ONSD was performed by Kruskal-Wallis test. Mann-Whitney U test with Bonferroni correction was conducted for all possible pair-wise comparisons and repeated measures analysis of variance (ANOVA) was used to compare the follow-up data of ONSD according to the clinical courses after operation. A receiver operator characteristic (ROC) curve was generated to determine the optimal cut-off point for identifying IICP. Sensitivity, specificity, positive predictive value and negative predictive value were assessed. Statistics were performed using SPSS V.19 (SPSS, Chicago, IL, USA) and MedCalc (www.medcalc.org).

RESULTS

A total of 134 patients were enrolled. The 134 individuals comprised 81 patients with IICP (60.5%), 27 patients without IICP (20.1%), and 26 unaffected control group (19.4%). Detailed information on the clinical characteristics of the patients is described in Table 1. The proportion of male and the mean age of the enrolled patients according to groups were as follows: patients with IICP, 52 males (64.2%), 64.4 ± 17.6 years; patients without IICP, 20 males (74.1%), 65.2 ± 17.8 years; control group, 9 males (34.6%), 60.8 ± 12.5 years. In patients with IICP, 42 (51.9%) presented with headache and vertigo, and 21 (25.9%) with altered mentality. In patients without IICP, 20 patients presented with headache or vertigo, and 7 (25.9%) displayed neurologic deficits including motor weakness, transient ischemic attack (TIA) and seizure. Hemorrhagic cases such as epidural hematoma, subdural hematoma, or intracerebral hemorrhage

(ICH), were found in 70 (86.4%) patients with IICP and 4 (14.8%) without IICP. For the control group, 20 (76.9%) cases of spinal stenosis or herniated nucleus pulposus and 6 (23.1%) of unruptured aneurysms were noted.

TABLE 1. Baseline characteristics of the study population (n=134)

Variables	IICP (n=81)	Without IICP (n=27)	Control group (n=26)
Age (years)	64.4 ± 17.6	65.2 ± 17.8	60.8 ± 12.5
Male (%)	52 (64.2%)	20 (74.1%)	9 (34.6%)
HTN (%)	17 (21.0%)	6 (22.2%)	14 (53.8%)
DM (%)	10 (12.3%)	2 (7.4%)	5 (19.2%)
Dyslipidemia (%)	7 (8.6%)	1 (3.7%)	4 (15.4%)
Presentation			
Headache/ Vertigo	42 (51.9%)	20 (74.1%)	0 (0%)
Motor weakness/ TIA/ Seizure	18 (22.2%)	7 (25.9%)	0 (0%)
Altered mentality	21 (25.9%)	0 (0%)	0 (0%)
Back pain	0 (0%)	0 (0%)	20 (76.9%)
Incidental finding	0 (0%)	0 (0%)	6 (23.1%)
Diagnosis			
EDH/ SDH/ ICH	70 (86.4%)	4 (14.8%)	0 (0%)
Cerebral infarction	6 (7.4%)	3 (11.1%)	0 (0%)
Tumor/ Hydrocephalus	5 (6.2%)	1 (3.7%)	0 (0%)
Cerebral concussion	0 (0%)	19 (70.4%)	0 (0%)
Unruptured aneurysm	0 (0%)	0 (0%)	6 (23.1%)
Spinal stenosis/ HNP	0 (0%)	0 (0%)	20 (76.9%)

Continuous data is presented as mean ± SD.

IICP = increased intracranial pressure, HTN = hypertension, DM = diabetes mellitus, TIA = transient ischemic attack, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage, EDH = epidural hemorrhage, SDH = subdural hemorrhage, HNP = herniated nucleus pulposus

The intra- and inter-observer agreements were excellent for estimating ONSD (κ= 0.91 and 0.88). In addition, the difference in ONSD between the right eye and the left eye was not significant ($p = .16$) and the concordance among the measurements on each eye was very high (ICC = 0.805, $p < .001$), thus showing an agreement between these measurements regardless of the location of the intracranial lesion. ONSD in patients with IICP (5.9mm, range 5.8–6.2mm) was significantly higher than those without IICP (5.2mm, range 4.8–5.4mm) ($p< .001$) and the normal control group (4.9mm, range 4.6–5.2mm) ($p< .001$). The serial measurements of ONSD (pre-operation, 1 h post-operation, and 2 weeks post-operation) were conducted in 16 of 81 patients in the IICP group (Table 2). The ONSD decreased significantly after 1 hour and 2 weeks post-operation ($F = 54.93$, $p < .001$; Figure 1). The difference of ONSD between patients without IICP and the normal control group did not reach statistical significance ($p= .31$). The area under ROC curve is 0.975. ONSD >5.5mm yielded a sensitivity of 98.77% (95% CI: 93.3% to 100%) and a specificity of 85.19% (95% CI: 66.3% to 95.8%) (Figure 2).

