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Ultrasound examination of the optic nerve in patients with clinical and imaging evidence of increased intracranial pressure

Abstract

of doctoral thesis for acquiring educational and scientific degree

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The dissertation paper contains a total of 112 pages, along with 32 figures and 5 tables. The List of References contains 178 titles, 7 of which are in the Cyrillyc alphabet and 171 in Latin alphabet.

The research, examinations, operative interventions and monitoring are carried out in the ICU and at the Neurosurgery Clinic at University General Hospital for Active Treatment "Sveta Marina" in the city of Varna.

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The PhD. candidate works at the ICU Clinic at the University General Hospital for Active Treatment "Sveta Marina" and is an assistant at the Department of Anaesthesiology, Intensive and Emergency Medicine at the Medical University in Varna city. The dissertation paper has been discussed, accepted and scheduled for presentation before a scientific panel of experts from the Department Council at the Department of Anaesthesiology, Intensive and Emergency Medicine at the Medical University "Prof. Paraskev Stoyanov", on March 16th, 2021.

The dissertation paper defense will be held on June 11th, 2021, 2:00pm, in Helege Hall, University General Hospital for Active Treatment "Sveta Marina", or online, if required.

Table of Contents:

Abbreviations used

IVP – Invasive Pulmonary Ventilation

BD – Brain Death

MAP – Mean Arterial Pressure

CPP – Cerebral Perfusion Pressure

CBV – Cerebral Blood Volume

CBF – Cerebral Blood Flow

CSF – Cerebrospinal fluid

IICP – Increased Intracranial Pressure

ONSD – Optic Nerve Sheath Diameter

ICP – Intracranial Pressure

CNS – Central Nervous System

US – Ultrasound

BBB – Blood–Brain Barrier

SAH – Subarachnoid Hemorrhage

GCS – Glasgow Coma Scale

CT – Computer Tomography

NMR – Nuclear Magnetic Resonance

PET-CT – Positron Emission Tomography-Computed Tomography

RE – Right Eye

LE – Left Eye

TP – Transverse Plane

SG – Sagittal Plane

1. INTRODUCTION

Increased intracranial pressure is a life-threatening condition. Unrecognized and untreated, it can lead to critical and irreversible brain damage and death. [30, 104, 157, 168] The symptoms of increased ICP are not a sensitive and specific marker. These are usually the reactive Cushing hypertension, Cushing's triad, reflex bradycardia, changes in respiratory function, changes in consciousness, headache, nausea and vomiting. These symptoms, unfortunately, in most cases occur when the ICP has reached values that are too high, damaging the brain.[72] Due to the impossibility of obtaining real information about ICP in any other way, the invasive measurement and monitoring, with all their risks and complications, have become the standard for patients with traumatic brain injury.[102]

The increased intracranial pressure is a pathological condition that is extremely common in intensive care and especially in neuro-intensive care units. Proper and timely therapy and behavior are of great importance for the final outcome of the disease, and they directly depend on early detection and diagnosis, which nowadays is most quickly made on the basis of computed tomography of the brain.[51, 110] CT in turn, is an imaging examination requiring expensive equipment, trained personnel; it has a high radiation load, requires transportation, which can sometimes be fatal due to the critical condition of the patient.

The search for alternative methods for early detection of increased ICP leads to the practical introduction of new methods and imaging examination to prove it. Such potential, alternative and new method is the ultrasound examination of the optic nerve diameter. The optic nerve, as part of the central nervous system, is surrounded by cerebrospinal fluid and meninges called the optic nerve sheath. Hayreh et al. prove that there is communication between the intracranial cerebrospinal fluid and the subarachnoid space of the optic nerve. It turns out that the diameter of the nerve increases seconds after a sharp increase in the ICP. [64] Helmke and Hansen confirmed that changes in intracranial pressure affected the diameter of the optic nerve sheath.[67]

Nowadays, the use of ultrasound examinations is an integral part of daily medical practice in intensive care units. Measurement of the diameter of the optic nerve is a relatively new, non-invasive and original method for the detection of increased ICP. It is fast, beam load-free, easy to perform by the patient's bedside, with the possibility of repeated recurrence and does not require continuous staff training. The need for rapid orientation and speedy diagnosis, as

well as screening of patients with suspected increased ICP to ensure adequate behavior, inspires our interest and forms the basis for the present study.

2. SUMMARIZED LITERATURE ANALYSIS

ICP is a complex quantity, and when increased, it is the reason for the development of a number of pathological processes, which, if left without therapy, eventually lead to decreased CPP, cellular hypoperfusion, edema and further increase in ICP. In practice, a vicious circle is reached, which must be broken in order to avoid severe, fatal and irreversible consequences.

Proper treatment and monitoring of ICP are an important stage in the complex treatment of critically ill patients with CNS pathology. Unfortunately, there is no ideal method of monitoring and therefore a benchmark for treatment at the moment. The clinician should be familiar with the limiting factors of invasive monitoring systems and use them in parallel with clinical and imaging examinations to extract valuable data about the patient's condition.

In recent years, ultrasound has become widely used in the comprehensive diagnosis and therapeutic manipulations of critically ill patients in intensive care units [41]. As a result, assessment of the diameter of the optic nerve by transbulbar ultrasound is an extremely useful tool for non-invasive detection of increased intracranial pressure and can be an integral part of the overall diagnostic and therapeutic behavior in critically ill patients.

An increase in intracranial pressure is directly transmitted to the subarachnoid space around the optic nerve, causing an increase in the amount of cerebrospinal fluid there, with a subsequent increase in the diameter of the nerve, whereas said increase is observed mostly at the beginning of the nerve – at about 3 mm behind the papilla.(68, 117) Knowing the normal boundaries of the ONSD is essential in order to interpret the ultrasound examination as a marker for intracranial hypertension. As with any novelty, great difficulties are encountered in standardizing normal dimensions. After studying the available data and results from various literature sources, we concluded that the dimension of the normal ONSD does not depend on gender, height, weight, age and ethnic origin. We adopted the view that the dimensions in the absence of pathology, in persons over 4 years of age, are between 4.7 and 5.9 mm, whereas a diameter of over 5.9 mm was adopted as a marker for increased ICP.

Based on the reviewed and studied literature sources, it can be concluded that ultrasound of the retro-orbital area of the optic nerve is a method that provides valuable information about the presence or absence of intracranial hypertension in patients with craniocerebral trauma or spontaneous cerebral hemorrhage. The data obtained through this method correlate well to the methods approved for this purpose – CT and invasive measurement of ICP. Our team shares the opinion of Geeraerts T. et al [47] and accepts an ONSD dimension of 5.8 mm, above which there is a high probability for intracranial hypertension.

ONSD ultrasound is an innovative method with huge potential, which could be used to successfully diagnose IICP under hydrocephalus, the correct placement of a ventricular drain or ventriculoperitoneal shunt, as well as their malfunction, due to numerous reasons.

Critically ill, comatose patients, those with IVP, with neurological pathology, require daily assessment of the current condition. Their pathology often requires them to be medically sedated and/or relaxed, which makes it difficult to impossible to make an adequate assessment of the disease progression. Daily monitoring of the said contingent of patients by US could be extremely valuable for the early detection of abruptly increased ICP and/or for the early diagnosis of BD, which has the potential to increase the organ donor pool. The tendency to report clearly the largest dimensions of the ONSD in patients with brain death is also easily noticeable.

As with most US examinations, the experience and training of the operator are crucial for the adequacy of the results obtained. Of particular importance is the development of a strictly standardized study protocol that would facilitate operators and minimize methodological errors, as exemplified in previous chapters of this paper with the publication of Ballantyne S. A. et al. (15) The structures that are the object of measurement are very small in size and errors in technique, incorrect measurement and misplacement of the cursors could lead to distortion of the study by obtaining false negative/false positive results, with a sharp decline in efficiency. (156)

In the literature we studied, the normal and pathological dimensions in children and newborns remain undetermined.

In Bulgaria, the transbulbar ultrasound method for the examination of ONSD has not yet gained popularity and we have not found studies concerning this area in our literature.

3. GOAL AND OBJECTIVES OF THE DISSERTATION PROJECT

Goal:

To study the importance of ultrasound examination of the optic nerve sheath diameter as a screening indicator of the intracranial pressure state

In order to achieve the set goal, our team set itself the following tasks:

1. To examine with US the optic nerve diameter in patients with clinical and CT data indicating increased ICP associated with acute disorders in the cerebral circulation

2. To examine with US the optic nerve diameter in patients with clinical and CT data indicating increased ICP associated with other brain diseases – tumors.

3. To examine with US the optic nerve diameter in newly admitted patients with alternating states of consciousness without any established cause for that.

4. To examine with US the optic nerve diameter in healthy individuals without clinical data indicating increased ICP

5. To compare the data from the US examination of the optic nerve diameter with the CT data in patients with imaging results for increased ICP.

6. To study the relation between ONSD dimensions in the transverse and sagittal plane.

4. CLINICAL STUDY OBJECT AND METHODS

4.1. Clinical Study Object.

We conducted the current prospective study within the basis of the Clinic of Anesthesiology and Intensive Care at the University General Hospital "Sveta Marina" in the city of Varna. In our work we decided to include 86 patients with proven pathological changes of the brain, leading to increased intracranial pressure. Some of those patients had been subjected to influences, methods and treatments affecting intracranial pressure, and have been admitted to the University General Hospital "Sveta Marina" for the period 2018-2020. A control group was also established, consisting of 52 healthy individuals. In all patients, without exception, the physician performing the optic nerve US examination, was the author of this dissertation.

The study design is experimental, clinical and with a control group, whereas we formed two large groups: experimental and control.

