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Can Serial Internal Optic Nerve Sheath Diameters Measured By Ultrasonography Predict The Prognosis Of Medical Intensive Care Patients?

Ultrasonografı Ile Yapılan İnternal Optık Sınır Kılıfı Çapının Serı Ölçümlerı Medıkal Yoğun Bakım Hastalarının Prognozunu Öngörebılır Mı?

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Özet

Amaç: Optik sinir kılıfı (OSK) subaraknoid boşluk, piamater tabakası ve optik sinir lif tabakasından oluşmaktadır. Subaraknoid boşluk olmaksızın OSK çapı (OSKÇ) internal OKS (iOSKÇ) olarak bilinmektedir. iOSKÇ alanı içerisinde vasküler ağ ile birlikte çok sayıda astrositler bulunmaktadır. Astrositlerin sistemik enfeksiyon, enflamasyon, pro-enflamatuvar sitokinler, bazı metabolik hastalıklar ve oksidatif stres ile şiştiği bilinmektedir. Aynı zamanda bu vasküler ağ Yoğun Bakım ünitesindeki (YBÜ) çoğu patoloji nedeniyle değişiklik gösterebilir. Bu çalışmada ultrasonografi ile ölçülen seri iOSKÇ değerleri ile yoğun bakımda yatmakta olan ve intrakraniyal patolojisi olmayan hastalardaki mortalite arasında ilişki araştırılmıştır.

Materyal ve metod:

Sağ ve sol göz için ortalama iOSKÇ değerleri sırasıyla (iOSKÇsağ) ve (iOSKÇsol) olarak ölçülmüştür. OiOSKÇ (iOSKÇsağ ve iOSKÇsol değerlerinin ortalamaları) ve FiOSKÇ (YBÜ 'de kabul anında ve sonlanım anında ölçülen OiOSKÇ değerlerinin farkı) hesaplandı.

Sonuçlar:

İnkraniyal patolojisi olmayan 35 hasta çalışmaya dahil edildi. Hayatta kalan ve kalmayan hastalar arasında FiOSKÇ ölçümleri arasında istatistiksel olarak anlamlı farklılık tespit edilmiştir (sırasıyla -0.35 [(-0.85)-(-0.10)], 0.60 [(0.21)-(1.00)] mm, p=0.0001). SOFA, APACHE II skoru ve FiOSKÇ ölçümleri arasında yapılan çok değişkenli analize göre FiOSKÇ mortalite açısından bağımsız risk faktörü olarak tespit edilmiştir (p=0.033, OR=10.66 %95 CI [1.21-93.92]). 0.25 mm'den büyük bir FiOSKÇ değerinin %75 sensitivite ve %95 spesifite ile mortalite açısından bir gösterge olduğu tespit edilmiştir. FiOSKÇ ölçümleri ile SOFA, total sıvı dengesi, sepsis durumu, serum albumin düzeyi ve GKS arasında iyi korelasyon tespit edilmiştir.

Sonuç:

Ultrasonografi ile yapılan seri iOSKÇ ölçümleri akut veya kronik intrakraniyal patolojisi olmayan hastalarda mortalite belirteci olarak kullanılabilir.

Anahtar kelimeler:

Optik sinir kılıf çapı, Ultrasonografi, Prognoz, Medikal YBÜ

Abstract

Aim: Optic nerve sheath (ONS) contains subarachnoid space, pia mater layer, and optic nerve fiber layer. ONS diamater (ONSD) without subarachnoid space is known as internal ONSD (iONSD). There are too many astrocytes and vascular network in iONSD area. Astrocytes are known to swell with systemic infection, inflammation, pro-inflammatory cytokines, some metabolic disorders, and oxidative stress. Also, this vascular network can vary by many ICU pathologies. This study investigated the relationship between serial iONSD measured with USG and the prognosis of critically ill patients who had no intracranial pathologies.

Material and method:

The mean iONSD values for the right eye (RiONSD) and left eye (LiONSD) were measured. MiONSD (the mean of RiONSD and LiONSD) and DiONSD (the difference of final and admission MiONSD of ICU stay) were calculated.

Results:

35 ICU patients without intracranial pathologies were included. There was a significant difference between survivors and non-survivors for DiONSD (-0.35 [(-0.85)-(-0.10)], 0.60 [(0.21)-(1.00)] mm respectively, p=0.0001). The multivariate analysis performed between DiONSD, SOFA, and APACHE II score (p=0.033, OR=10.66 %95 CI [1.21-93.92]) indicated that DiONSD was an independent risk factor for mortality. DiONSD values greater than + 0.25 mm was determined to be a predictor of mortality with 75% sensitivity and 95% specificity (LR=14.25, AUC=0.905, p=0.0001). There was a good corelation between DiONSD values and SOFA score, total fluid balance, sepsis, serum albumin level, and GCS level.