Illustrative case (patient 13 in Table 2)

A 57-year-old man presented with a sudden onset of left hemiparesis. Diffusion MRI revealed acute cerebral infarction in the territory of the middle cerebral artery on the right side with ONSD of 5.2mm (Figures 3A and B). Two days later, the patient became drowsy and the right-sided hemiplegic despite anti-platelet medication and intravenous mannitolization. Brain CT scans displayed aggravation of cerebral edema. Follow-up of ocular US showed increased ONSD of 6.3mm (Figures 3C and D). Emergent decompressive craniectomy and wide duroplasty were performed to relieve the IICP. Post-operative CT scans demonstrated a decrease in midline shift with ONSD of 5.8mm (Figures 3E and F). The patient underwent further hypothermic therapy after surgical decompression. CT scans taken after 2 weeks after operation showed a substantial improvement in the extent of midline shift with ONSD of 5.4mm (Figures 3G and H).

TABLE 2. Follow-up data of optic nerve sheath diameter according to the clinical courses

Patient	Age	Sex	Diagnosis	Operation	Mean ONSD (mm)		
					Pre-operation	1 hour after operation	2 weeks after operation
Patient 1	57	Male	Chronic SDH	Burr hole trephination	5.3	5.2	5.0
Patient 2	34	Male	EDH	EDH removal	6.0	5.3	4.9
Patient 3	66	Male	Chronic SDH	Burr hole trephination	5.7	5.3	5.2
Patient 4	65	Male	IVH	EVD	5.7	5.7	5.3
Patient 5	21	Male	Acute SDH	Craniectomy	6.8	6.4	5.5
Patient 6	73	Male	ICH	ICH removal	6.3	5.9	5.2
Patient 7	70	Male	Non-lesional SAH	EVD	6.4	6.4	5.9
Patient 8	72	Female	Hydrocephalus	EVD	6.3	6.3	5.5
Patient 9	75	Female	Acute SDH	Craniectomy	6.8	6.6	4.8
Patient 10	73	Male	ICH	Craniectomy	5.9	5.3	4.6

Patient 11	37	Male	ICH	Craniectomy	6.5	5.9	5.4
Patient 12	76	Female	Acute SDH	Craniectomy	6.2	5.7	4.7
Patient 13	57	Male	Acute infarction	Craniectomy	6.3	5.8	5.4
Patient 14	76	Female	Acute infarction	Craniectomy	5.6	5.4	4.5
Patient 15	53	Female	EDH	EDH removal	5.8	5.3	4.7
Patient 16	68	Female	ICH	Craniectomy	6.0	5.6	5.4

SDH = subdural hematoma, EDH = epidural hematoma, IVH = intraventricular hemorrhage, EVD = extraventricular drainage, ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage

FIGURE 1. Repeated measures ANOVA was used to compare ONSD after operation. The ONSD decreased significantly after 1 hour and 2 weeks post-operation ($F = 54.93$, $p < .001$)