The experimental group included patients with rapidly developing processes leading to increased intracranial pressure; patients with slowly developing processes leading to increased intracranial pressure; patients admitted in a coma, with unclear genesis, and patients with brain death, who were divided into separate subgroups, depending on the type of pathology and the rate of development of the disease process:

1) First group – patients with acute and fast disease development (acute vascular incidents): instances of subdural, epidural, intracerebral, subarachnoid hemorrhage and ischemic cerebral infarctions.

2) Second group – patients with brain tumors where the disease process of the brain has developed gradually, admitted for scheduled surgical treatment.

3) Third group – patients admitted to the intensive care unit with quantitative changes in consciousness, without any clear or proven cause of such change.

4) Fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, as they are a priori with highest ICP.

The control group included clinically healthy individuals who did not have any statistically significant differences in terms of age and gender compared to the patients in the experimental group. These were healthy volunteers, employees at the Clinic of Anesthesiology and Intensive Care of the University General Hospital "Sveta Marina" in Varna, who presented no history or clinical data suggesting increased ICP.

The purpose of such distribution was to assess whether the duration and rate of the pathological process are related to changes in the ultrasound dimensions of the optic nerve, as well as to specify the information that the ultrasound examination gives us in the various disease processes that are common in the intensive care units and represent a great challenge for doctors in ICUs. The medical case history of each patient was obtained personally from the patient and that was not possible – from family members and documents. All patients were divided by age, gender, body weight, ASA risk, diagnosis. All patients (family members) and volunteers were presented with a detailed explanation of the nature of the study itself *(Appendix 3)* and an informed consent was requested (in compliance with and approved

by the Ethics Committee for Scientific Research; ECSR) at The Medical University in Varna. Said consent was obtained either from the respective patients or from their authorized representative in cases of patients with changes in consciousness. *(Appendix 2)*

There are diseases and conditions in which ultrasound measurement of the optic nerve is impossible or insufficiently informative: severe trauma to the bulb, diseases and tumors of the optic nerve itself, sarcoidosis, pituitary tumors, pregnancy, Graves' disease. In these conditions, the nerve itself is swollen and of increased diameter, but this is not due to increased ICP, which means that they must be excluded from the group. Therefore, we formed inclusion and exclusion criteria as follows:

Inclusion	**Exclusion**
1. Older than 18 years of age 2. Patients with history of and/or clinical data suggesting IICP 3. Computed tomography of the head and US examination of the optic nerve, with a time interval between the two examinations not exceeding 1 hour (except for patients with brain tumors and other chronic processes)	1. Severe eye injuries 2. Diseases and tumors of the optic nerve itself 3. Sarcoidosis 4. Pituitary tumors 5. Pregnancy 6. Graves' disease 7. Older than 18 years of age

4.2. Clinical study methods

4.2.1. Clinical methods

4.2.1.1. Medical case history

All patients and tested subjects or their relatives were asked questions about the onset and duration of symptoms, the nature of the complaints, and specifically about symptoms related to IICP (headache, nausea, vomiting, motor deficit), medication, underlying diseases , with particular emphasis on past diseases associated with trauma and/or inflammation of the optic nerve or bulbus itself, Graves' disease, sarcoidosis, sella turcica formations.

4.2.1.2. Clinical examination

From all patients we obtained a brief neurological status, GCS assessment, Babinski group reflexes, presence or lack of Cushing's Triad, neck rigidity, as well as size and reaction of pupils against light.

For patients with severe pathology who were in a deep, non-reactive coma, without spontaneous respiratory activity, included in the "potential donor" category, we performed a clinical examination to prove brain death. Said examination consisted of a few brief tests of the stem reflexes:

- pupillary light reflex

- corneal reflex

- oculovestibular and oculocephalic reflex

- pharyngeal and cough reflex

- facial movements with pain stimulus: in brain death there is no response to painful stimuli in the trigeminal (facial) area – temporomandibular joint, supraorbital sulcus; no facial reaction or grimace upon painful stimuli in the somatic areas such as neck, thorax, limbs, abdomen, pressure on the nail beds, etc.

- atropine test – in many countries this test is not mandatory; it evaluates the same deep area of the stem that is evaluated in the apnea test

- apnea test: aims to demonstrate loss of respiratory function of the stem

We performed an apnea test as the last method of confirmation, after the four-vessel angiography (described in the imaging methods), due to the risk of additional nerve damage in the absence of brain death.

4.2.2. Laboratory methods

Hemogram, biochemistry, coagulation, ionogram, BGA – for adequate control of hyperventilation and for categorization of patients according to ASA.

4.2.3. Imaging, diagnostic methods

4.2.3.1. Specific methodology and principles in ultrasound examination and evaluation of the optic nerve

For the purposes of this study, our team used a mobile ultrasound device “SonoScape X3 Laptop Color Doppler Ultrasound”, set on a transport cart (Fig. 6).

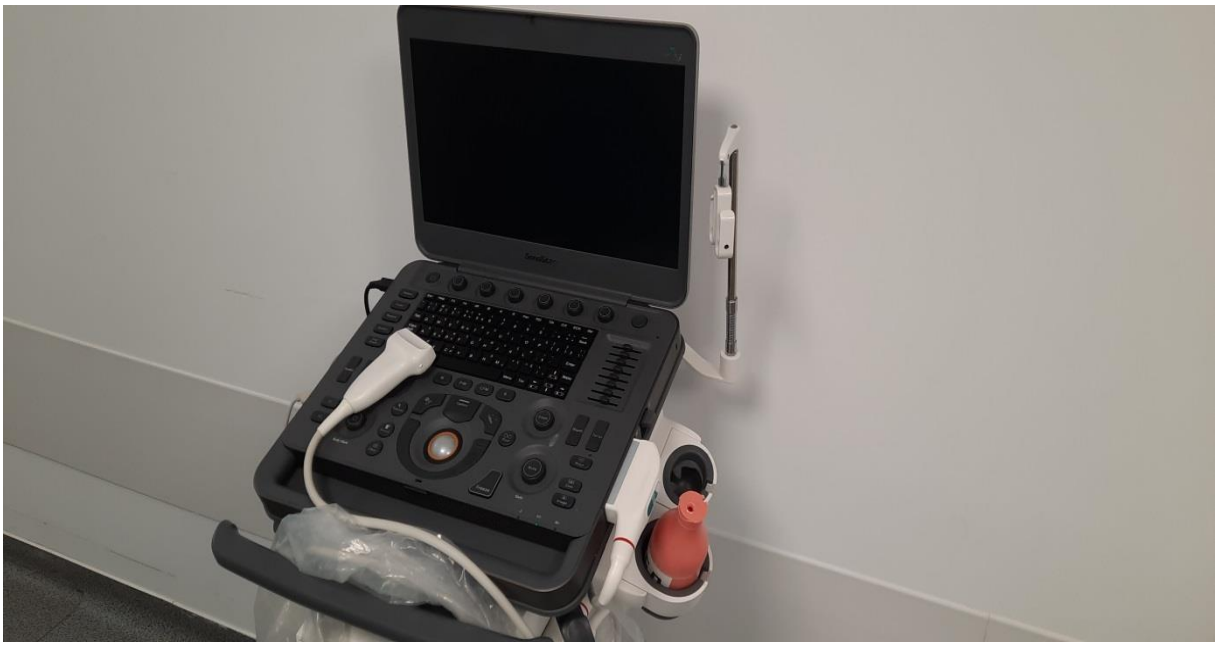

Figure 6 SonoScape X3 Laptop Color Doppler Ultrasound

The transducer was high frequency one, 10 – 17 MHz, linear, so that we could get a good image of the surface structure that we examined. The frequency was set at 10 MHz, as the best compromise between wave penetration and picture quality. The waves depth of penetration was 4 cm, and it was sufficient to visualize all objects of interest to our team, whereas the gain was minimized as much as possible so as to clearly see the boundary between the echogenic subarachnoid space and the hypoechoic dura mater. Patients were placed in a horizontal position on their backs. This was followed by an application of a copious amount of gel (about 1 cm) on the eyelid of the respective eye, which aims to minimize the pressure on the bulb, as well as to improve the conductivity between the two media. Before and after the examination, all contact surfaces were thoroughly cleaned with a disinfectant spray to prevent cross-contamination between patients. The next step was to carefully place the transducer on the gel located on the eyelid, without any force or pressure on our part. The transducer was placed transversely (Fig. 7) on the temporal part of the upper eyelid, and we made sure that the waves did not pass through the structures of the eye (front, rear eye chamber, lens) to avoid scattering of the waves and to use the good vitreous body conductivity. After obtaining a satisfactory image – hypoechoic nerve, hyperechoic subarachnoid space, hypoechoic dura mater and localization of their entry into the ocular bulb (Fig. 9), we would measure and then change the position of the transducer and place it in sagittal plane. (Fig. 7), followed by a new measurement of the sagittal dimensions of the optic nerve.