Conclusion:

iONSD measurement with USG can be used to determine the prognosis of ICU patients who have no intracranial acute or chronic pathologies.

Key words:

Optic Nerve Sheath Diameter, Ultrasonography, Prognosis, Medical ICU

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Introduction

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is still the most commonly used scoring system for prediction of mortality in ICU.[1] However, APACHE II score give a single predicted mortality value and do not dynamically reflect the predicted mortality according to the daily physiological data of the patients in further days of ICU stay. At this point, the Sequential Organ Failure Assessment (SOFA) score can be more useful because it can be calculated on a daily basis.1 SOFA score can estimate the mortality of ICU patients especially if there is an increase in SOFA score in the first 72 hours or it can be use for long term ICU mortality.[2-3] However, the daily calculating of SOFA score after the first 5 days of ICU admission was shown to not contribute to predicting mortality of ICU patients.[4] Also, there is no single and simple bedside parameter that can predict mortality on a daily basis in ICU patients.

The measurement of optic nerve sheath (ONS) diameter (ONSD) with Ultrasonography (USG) has become popular because this non-invasive method is inexpensive, repeatable, and applied easily at bedside.[5] When ONS is examined with a high-resolution USG device, ONS is known to consist of hypoechoic optic nerve fiber layer (ONFL), hyperechoic pia mater layer (PML), hypoechoic subarachnoid space, and hyperechoic dura mater layer from inside to outside.[6] Based on this anatomical structure, ONSD can be measured internally (iONSD) or externally (eONSD).[7] This ultrasonographic differentiation has recently begun to be used in the measurement of ONSD. The eONSD measurement is useful for non-invasive monitoring of traumatic or non-traumatic increased intracranial pressure (ICP) because eONSD consists of subarachnoid space, and subarachnoid space expands in increased ICP.[5-7] But, iONSD area consists of only ONFL and PML. ONFL contains too many astrocytes.[8] This issue is important because astrocytes are well-known to swell with the presence of factors such as systemic infection, inflammation, pro-inflammatory cytokines, some metabolic disorders, and oxidative stress.[9-11] Also, ONFL layer and pial vascular plexus in PML consist of highly distributed arterioles and venules.[12] As a result, the conditions that produce intracranial vascular dilatation may cause enlargement in the ONFL layer and PML. Therefore, we believe that the measurement of iONSD with USG is associated with some pathological conditions that are frequently seen in medical ICU patients (MICUP) except for increased ICP condition. This issue has not been investigated before. Therefore, we planned this prospective study to investigate the prognostic significance of serial iONSD measurements and to compare the ability of mortality prediction of iONSD measurement with APACHE II and SOFA scores in MICUP with no acute or chronic intracranial pathologies.

Material and Methods

This study was approwed by Gazi Universitesi Klinik Araştırmalar Etik Kurulu (decision number and date: 25.12.2017 / 615)

Patient population:

Patients who had no acute or chronic intracranial pathologies, were older than 18 years of age, and hospitalized in the Medical Intensive Care Unit of Gazi University Medical Faculty Hospital between August 01, 2017 and February 01, 2018 were included in this prospective observational study. Patients who were admitted to ICU for the first time were included in this study. Patients who had acute or chronic intracranial pathologies during ICU admission were excluded from the study. Patients with new-onset impaired consciousness during ICU stay were evaluated neurologically in detail, and cranial imagings (Cranial CT or MRI) were performed when necessary. If an intracranial pathology was found in the imaging (for example intracranial bleeding, ischemic stroke, etc.), the patient was excluded from the study. Patients who stayed less than 48 hours in the ICU were excluded from the study. The approval of the local ethic committee was taken with the date of December 25, 2017 and number of 615. Written informed consent was obtained from the patients and/or their relatives. This study was performed in accordance with the Declaration of Helsinki Principles.

Patient clinical data:

Demographic data, ICU admission diagnosis, APACHE II, and SOFA scores of the patients were recorded. Also, GCS (Glasgow coma scale), vital signs, total fluid balances, routine laboratory tests, invasive or noninvasive mechanical ventilation requirements, PEEP (Expiratory end-positive pressure) levels, sedative and vasopressor drug levels, hemodialysis and continuous renal replacement therapies were recorded at the same time with each iONSD measurements in the patients.

USG device:

In this study, a standard USG device (S7 model, GE Healtcare, General Electric Company, USA) was used. The 11 MHz linear probe of this USG device was used for iONSD measurement.