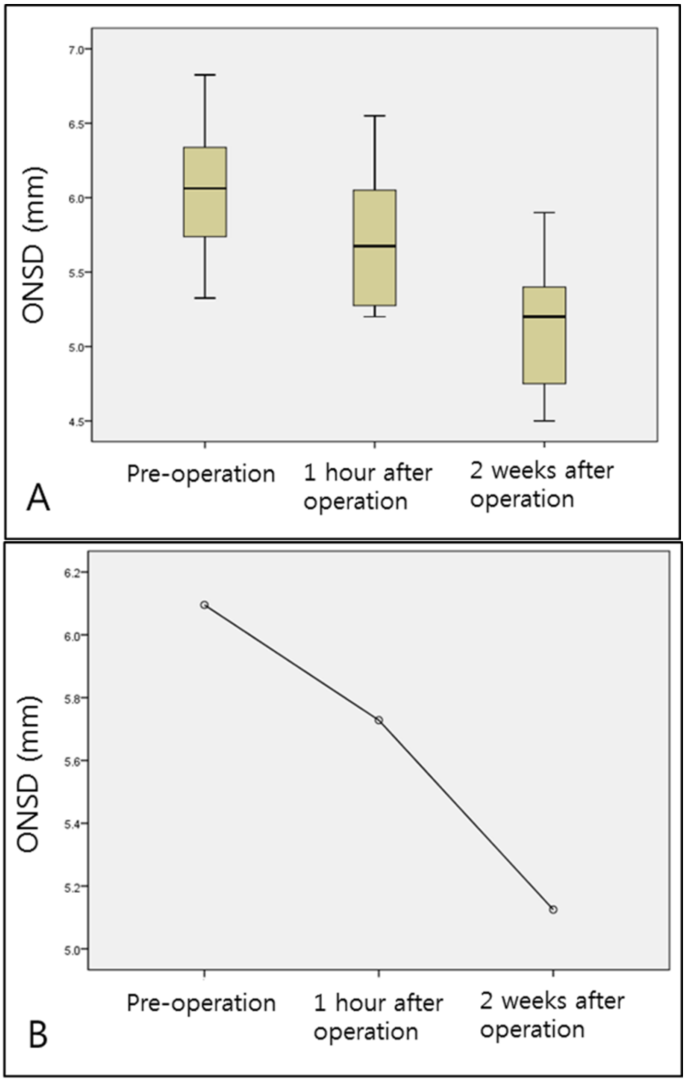
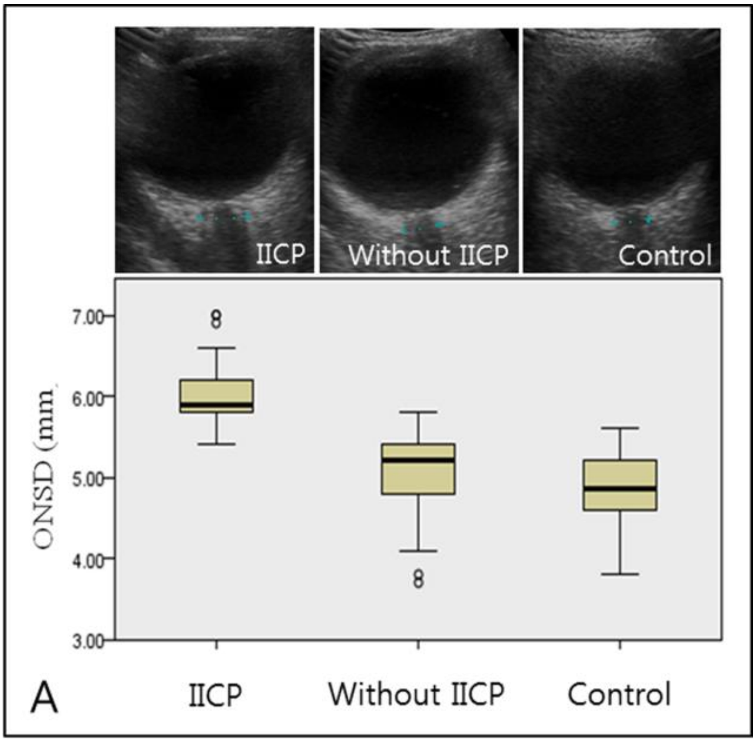


FIGURE 2. A, Optic nerve sheath diameter (ONSD) in patients with increased intracranial pressure (IICP), without IICP and normal control group. The bar represents the median value and 25th -75th percentile. ONSD in patients with IICP (5.9mm, range 5.8–6.2mm) is significantly higher than those without IICP (5.2mm, range 4.8–5.4mm) ($p<0.001$) and normal control group (4.9mm, range 4.6–5.2mm) ($p<0.001$). **B,** The area under the receiver operator characteristic curve is 0.975. ONSD >5.5mm yielded a sensitivity of 98.77% (95% CI: 93.3% to 100%) and a specificity of 85.19% (95% CI: 66.3% to 95.8%).