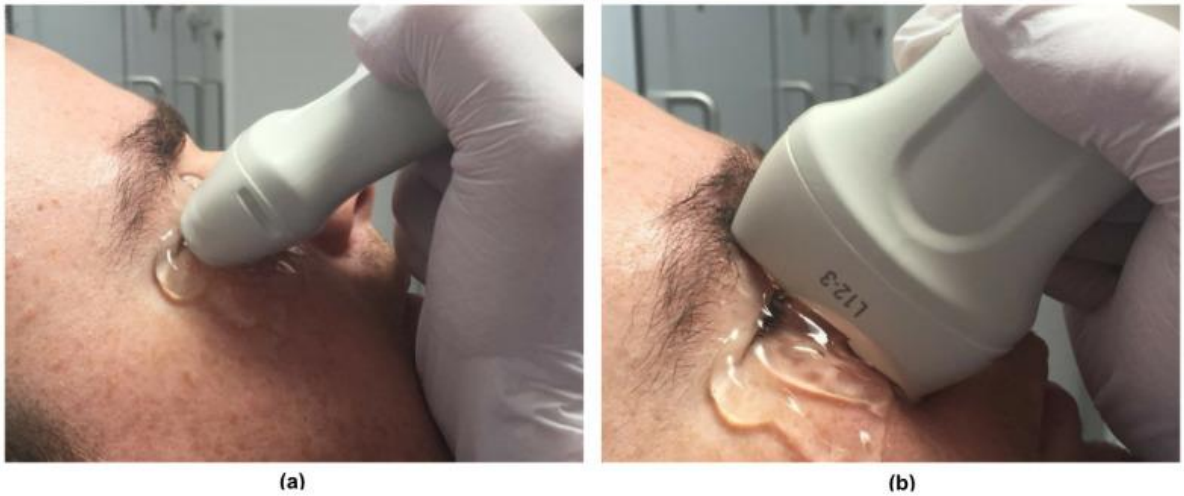

Figure 7 (a) – ONSD dimension measurement in the transverse plane; (b) – ONSD dimension measurement in the sagittal plane(45)

The measurement was performed as follows:

1. We drew a measurement line, 3 mm long, beginning behind the retina at the point where the optic nerve enters the bulb (Fig. *6 and Fig. 10.*

2. We measured the distance between the hypoechoic border of the dura on both sides of the nerve, whereas the measuring line was projected perpendicularly, passing through the end of the first line. *(Fig. 11.*

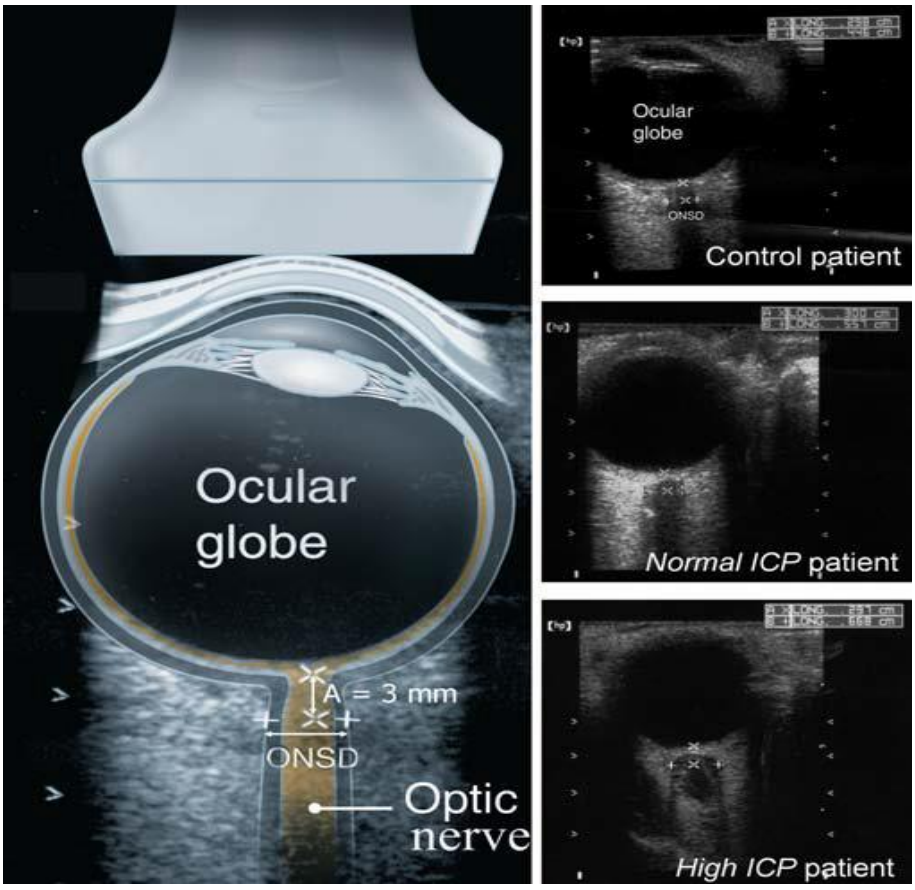

Fig. 8. US image of an eye and optic nerve, transverse plane, of a patient without IICP and of a patient with craniocerebral trauma and IICP (48)

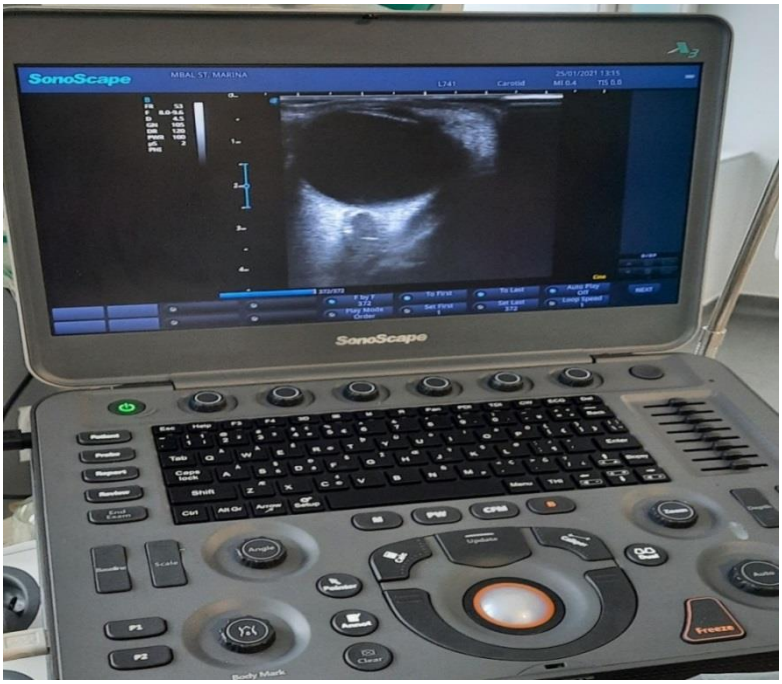

Figure 9. Optic nerve localization

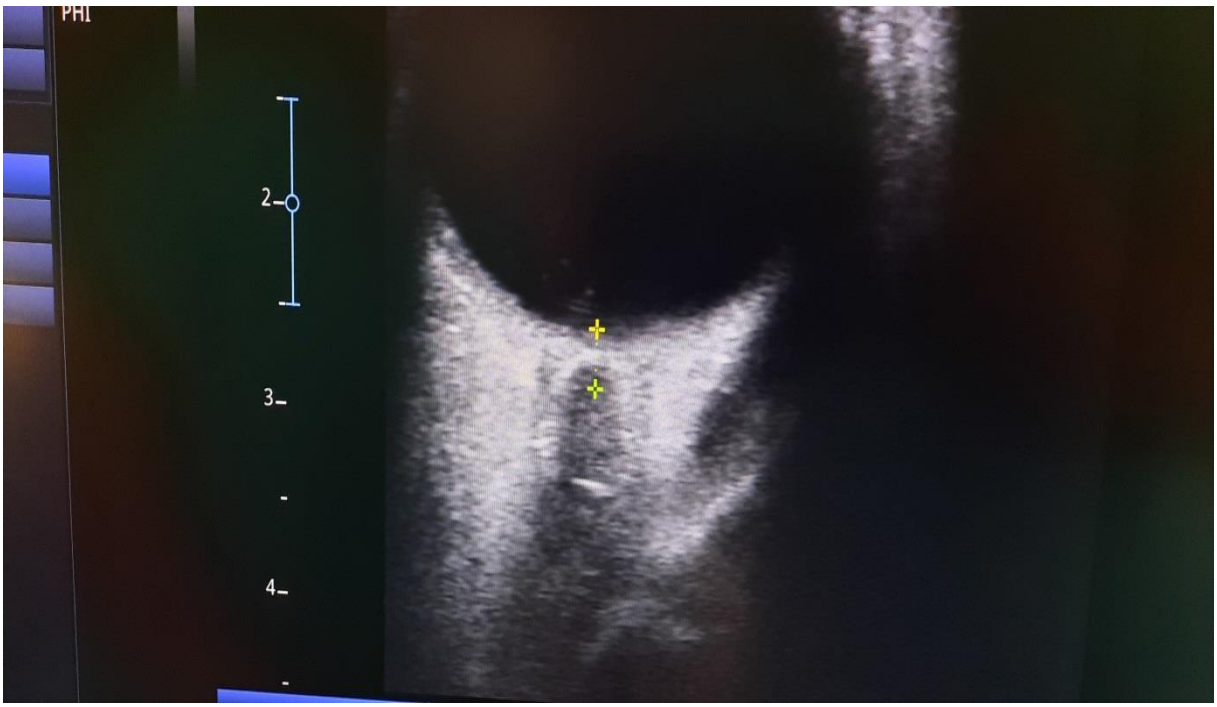

Figure 10. Drawing a measurement line from the retina, 3 mm in length

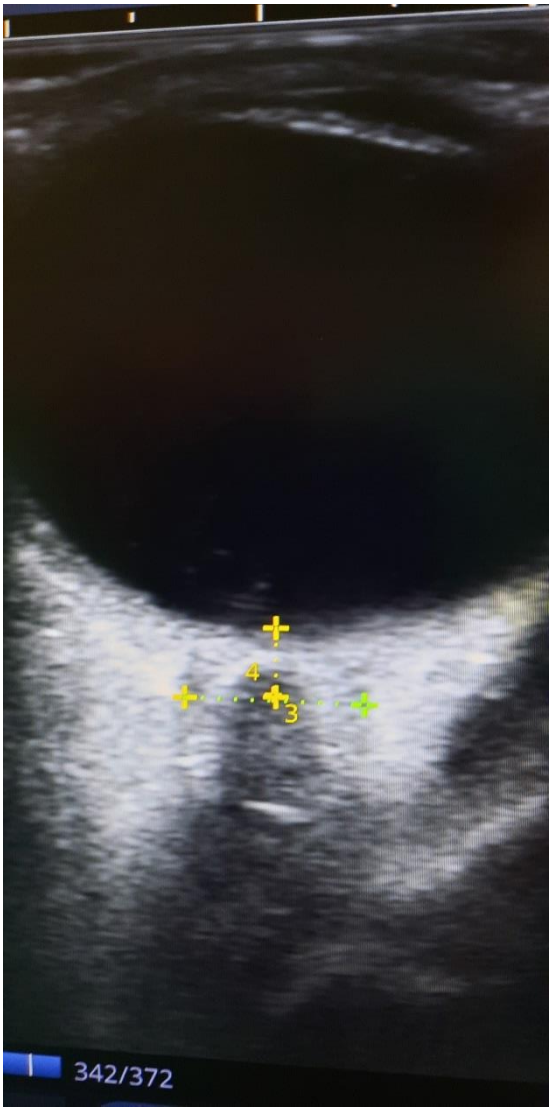

Figure 11. Measurement of the ONSD, 3 mm after the optic nerve has entered the eye

In the same way, the size of the ONSD was measured with a sagittally placed transducer. With the methodology thus described, we made one measurement in each plane (sagittal and transverse) of the left and right nerves and obtained a total of four sizes.