Measurement method:

iONSD measurements via USG device were performed by a single physician. This physician had sufficient theoretical and practical knowledge about using USG devices and ONSD measurements. The linear probe was used for iONSD measurement and the depth was set to 4 cm. iONSD measurement was taken at the transverse axis for each eye of the patients and repeated three times. Attention was given to distinguish the ONFL, PML, subarachnoid space, and the outer and inner edges of subarachnoid space. Measurements were taken as the distance between the points of the conjunction of subarachnoid space and PML at 3-mm distance from the vitreoretinal junction, where the iONSD was the thickest. (Figure 1).

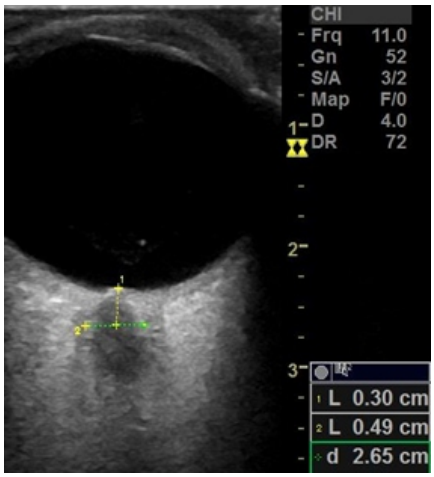

Figure 1: Internal Optic Nerve Sheath Diameter measurements at transverse section

At the same time, the measurements were taken as perpendicular to the direction of the optic nerve axis. The mean iONSD measurement values for the right eye (RiONSD) and the mean iONSD measurement values for the left eye (LiONSD) were calculated after three repeated iONSD measurements for each eye. The average of these RiONSD and LiONSD values was also calculated and named as MiONSD (Mean of RiONSD and LiONSD). The admission MiONSD measurements were calculated within the first 24 hours of ICU stay. The final MiONSD measurements of the patients were calculated within the last 24 hours before discharge or death (For this reason, MiONSD measurements were performed every day in patients whose general condition was getting worse). Finally, after discharge from ICU or after death, the difference between final and admission MiONSD were also calculated and named as DiONSD (DiONSD was calculated by subtracting admission MiONSD from final MiONSD). There was at least 24 hours between the admission and final measurements of MiONSD.

Statistical Analysis:

Data were statistically analyzed using IBM SPSS statistical software version 22. P values lower than 0.05 were considered as statistically significant. Continuous variables were described as median and interquartile ranges. Categorical variables were presented as frequencies and percentages. The Mann-Whitney U test was used to compare the continuous variables between the two independent groups and the Wilcoxon sign test was used to compare the continuous variables between the two dependent groups. Chi-square test was used to compare categorical variables. The Spearmen correlation test was used to determine the correlation between the variables. The logistic regression analysis was performed to determine the variables which were independently related to mortality. After the determination of independent risk factors for mortality, ROC (Receiver Operating Characteristic) curve analyses were performed.

Results

35 patients were included in this study. Demographic data of the patients and diagnoses during ICU admission are presented in Table 1.

Table 1: Demographic and admission characteristics of the study patients

	N=35
Age (Years)*	71 [53-80]
Gender, F/M (n)	16 / 19
Invasive mechanical ventilation, n (%)	16 (45.7)
Non-invasive mechanical ventilation, n (%)	5 (14.3)
Mortality, n (%)	16 (45.7)
Admission diagnosis	
Severe Infection, n (%)	29 (82.9)
Pulmonary, n (%)	25 (71.4)
Sepsis/septic shock, n (%)	24 (68.6)
Renal, n (%)	13 (37.1)
Cardiovasculary, n (%)	8 (22.9)
Solid Tumor, n (%)	7 (20)
Hepatobiliary, n (%)	5 (13.9)

*Data are presented as median and [interquartile range]; N, n: number; F: female; M: male;

Patients were divided into two groups as survivors and non-survivors. Some clinical data which had a significant difference according to mortality are presented in Table 2.