IICP
Without IICP
Control
7.00
6.00
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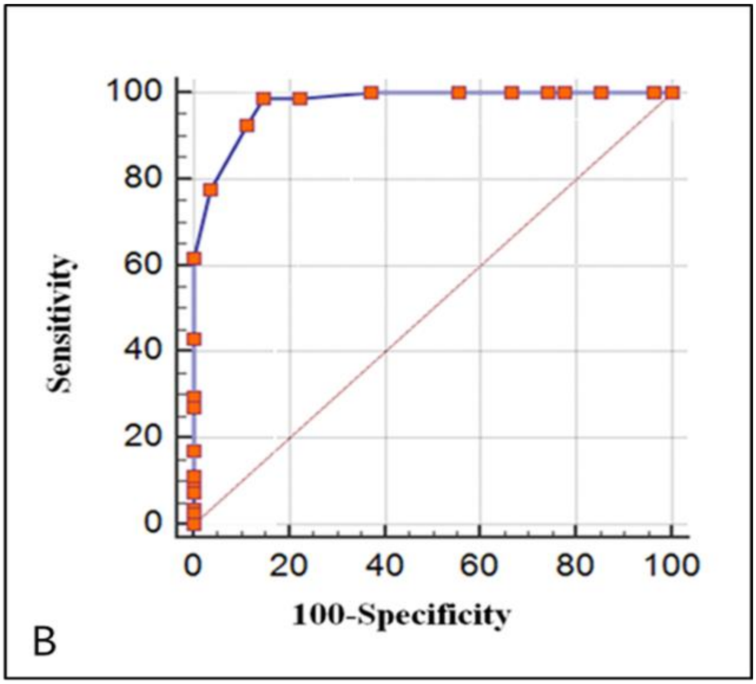
ONSD (mm
A
IICP
Without IICP
Control


100
80
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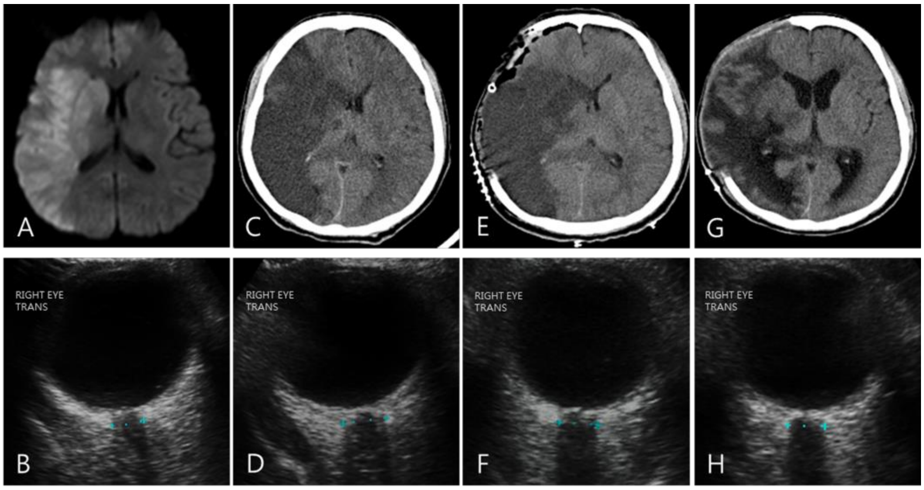
Sensitivity
0
20
40
60
80
100
100-Specificity
B

FIGURE 3. A and B, A 57-year-old man presented with left hemiparesis because of acute middle cerebral infarction on the right side seen on diffusion magnetic resonance imaging. Optic nerve sheath diameter (ONSD) on the right side was measured at 5.2 mm. **C and D,** The level of consciousness decreased to drowsy on the 2nd day with aggravation of cerebral edema seen on brain computed tomography (CT). ONSD on the right side increased to 6.3mm. **E and F,** Decompressive craniectomy decreased midline shift with ONSD of 5.8mm. **G and H**, CT scans taken after 2weeks after operation showed a substantial improvement in the extent of midline shift with ONSD of 5.4mm.



DISCUSSION

The present study showed that ONSD in patients with IICP had a mean size of 5.9mm (range 5.8–6.2mm), which was significantly higher than patients without IICP (5.2mm, range 4.8–5.4mm) or normal controls (4.9mm, range 4.6–5.2mm). The optimal ONSD cut-off point for identifying increased ICP was 5.5 mm which had a sensitivity of 98.77% and a specificity of 85.19%.