We set ourselves the goal of measuring the ONSD within 10 to 60 minutes before or after the CT/angiography of the brain, as we thought that the information obtained in this way will be as accurate as possible and we will avoid missing any changes in the ICP values due to the dynamic condition of patients. The exceptions to this were patients from group 2, due to the slow growth of pathological processes and the planned nature of the therapeutic strategy. For these patients we did not observe the maximum interval of 60 minutes between the computed tomography and the ultrasound.

Patients from group 1 (rapidly developing processes) were admitted to the intensive care unit immediately after diagnosis with CT of the brain and their first ultrasound examination was performed at 10 to 60 minutes between the CT and the US. Preoperatively, before administering anesthesia, we also performed an ultrasound examination.

For the patients in group 2 (slowly developing processes), the ultrasound examination carried out before administering anesthesia was considered as first examination.

For the patients in group 3 (admitted in a coma, unclear cause) we carried out the first US examination within 10 to 60 minutes and that was followed by a CT of the brain.

In group 4 (brain death) the first and only US examination was carried out right after establishing the diagnosis with a 4-vessel angiography.

4.2.3.2. Methodological principles in the diagnosis and assessment of increased intracranial pressure by computed tomography of the brain

To objectify pathological processes and IICP, we performed non-contrast computed tomography of the head. Two computed tomography scanners were used – 128 slices high-resolution 4-dimensional scanner Siemens Somatom Definition Dual Source, and a spiral computed tomography scanner Siemens Spirit Somatom (Fig. 7). In a large percentage of cases, patients underwent tomography immediately before admission to the anesthesiology and intensive care unit. For the other patients, the scan was performed after transporting them to the imagery diagnostics ward. For the patients who needed IVP, we used a Draeger Oxylog transport respirator and monitored their pulse oximetry, blood pressure (non-invasive), and ECG.

Figure 12. 128 slice, 4-dimensional computed tomography scanner Siemens Somatom Definition Dual Source

Non-contrast scanning is the main imaging diagnostic method to detect pathological processes in the brain and increased intracranial pressure. It is a highly sensitive method, characterized by short procedural time and relatively common equipment. All patients with acute onset process (craniocerebral trauma, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, ischemic brain injury) and those with gradually developing processes (brain tumors) underwent CT of the head. CT scan of the brain was carried out for all patients admitted to the intensive care unit, in a coma of unknown origin.

There are clear criteria to determine the presence of increased intracranial pressure and the very examination provides valuable information about the root cause. Each of the patients included in the first, second and fourth groups of our work underwent one or more CT scans. The findings, on the basis of which we would assume increased intracranial pressure, were the following:

1. Cerebral edema

- Compression of the lateral ventricles

- Compression/disappearance of the third and fourth ventricles and the basilar cistern with loss of the normal “smiley” face

- Disappearance of sulci

- Loss of differentiation between gray and white brain matter

2. Hydrocephalus

- Compression/disappearance of the basilar cistern with loss of the normal “smiley” face

- Disappearance of sulci

- Enlarged lateral ventricles

- Enlargement and prominence of the temporal horns of the lateral ventricles, which are normally very small

- Enlarged third ventricle

3. Space-occupying processes with a “mass” effect

- Epidural, subdural, intracerebral hematomas and tumors – with dislocation along the midline of over 5 mm and an approximate volume above 25 ml.

- Subarachnoid hemorrhage

4.2.3.3.Methodological principles in the implementation of four-vessel cerebral angiography

After conducting a clinical test and fulfilling the criteria for brain death, the patients were transported to the angiography hall at the University Hospital “Sveta Marina” to perform four-vessel cerebral angiography. For all patients a Draeger Oxylog transport respirator was used. Pulse oximetry, blood pressure (non-invasive) and ECG were also monitored.

The classic four-vessel angiography has long been the gold standard for assessing cerebral blood flow in brain death, as it does not depend on hypothermia or CNS depressants, but there are naturally transport inconveniences, contrast nephrotoxicity, and the invasiveness of the procedure. An angiographic device was used – a Siemens Artis Zee monoplane, equipped

with a Leonardo workstation with multifunctional software and the possibility for 3D reconstructions. The angiographic device has the option for digital subtraction angiography (DSA), mapping (RoadMap) and rotational angiography. (Fig.) 13). After catheterization of the femoral artery, the cerebral circulation was reached and the absence of intracranial blood flow was established by applying contrast material.

Immediately after that, we examined the optic nerve by ultrasound.

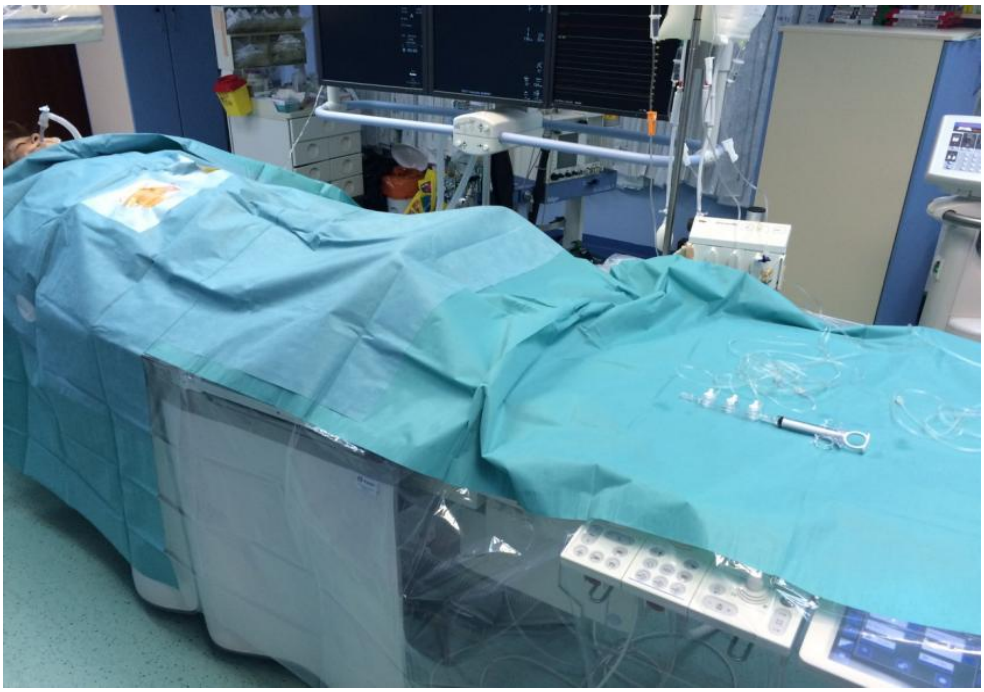

Figure 13 Positioning of a patient with suspected brain death at the angiographic table

4.2.4. Treatment methods

4.2.4.1. Neurosurgical activity performed under general anesthesia

In patients undergoing craniotomy for the purpose of evacuation of a process that takes up volume (tumors, sub- and epidural hematomas or decompressive craniectomy), we examined the size of the ONSD, using the already described ultrasound method, before administering anesthesia and postoperatively before extubation, after completing the decompression of the brain parenchyma. The anesthesiology device we used was a Drager Primus Anesthesia Workstation connected to a Drager Infinity Kappa patient monitor. The administration of the general anesthesia was standard, intravenous, and the anesthesia was maintained with an inhalation anesthetic. The patient received premedication with midazolam as a bolus dose of 0.01-0.02 mg/kg and fentanyl as a bolus dose of 1 to 2 mcg/kg, followed by application of 1

mg of the non-depolarizing relaxant pipecuronium as a “precurarization” for maximum protection of against additional increase in ICP due to the use of a depolarizing relaxant. Intravenous administration was performed with propofol, at a dose of 1 to 2.5 mg/kg, and after disappearance of the blink reflex, the depolarizing relaxant succinylcholine was administered at a dose of 1 mg/kg. The described method provided ideal conditions for endotracheal intubation. Anesthesia was maintained with the inhaled anesthetic sevoflurane and additional, intermittent applications of fentanyl and pipecuronium. To antagonize the non-depolarizing relaxant, galantamine was used prior to extubation at a dose of 0.1 to 0.3 mg/kg. Under appropriate conditions (restored consciousness, breathing rate below 30/min, tidal volume over 6 ml/kg, stable hemodynamics, no need for catecholamine infusion) the patient would be extubated, while in cases where such conditions were absent, we would sedate the patient and transport him to the intensive care unit, with subsequent placement of IVP.