Table 2: Some clinical data which has statistically significant differences according to mortality in study group

Parameters	All patients (n=35)	Survivors (n=19)	Non-Survivors (n=16)	P values
At the admission of ICU				
APACHE II score †	25 [18-29]	20 [15-24)	29.5 [25.75-34.5]	***0.0001**
SOFA Score †	5 [4-9]	5 [3-6]	8 [4.25-14.75]	***0.006**
GCS Level †	14 [8-15]	15 [13-15]	10 [4.25-11.75]	***0.01**
Serum BUN (mg/dl) †	36 [25-57]	25 [13-36]	52.5 [38.25-83.5]	***0.001**
Serum Creatinin (mg/dl) †	1.15 [0.7-2.2]	0.74 [0.6-1.52]	1.64 [0.84-3.58]	***0.009**
Serum Albumin (mg/dl) †	2.5 [2.1-3.1]	2.6 [2.32-3.27]	2.15 [1.92-2.93]	***0.016**
Total Fluid Balance (ml) †	1020 [(-300) - (2850)]	765 [(-460) - (1020)]	2994.5 [(443.7) – (7278)]	***0.034**
Sepsis, n(%)	24 (66.7)	10 (52.6)	14 (87.5)	***0.027**
Hepatobiliary diseases, n(%)	5 (13.9)	0 (0)	5 (31.3)	***0.013**
Admission MiONSD † (mm)	4.70 [4.20-5.15]	4.65 [4.30-5.15]	4.90 [4.11-5.35]	0.806
At the final of ICU stay				
Serum BUN (mg/dl)†	35 [25.5-54.25]	28 [19-37]	54 [35-83]	***0.0001**
Serum Creatinin (mg/dl) †	1.56 [0.68-1.7]	0.78 [0.55-1.2]	1.73 [0.75-2.52]	***0.005**
Serum Albumin (mg/dl)†	2.38 [2.08-2.8]	2.6 [2.36-3.3]	2 [1.8-2.3]	***0.001**
Total Fluid Balance (ml) †	1945 [(-630) - (7664)]	980 [(-2763) - (2640)]	7844.5 [(1650) – (17655)]	***0.001**
Sepsis, n(%)	16 (44.4)	0 (0)	16 (100)	***0.0001**
Increased MiONSD, n (%)	17 (48.6)	2 (10.6)	15 (93.8)	***0.0001**
Final MiONSD † (mm)	4.65 [4.15-5.20]	4.20 [3.65-4.80]	5.27 [4.72-5.65]	***0.0001**
DiONSDs † (mm)	-0.05 [(-0.5)-(0.65)]	-0.35 [(-0.85)-(-0.10)]	0.60 [(0.21)-(1.00)]	***0.0001**

*There is a statistically significant difference, †Data are presented as median and [interquartile range]

APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA Score: Sequential Organ Failure Assessment score; GCS: Glasgow Coma Score; iONSD: Internal Optic Nerve Sheath Diameter; MiONSD: Mean of Left iONSD and Right iONSD; DiONSDs: Difference betwe en Final MiONSD and Admission MiONSD; mm: milimeter; ml: mililiter; mg/dl: milligram/deciliter;

There was no significant difference between survivors and non-survivors for admission MiONSD, but there was a significant difference between survivors and non-survivors for final MiONSD and for DiONSD (Table 2). DiONSD was found to be an independent risk factor for mortality according to the results of multivariate analysis between DiONSD, SOFA and APACHE II scores (Table 3).

Tablo 3: Results of logistic regression analysis to determine independent risk factors for mortality

Parametre	P value	Exp (B)	%95 CI
DiONSDs	**0.033**	**10.663**	**1.210-93.925**
APACHE II score	0.247	1.150	0.908-1.458
SOFA score	0.346	1.337	0.731-2.445

iONSD: Internal Optic Nerve Sheath Diameter; MiONSD: Mean of Left iONSD and Right iONSD; DiONSDs: Difference between Final MiONSD and Admission MiONSD; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment

When the effect of DiONSD on the mortality was investigated with ROC (Receiver Operating Characteristic) analysis, AUC (Area under curve) was calculated as 0.905 (p = 0.0001) (Figure 2).

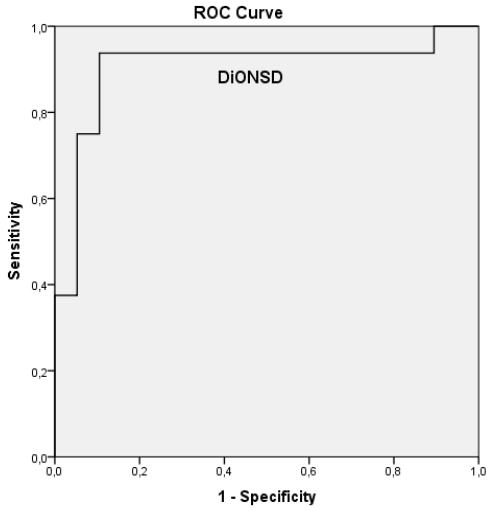

Figure 2: ROC (Receiver Operating Characteristic) curve analysis (relationship between mortality and DiONSDs, Area under curve (AUC) = 0.905, p value = 0.0001)

iONSD: Internal Optic Nerve Sheath Diameter; MiONSD: Mean of Left iONSD and Right iONSD, DiONSDs: Difference between Final MiONSD and Admission MiONSD

DiONSD values greater than +0.25 mm were found to be a predictor for mortality with 75% sensitivity and 95% specificity (LR= 14.25). There was also a correlation between DiONSD and SOFA score (r=0.705, p=0.0001), total fluid balance (r=0.561, p=0.0001), PEEP value (r=0.617, p=0.0001), serum albumin level (r=-0.348, p=0.044), sepsis (r=0.655, p=0.0001), and GCS (r=-0.576, p=0.0001).