Invasive ICP monitoring method has been a gold standard for the evaluation of IICP. However, limitations include potential complications, such as hemorrhage or infection, and limited technical availability in institutions without a neurosurgeon (4). Accordingly, feasibility of non-invasive methods like transcranial Doppler, tympanic membrane displacement, US, CT and MRI have been investigated as the invasive ICP monitoring with a reference value. ONSD that defines the dural sheath diameter surrounding the optic nerve can be measured due to its cerebrospinal fluid (CSF) connection to the intracranial subarachnoid space. Liu et al. (9) reported that subarachnoid space pressure of ONSD showed a liner correlation with ICP change. Moretti et al. (10) showed that optimal ONSD cut-off point to define increased ICP (>20mmHg) was 5.2mm with a 93.1% sensitivity and 73.9% specificity in 63 patients with spontaneous ICH. Geeraerts et al. (11) reported that adults with high ICP, defined as ICP >20mmHg for more than 30 min in the first 48 hours after trauma, had a higher ONSD value (6.3 ± 0.6 mm) than normal ICP (5.1 ± 0.7 mm) or control group (4.9 ± 0.3). Beyond the comparative tests between ONSD by ocular US and invasive ICP monitoring, ONSD correlated well with IICP seen on CT findings. Tayal et al. (2) suggested that ONSD can be an alternative to CT for detecting IICP patients who visit the ED. In their study, ONSD over 5mm had 100% sensitivity and 63% specificity in detecting increased ICP. Girisgin et al. (1) also reported that IICP patients had higher mean ONSD than control group (6.4 mm in the IICP group vs. 4.6 mm in the control group). Nevertheless, ethnic differences could be a confounding factor to set the optimal ONSD to define IICP. Ozgen et al. (12) reported a mean ONSD of 4.4 mm as seen on CT in 100 healthy Turkish volunteers. Lee et al. (13) showed a mean ONSD of 4.1 mm ranging from 2.9 to 5.3 mm in Korean population using CT scan. Ko et al. (14) also reported that the mean ONSD on MRI was 4.37mm in patients with normal ICP. In their study, ONSD was not significantly different according to age, sex and underlying diseases. Maude et al. (15) reported a relative narrow range of ONSD (4.24–4.83mm) in healthy volunteer in Bangladesh than that of United Kingdom (2.5–4.1 mm) (16) or Greece (2.2–4.9 mm) (17). Our study Accordingly, we think that optimal cut-off point of ONSD for IICP could be better defined differently according to ethnicity. Mean normal ONSD (4.9 mm, range 4.6–5.2 mm) in the Korean population tended to be higher and the range was relatively narrower compared with previous reports for a single ethnicity. However, the ranges of the mean normal ONSD reported in other previous studies were wide (4.4–5.0 mm) (2, 3, 8, 10, 11); thus, the results of our study could be acceptable.

Recently, Wang et al. (4) assessed the mean ONSD and optimal value for defining IICP in a Chinese population. The mean ONSD in normal individuals was 3.55 ± 0.38mm. The optimal cut-off point for IICP was 4.1 mm, which yielded a 95% sensitivity and 92% specificity. However, defining IICP based on lumbar puncture and disease severity in the study was a concern to the interpretation of the results. CSF pressure assessed by lumbar puncture tends to exhibit higher level than actual ICP in children (18). Lenfeldt et al. (19) showed that lumbar puncture opening pressure was consistently higher than ICP in adult patients with normal pressure hydrocephalus. Warden et al. (20) also reported that CSF pressure by lumbar puncture overestimated the ICP within a range of 300 mm H_2O. Regarding the disease severity, the authors only included patients who were managed conservatively in the general ward. Accordingly, the reported optimal cut-off of 4.1 mm in the Chinese subjects could not accurately reflect IICP patients who may require invasive treatments in ED or ICU. The aim of the present study was to investigate optimal cut-off points to indicate IICP in Korean population. The optimal ONSD cut-off point was 5.5 mm, which was higher than that of the Chinese population based on CSF pressure by lumbar puncture (4).

Serial check-up of intracranial lesions can be challenging for ICU patients, in particular unstable patients who have multiple drains or fluid lines. Although no data concerning adverse events during transfer to radiologic tests are available in Korea, an incidence rate up to 71% has been reported (21, 22). Moreover, transfer of patients is usually done with an intern doctor or a physician assistant who may not yet have enough experience in dealing with unexpected complications during transfer (22). In such circumstances, ONSD by ocular US can provide crucial information about the ICP at the patient' bedside within 5 minutes. Accordingly, the need to conduct brain CT scans could be decreased while avoiding unnecessary complications during transfer. Furthermore, we performed serial measurements of ONSD for 16 of 81 patients in the IICP group who underwent surgery and demonstrated the correlation between ONSD and radiologic imaging finding. Therefore, US measurement of ONSD can be useful for serial check-up of intracranial lesions.