4.2.4.2. Mechanical ventilation

We used respirators “Drager Evita XL Ventilator”, “HAMILTON GALILEO VENTILATOR” or “Drager Evita 2 Dura Ventilator”, in “SIMV” mode to ventilate patients with increased ICP, with quantitative deviations in consciousness and GCS below 8 points, with indications for mechanical ventilation. We sedated them with midazolam, starting with an intravenous bolus dose of 0.05 mg/kg and proceeded with a continuous intravenous infusion, at a dose of 0.03 – 0.1 mg/kg/hour. In parallel with midazolam, we administered morphine with an initial bolus dose of 0.08 mg/kg and subsequent continuous intravenous infusion at a dose of 0.01 – 0.1 mg/kg/hour, with our goal being to achieve RASS: -4. Deep sedation was a priority for us, due to the known negative effects on ICP, due to non-synchronization with mechanical ventilation, coughing and straining. In the cases of CT data indicating extremely IICP, we applied therapeutic, moderate hyperventilation to influence the intracranial hypertension, with target PaCO2 values between 30 – 35 mmHg, which was estimated by taking into account the values of „$ETCO_2$“ and adding 5 mmHg to the monitor value. Our team would measure ONSD prior to hyperventilation, at the first hour, the fourth hour and after 24 hours, respectively prior to the first dose of mannitol, at the twentieth minute and at the first hour.

4.2.4.3. Mannitol administration

Given the CT data indicating extremely IICP we would apply intravenous mannitol 10% at a dose of 1.5g/kg for a 24-hour period, divided into 4 equal administrations, with a single dose applied for a duration of 20 minutes. A measurement was done prior to infusion, 20 min after the end of infusion and 1 hour after infusion.

4.2.5. Statistical methods

Data is analyzed with IBM SPSS, version 23. The normality of distribution of continuous variables was tested by a Shapiro-Wilk and Kolmogorov-Smirnov test, for one sample.

Continuous variables that follow a normal distribution are represented by mean value and standard deviation (SD). Variables that do not follow a normal distribution and/or include very remote and extreme values are represented by a median and interquartile range (IQR).

The mean values of the normally distributed variables were compared through Student's t-test (for two independent samples or for two correlated samples) and through ANOVA (for more than two samples). Post Hoc tests were used to determine differences when comparing the mean values of more than two normally distributed variables.

The frequencies of the category variables were compared by nonparametric tests (Pearson's X2 or Fisher's exact test).

Nonparametric Wikoxon Sign Rank Test was used to compare two dependent (correlated) variables that do not follow a normal distribution.

Correlation analysis (Pearson correlation coefficient for linearly dependent variables, Spearman Rho rank correlation coefficient for variables that do not follow a normal distribution and/or include very remote and extreme values) was applied to determine the strength and direction of dependencies.

The tests were performed at a significance level $\alpha = 0.05$ or $p < .05$

5. RESULTS

The experimental group included a total of 86 patients with a mean age of 59.9 (SD = 16.6) years. The control group included 52 healthy individuals with a mean age of 58.2 (SD = 6.02) years. There was no statistically significant difference in the age of the patients from the experimental and the control group ($t = 0.877$; $p = .383$).

The experimental group includes 49 (56,9%) male and 37 female individuals. The control group includes 27 (51,9%) male and 25 female individuals. There was no statistically significant difference in the gender of the patients from the experimental and the control group ($X^2 = 0,334$; $p = ,563$).

For the purposes of the study, the experimental group was divided into 4 subgroups, according to the disease characteristics of the patients, which are considered in the subsequent analyzes.

The first group included 43 patients with rapidly developing processes leading to increased intracranial pressure. The second group included 14 patients with slowly developing processes leading to increased intracranial pressure. The third group consisted of 14 patients who were in a coma of unclear genesis, and the fourth group included 15 patients with proven (clinically and instrumentally) brain death.

5.1. Age and underlying diseases

The age of the patients in the four groups as well as in the control group followed a normal distribution (Kolmogorov-Smirnov test with Lilliefors Significance Correction: $.16 \leq p \leq .20$). Parametric tests are applied.

The age of the patients from the first group – rapidly developing processes leading to increased intracranial pressure, varies between 21 and 91 years, with a mean age of 61.95 years (SD = 14.72).

The age of the patients from the second group – slowly developing processes leading to increased intracranial pressure, varies between 23 and 80 years, with a mean age of 59.14 years (SD = 18.19).

The age of the patients from the third group – patients admitted to the intensive care unit, in a coma of unknown cause, varies between 22 and 87 years, with a mean age of 68.43 years (SD = 18.02).

The age of the patients from the fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, varies between 21 and 64 years, with a mean age of 47 years (SD = 12.12).

The age of the patients in the control group varied between 43 and 68 years, with a mean age of 58.21 years (SD = 6.02).

The descriptive statistics of age in each studied group are presented in *Table 1*. *Figure 15* shows a graphic representation of the mean age values in the studied groups.

A statistically significant difference was established in the age of the patients from each group (F = 5,869, p < .001). According to the applied post-hoc test, the age difference was statistically significant between the first and fourth group (p = .001), the third and fourth group (p = .001) and the fourth and the control group (p = .032). In view of the subsequent analyzes that included the control group, we did not find a statistically significant difference in the age of the patients from the first and the control group (t = 1,562; p = .124), as well as between the second and control group (t = 0,189; p = .853).

Table 1. Descriptive age statistics in each studied group

Age

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Rapidly developing processes	43	61,95	14.721	2,245	57,42	66,48	21	91
Slowly developing processes	14	59,14	18,195	4,863	48,64	69,65	23	80
Patients in a coma	14	68,43	18,020	4,816	58,02	78,83	22	87
Brain dead patients	15	47,00	12,124	3,130	40,29	53,71	21	64

Controls	52	58,21	6,021	,835	56,54	59,89	43	68
Total	138	59,29	13,599	1,158	57,00	61,58	21	91

Figure 14 shows the percentage in the distribution of underlying diseases among the studied individuals. The main comorbidity in the study population was represented by hypertension, ischemic heart disease, diabetes mellitus, chronic heart failure and chronic obstructive pulmonary disease.

Figure 14 Distribution of underlying diseases among the studied individuals

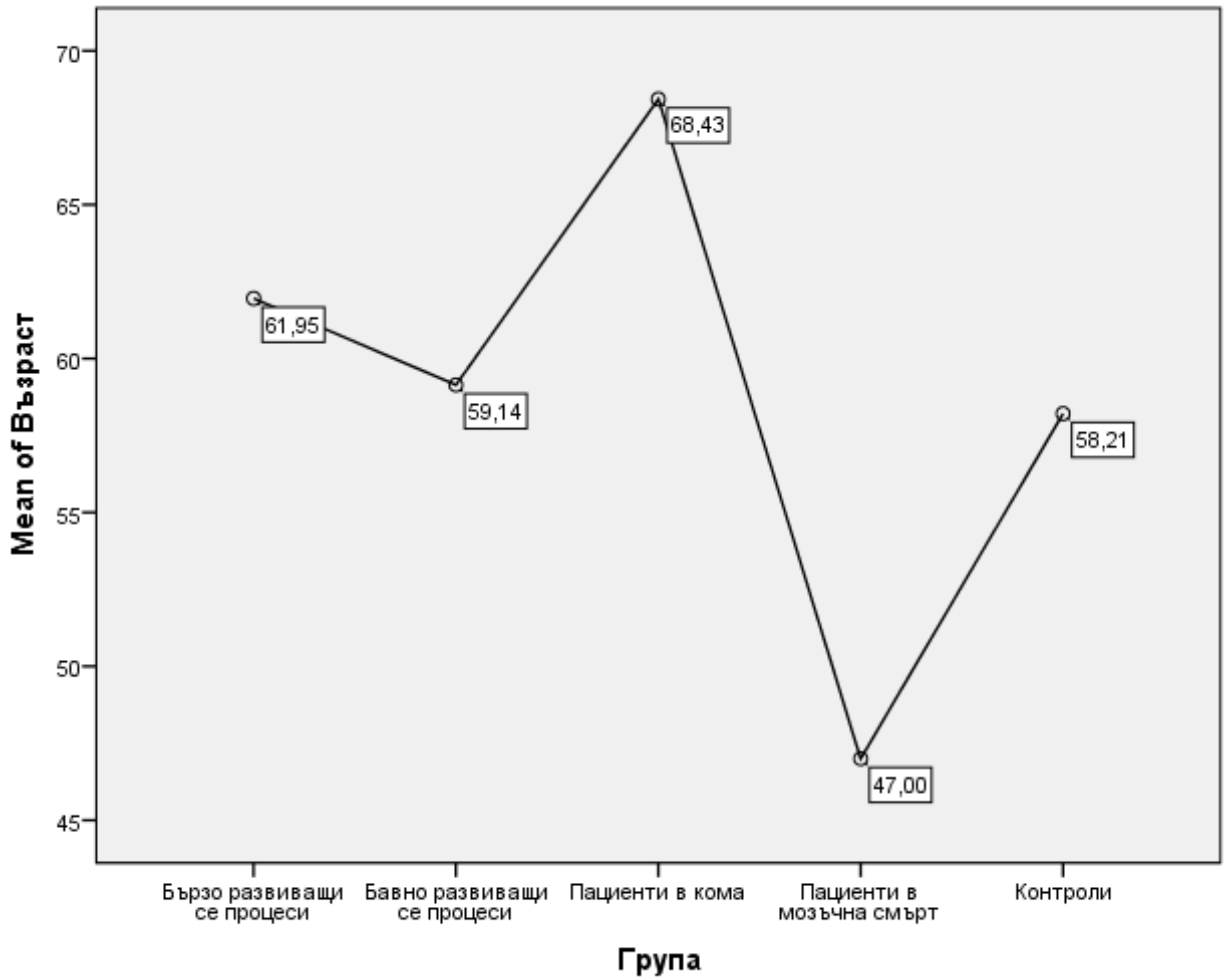

Figure 15. Graphics of the mean age in each studied group

5.2. Gender

The distribution of patients by gender is shown in Figure 16 and is as follows:

- First group: 26 (63,4%) males and 17 females
- Second group: 33 (57,9%) males and 24 females
- Third group: 8 (57,1%) males and 6 females
- Fourth group: 8 (53,3%) males and 7 females
- Control group: 27 (51,9%) males and 25 females

No statistically significant difference in the gender of the patients was found between the different studied groups (X^2 = 0,573; p = .903).