Discussion

The results of this study showed that the change in daily iONSD measurement with USG could be used as an indicator of mortality in MICUP. According to this study, the presence of an increase of at least 0.25 mm in the MiONSD measurement in the following days compared to the ICU admission day was required to estimate mortality. The study also indicated that if there was an increase in iONSD value within days, it could be considered that the patient's condition was getting worse. This case was particularly supported by the fact that DiONSD well-correlated with the concurrent SOFA score. We believed that this method could easily evaluate the risk of ICU mortality on a daily basis.

The optic nerve consists of the head, intraorbital, intracanalicular and intracranial parts.8 The area in which ONSD can be measured with USG is the intraorbital part of the optic nerve. Within this area, the optic nerve fibers are myelinated and these myelin sheaths are mainly composed of astrocytes.8,13 It has been shown in the laboratory setting that short-term hypoxemia with systemic inflammation causes swelling of astrocytes.10 Some pathologies such as early ischemia, meningitis, hyponatremia, hyperammonemia, diabetic ketoacidosis, hyperbiluribinemia, and uremia are known to cause cytotoxic astrocytes swelling.11 This phenomenon is associated with deterioration of intracellular energy production. It is known that nitric oxide or the end products of arachidonic acid released from endothelium due to endothelial damage cause astrocytes swelling.9 All the above-mentioned pathologies are frequently seen in ICU patients. Therefore, swelling of astrocytes and thickening of iONSD may be expected in ICU patients depending on the severity of these pathologies.

Did increased ICP affect our results? The subarachnoid space in ONS is connected to the subarachnoid space in the brain by the optic canal, and when ICP increases, ICP pressure is transferred to the optic nerve sheath by the cerebrospinal fluid.14 However, we did not measure subarachnoid space, we measured only the total diameter of inner ONSD as PML and ONFL. Even so, we cannot say that increased

ICP cannot influence iONSD measurement. The study of Topcuoglu et al. indicated that iONSD changed with increased ICP.7 However, in this study, most of the patients had serious intracranial pathologies, which caused increased ICP status, for example, brain death or cerebrovascular events. In our study, these patients, who had intracranial pathologies, were excluded. Therefore, we think that the increase in intracranial pressure had no significant effect on the results obtained in our study. However, since there was no simultaneous invasive ICP measurement in our patients, we could not determine whether there was an actual effect of ICP increase in our iONSD measurement. Actually, we could not perform invasive ICP monitoring for our patients because there was no indication for this.15

We preferred measuring iONSD instead of eONSD to eliminate the effect of increased ICP on the results of our study and measuring the swelling effect of some pathologies which were listed above on astrocytes. Therefore, as also understood by a review of literature, the iONSD measurement was first used in our study in order to determine the prognosis of MICUP with no acute or chronic neurological problems. The current study had some limitations. For example, it was a single-centered study with a small group of patients. Also, invasive ICP measurement was not performed at the same time. Apart from this, another limitation is that fundus examination, which is a non-invasive technique to investigate intracranial pressure, was not applied in our study. Still, it is a valuable study in that this was the first study on MICUP, who were known to have no acute or chronic intracranial pathologies, unlike the previously studied patient groups.

Conclusion

Serial iONSD measurement with USG is a feasible, easy, non-invasive, and bedside applicable method that can be employed to determine the prognosis in MICUP with no intracranial acute or chronic pathologies.

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Author's Contributıons

1. Uğur Özdemir, Contribution: Obtaining clinical data from patients, detecting appropriate patients, collecting ultrasonography measurement data and images, analyzing data, researching literature, writing the article.
2. Şeyma Yıldız, Contribution: Assisting in obtaining clinical data from patients
3. Derya Başak Tanburoğlu, Contribution: Assisting in obtaining clinical data from patients, researching literature.
4. Melda Türkoğlu, Contribution: Critical reading and evaluation
5. Gülbin Aygencel, Contribution: Obtaining clinical data from patients, detecting appropriate patients, researching literature, writing the article.

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