There are some limitations in this study. Intra-or inter-observer variation are concerns. Previous studies (16, 23) showed ±0.1-0.2 mm of intra-observer and ±0.2-0.3 mm of inter-observer variation. Ballantyne et al. (16) reported that intra-and inter-observer variation reduced after the first 17 examinations. In this study, we also had excellent agreements for estimating ONSD (κ= 0.91 of intra- and 0.88 of inter-observer agreements, respectively). Accordingly, we think that ONSD measured by ocular US can be an easily handled method to detect IICP with low intra- and inter-observer variation, although standardization efforts are necessary. Second, direct comparison between ONSD and invasive ICP monitoring was not performed. We do not advocate that ONSD seems to be accurate enough as an alternative to invasive ICP monitoring or radiologic tests, such as CT or MRI in all circumstances. However, we think that ONSD could be used as a screening method for the detection or serial monitoring of IICP in ED or ICU. Nevertheless, further study on the correlation between ONSD and invasive ICP monitoring is required in Koreans. In addition, the small sample size of the normal control group which included patients diagnosed with unruptured aneurysm could be the reason why the mean ONSD of normal controls in this study was higher than in other ethnicities.

CONCLUSION

The optimal cut-off point of ONSD for identifying IICP was 5.5mm. ONSD seen on ocular US can be a feasible method for detection and serial monitoring of ICP.

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국문 초록

뇌병변을 가진 한국 성인의 뇌압상승을 진단하기 위한 안구 초음파로 측정한 시신경초 직경의 역치에 대한 연구

목적: 안구 초음파를 이용하여 측정한 시신경초 직경은 뇌압상승과 연관되어 있다고 이미 알려져 있다. 그러나 뇌압상승을 나타내는 시신경초 직경의 역치와 정상 신신경초 직경의 범위에 관한 대부분의 연구는 서양인을 대상으로만 이루어 졌다. 시신경초 직경의 인종간의

차이를 고려하였을 때, 기존의 연구들은 한국인들의 뇌압상승과 시신경초 직경의 연관성에 정확하게 반영하기에는 무리가 있다. 따라서 이 연구는 한국인들의 정상 시신경초 직경의 범위와 뇌압상승을 나타내는 시신경초 직경의 역치를 알아보기 위해 진행되었다.

대상과 방법: 이 연구는 뇌압상승이 의심되는 환자들을 대상으로 다기관 전향적 연구로 진행되었다. 13-MHz 초음파 탐침을 이용하여 안구로부터 3mm 떨어진 지점에서 시신경초 직경을 측정한다. 영상학적 검사에서 심한 뇌부종, 중심선 밀림, 뇌실 압박, 대뇌홈 소멸, 회백질/백질 구분의 소멸, 경겸상막 뇌탈출증이 관찰되면 뇌압상승이 있는 것으로 정의 내렸다. 시신경초 직경의 결과는 중앙값으로 나타내었고, 질환군에 따라 시신경초의 직경의 차이를 분석하였다. 뇌압상승을 나타내는 시신경초 역치를 알기 위해 수신자 동작특성 곡선을 이용하였다.

결과: 총 134명의 환자가 이 연구에 동록이 되었다. 환자들은 뇌압상승집단(n=81, 60.5%), 비뇌압상승집단(n=27, 20.1%), 정상 대조군 집단(n=26, 19.4%) 의 세 집단으로 분류되었다. 뇌압상승집단(5.9mm (5.8-6.2))은 비뇌압상승집단(5.2mm (4.8-5.4)) (p< .01)과 정상 대조군 집단(4.9mm (4.6–5.2)) (p< .001)에 비해서 시신경초 직경이 유의하게 높았다. 그에 비해 비뇌압상승집단과 정상 대조군 집단 간에는 유의한 차이가 없었다 (p= .31). 뇌압상승을 나타내는 시신경초 직경의 역치는 5.5mm 이고, 민감도는 98.77%, 특이도는 85.19% 로 산출되었다.

결론: 뇌압상승을 나타내는 시신경초 직경의 역치는 5.5mm 이였다. 안구초음파를 이용한 시신경초 직경의 측정은 한국성인환자들에 대해 뇌압상승의 발견과 순차적인 뇌압모니터를 위한 유용한 방법이 될 수

있을 것이다.

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주요어: 뇌압상승, 시신경초 직경, 역치, 초음파

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