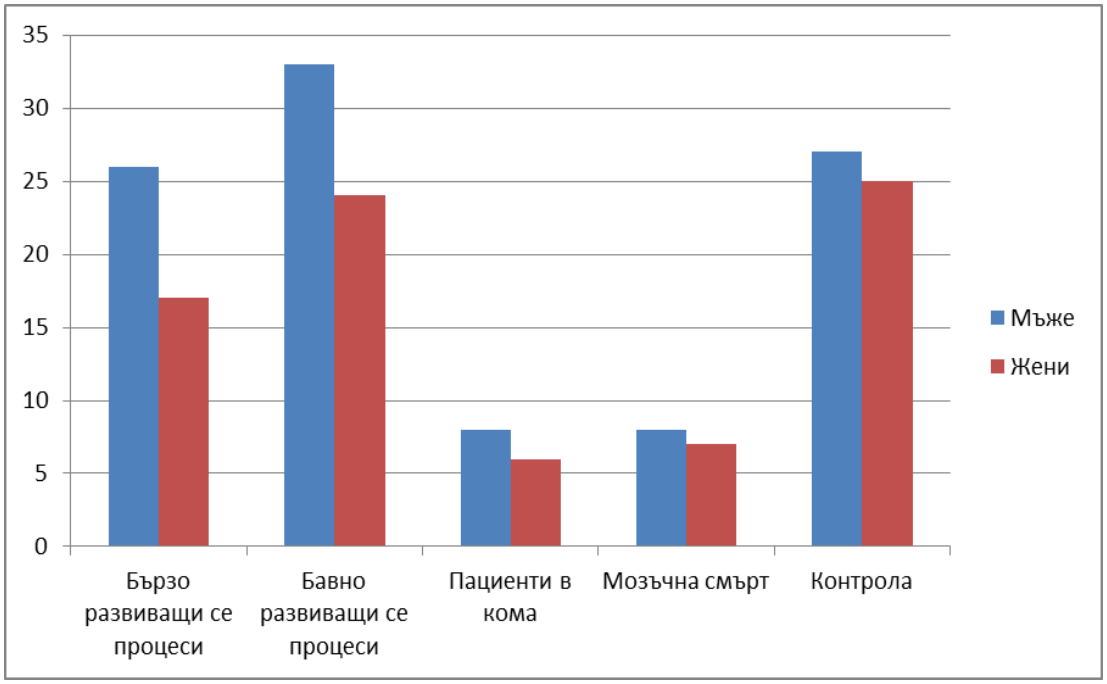

Figure 16. Gender distribution of patients in groups

In view of the subsequent analyzes that included the control group, we did not find any statistically significant differences between the gender of the patients from the first and the control group (X^2 = 0,696; p = .404), as well as between the second and the control group (X^2 = 0,016; p = .898); the third and the control group (X^2 = 0,121; p = .728); the fourth and the control group (X^2 = 0,009; p = .923).

No statistically significant difference was found in the ONSD dimensions of the measured optic nerves between men and women (for all groups .122 ≤ p ≤ .229)

5.3 Results from first US examination

5.3.1. Right eye US/Transverse plane

The measurements of the optic nerve via US of right eye/transverse plane for all studied groups, including the control group, followed a normal distribution (Shapiro-Wilk test: .077 ≤ p ≤ .731). Parametric tests are applied.

The measurement of the patients from the first group – rapidly developing processes leading to increased intracranial pressure (hematomas), varies between 5.9 and 7.6 mm, with a mean dimension of 6.71 years (SD = 0.363).

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure (tumors and hydrocephalus), varies between 6.0 and 7.2 mm, with a mean dimension of 6.61 mm (SD = 0.428).

The measurement of patients from the third group – patients admitted to the intensive care unit, in a coma of unknown origin, varies between 5.0 and 7.5 mm, with a mean dimension of 5.94 (SD = 0.738) mm.

The measurement of patients from the fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, varies between 5.9 and 8.1 mm, with a mean dimension of 7.12 (SD = 0.643) mm.

The lowest measurement values were from patients in the control group, which varied between 4.8 and 6.1 mm, with a mean dimension of 5.41 (SD = 0.31) mm.

The descriptive measurement statistics are outlined in Table 2 and Figure 17.

Table 2. Descriptive characteristics of ONSD measurements of R.E/T. P. Upon first examination in the different groups

US R.E./T. P. First examination

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Mini-mum	Maxi-mum
					Lower Bound	Upper Bound		
Rapidly developing processes	43	6,714	,3629	,0553	6,602	6,826	5,9	7,6
Slowly developing processes	14	6,614	,4276	,1143	6.367	6.861	6.0	7.2
Patients in a coma	14	5.936	,7376	,1971	5.510	6.362	5.0	7.5
Brain dead patients	15	7.120	,6428	,1660	6.764	7.476	5.9	8.1
Controls	52	5.408	,3105	,0431	5.321	5.494	4.8	6.1
Total	138	6.177	,7909	,0673	6.044	6.310	4.8	8.1

A statistically significant difference was established when measuring the optic nerve among the observed groups (F = 77,686; p = .001). After a post-hoc test, that difference turned out to be statistically significant (.001 ≤ p ≤ .025) for all comparisons between the groups, except for the measurements between the first and second group (p = 1.0).

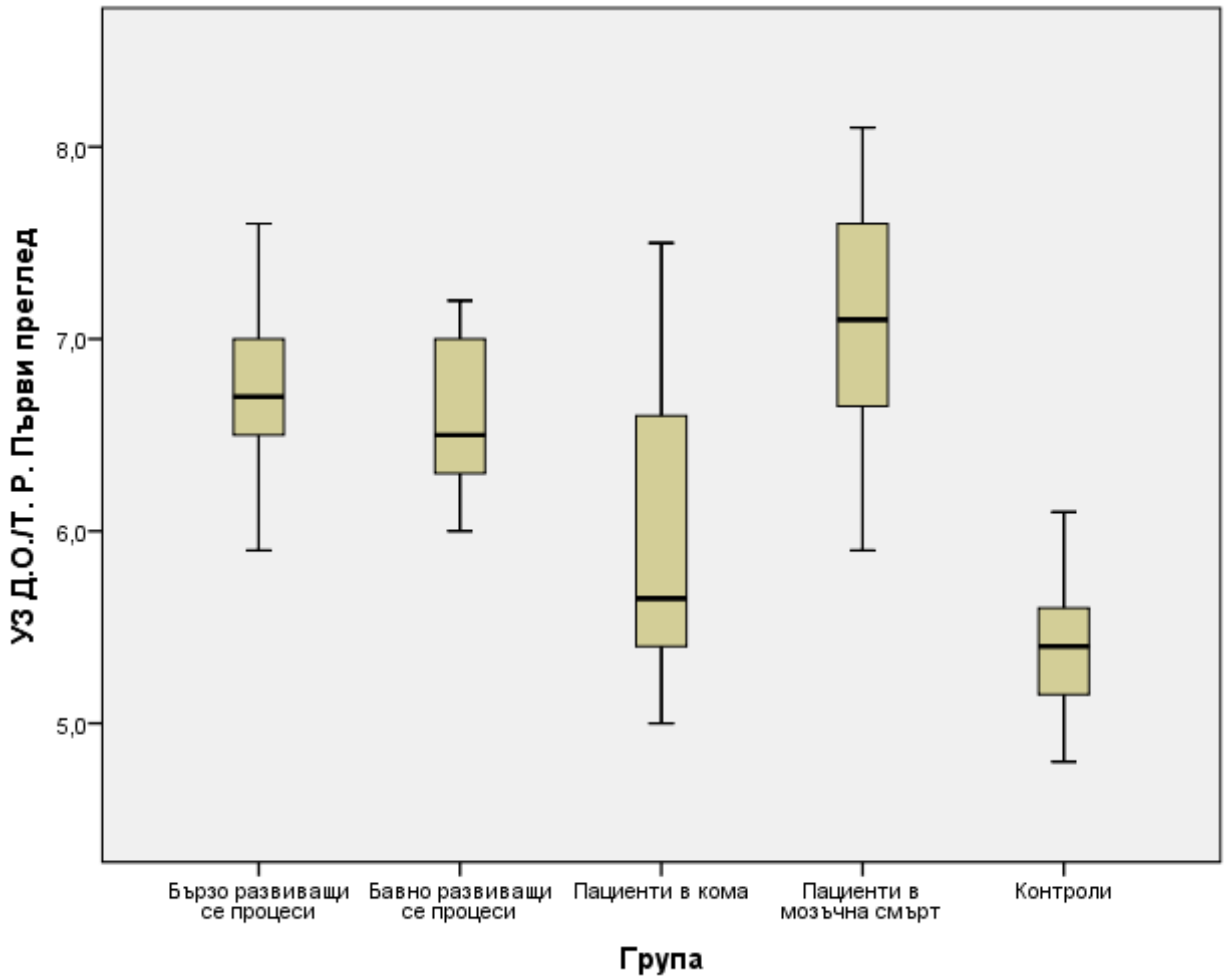

Figure 17. Descriptive statistics of ONSD measurements of R.E./T P. Upon first examination in the different groups

Figure 18 shows a diagram of the mean values of ONSD measurements of R.E./T. P. upon first examination, for each of the examined groups.

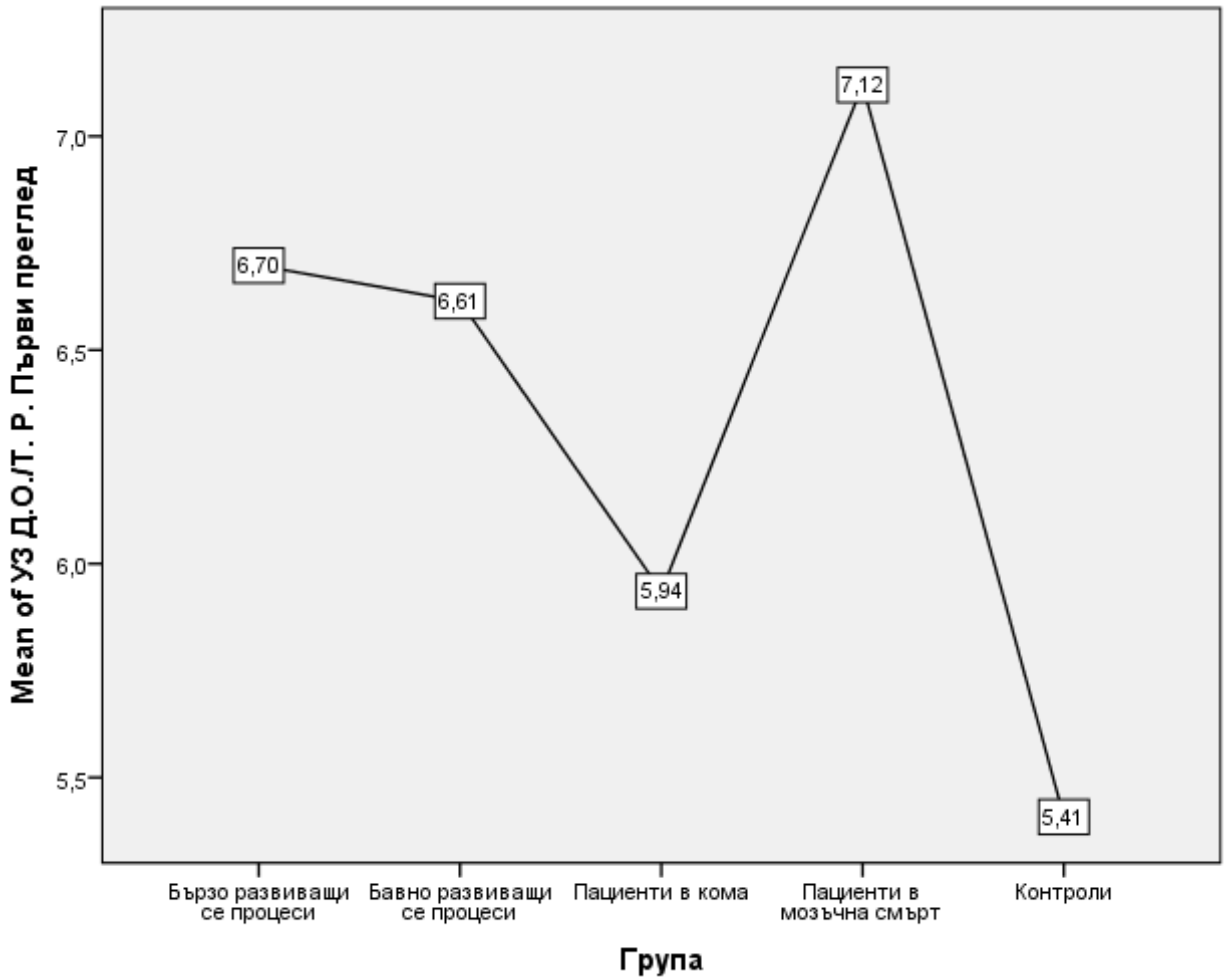

Figure 18. Diagram showing mean measurement values of ONSD of R.E./T. P. upon first examination in the compared groups

5.3.2. US left eye/Transverse plane

The measurements of the optic nerve via US of left eye/transverse plane for all studied groups, including the control group, followed a normal distribution (Shapiro-Wilk test, $16 \leq p \leq .3$). Parametric tests are applied.

The measurement of the patients from the first group – rapidly developing processes leading to increased intracranial pressure, varies between 6.1 and 7.5 mm, with a mean dimension of 6.72 (SD = 0.302) mm.

The measurement of the patients from the second group – slowly developing processes, leading to increased intracranial pressure, varies between 6,2 and 7,7 mm, with a mean dimension of 6,75 (SD = 0.39) mm.

The measurement of patients from the third group – patients admitted to the intensive care unit, in a coma of unknown origin, varies between 5.0 and 7.8 mm, with a mean dimension of 5.96 (SD = 0.767) mm.

The measurement of patients from the fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, varies between 5.9 and 8.1 mm, with a mean dimension of 7.18 (SD = 0.638) mm.

The lowest measurement values were from patients in the control group, which varied between 4.8 and 6.1 mm, with a mean dimension of 5.44 (SD = 0.329) mm.

The descriptive measurement statistics are outlined in Table 3 and Figure 19.

Table 3. Descriptive characteristics of ONSD measurements of L.E./T.P. at first examination in each group

US of L.E./T.P. First examination

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Rapidly developing processes	43	6.716	,3015	,0460	6.623	6.809	6.1	7.5
Slowly developing processes	14	6.750	,3898	,1042	6.525	6.975	6.2	7.7
Patients in a coma	14	5.957	,7673	,2051	5.514	6.400	5.0	7.8
Brain dead patients	15	7.180	,6383	,1648	6.827	7.533	5.9	8.1
Controls	52	5.438	,3291	,0456	5.347	5.530	4.8	6.1
Total	138	6.212	,7911	,0673	6.078	6.345	4.8	8.1

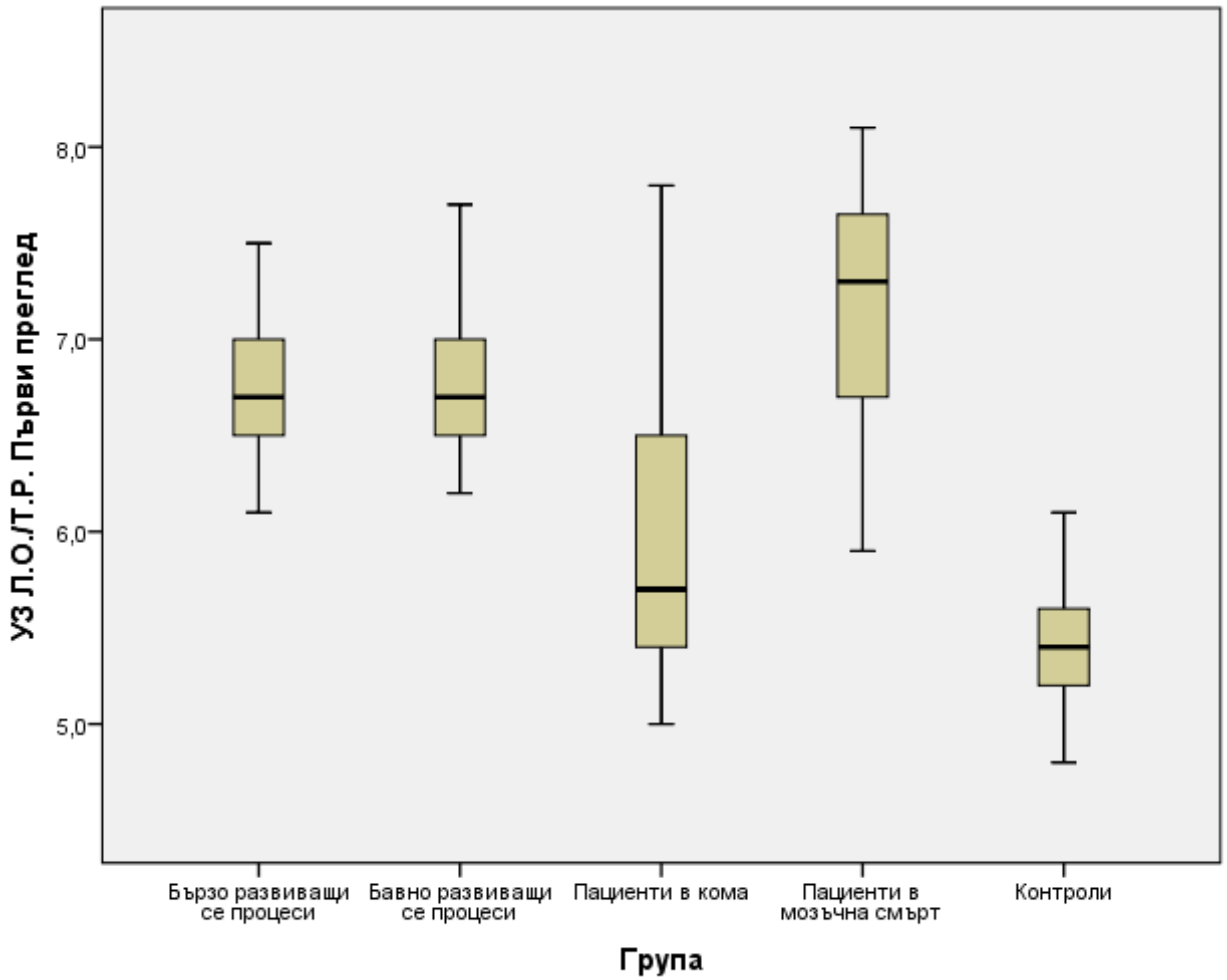

Figure 19. Descriptive statistics of ONSD of L.E./T.P. at first examination in each group

A statistically significant difference was established when measuring the optic nerve among the observed groups ($F = 82.288$; $p = .001$). After a post-hoc test, that difference turned out to be statistically significant ($.001 \leq p \leq .005$) for all comparisons between the groups, except for the measurements between the first and second group ($p = 1.0$) and the second and fourth group ($p = .081$).

Figure 20 shows a diagram of the ONSD dimensions mean values of the L.E./T.P. at first examination, for each examined group.

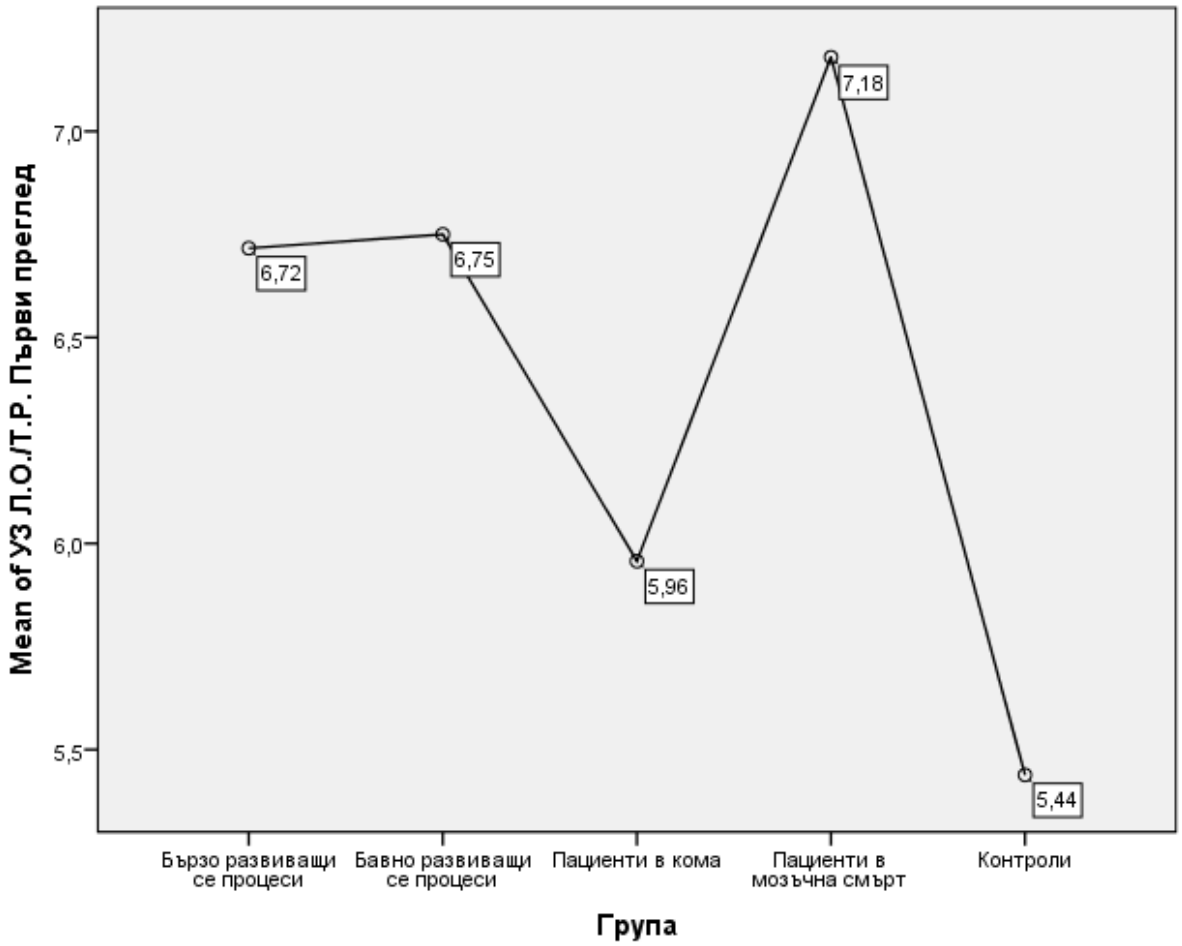

Figure 20. Diagram of the mean ONSD measurements of L.E./T.P. at first examination of the groups

5.3.3. Right eye US/Sagittal plane

The measurements of the optic nerve via US of right eye/sagittal plane for all studied groups, including the control group, followed a normal distribution (Shapiro-Wilk test: $.13 \leq p \leq .63$). Parametric tests are applied.

The measurement of the patients from the first group – rapidly developing processes leading to increased intracranial pressure (hematomas), varies between 5.7 and 7.5 mm, with a mean dimension of 6.65 (SD = 0.36) mm.

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure (tumors and hydrocephalus), varies between 6.0 and 7.1 mm, with a mean dimension of 6.57 (SD = 0.401) mm.

The measurement of patients from the third group – patients admitted to the intensive care unit, in a coma of unknown origin, varies between 4.9 and 7.5 mm, with a mean dimension of 5.83 (SD = 0.755) mm.

The measurement of patients from the fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, varies between 5.8 and 8.0 mm, with a mean dimension of 7.06 (SD = 0.623) mm.

The lowest measurement values were from patients in the control group, which varied between 4.8 and 6.0 mm, with a mean dimension of 5.37 (SD = 0.293) mm.

The descriptive measurement statistics are outlined in Table 4 and Figure 21.

Table 4. Descriptive characteristics of ONSD measurements of R.E./S.P. at first examination in each group

US of R.E./S.P. at first examination

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Mini-mum	Maxi-mum
					Lower Bound	Upper Bound		
Rapidly developing processes	43	6.651	,3595	,0548	6.541	6.762	5.7	7.5
Slowly developing processes	14	6.571	,4008	,1071	6.340	6.803	6.0	7.1
Patients in a coma	14	5.829	,7549	,2018	5.393	6.264	4.9	7.5
Brain dead patients	15	7.060	,6231	,1609	6.715	7.405	5.8	8.0
Controls	52	5.369	,2927	,0406	5.288	5.451	4.8	6.0
Total	138	6.121	,7806	,0664	5.990	6.252	4.8	8.0

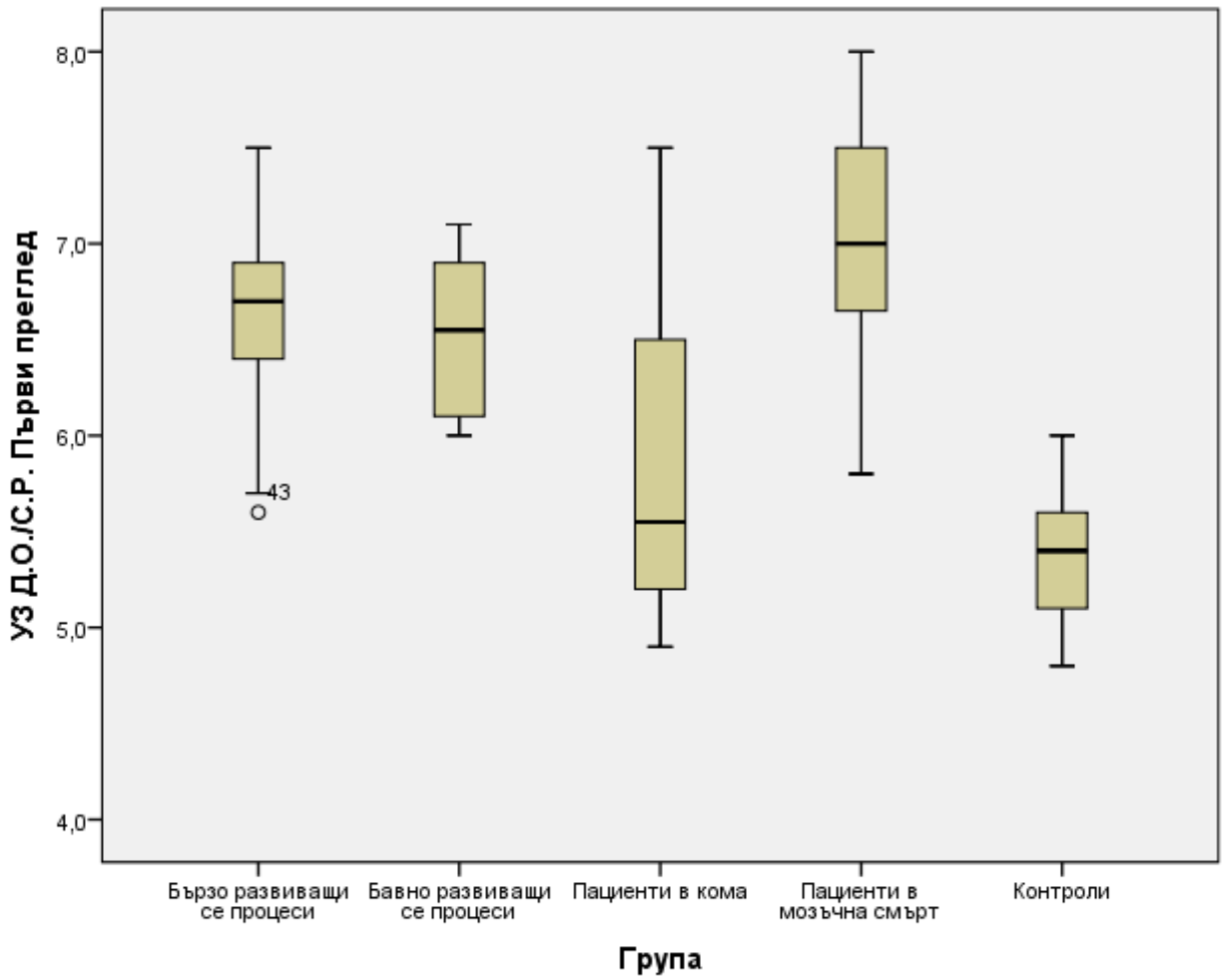

Figure 21. Descriptive statistics of ONSD of R.E./S.P. at first examination in each group

A statistically significant difference was established when measuring the optic nerve among the observed groups ($F = 78.97$; $p = .001$). After a post-hoc test, that difference turned out to be statistically significant ($.001 \leq p \leq .028$) for all comparisons between the groups, except for the measurements between the first and second group ($p = 1.0$).

Figure 22 shows a diagram of the ONSD dimensions mean values of the R.E./S.P. at first examination, for each examined group.

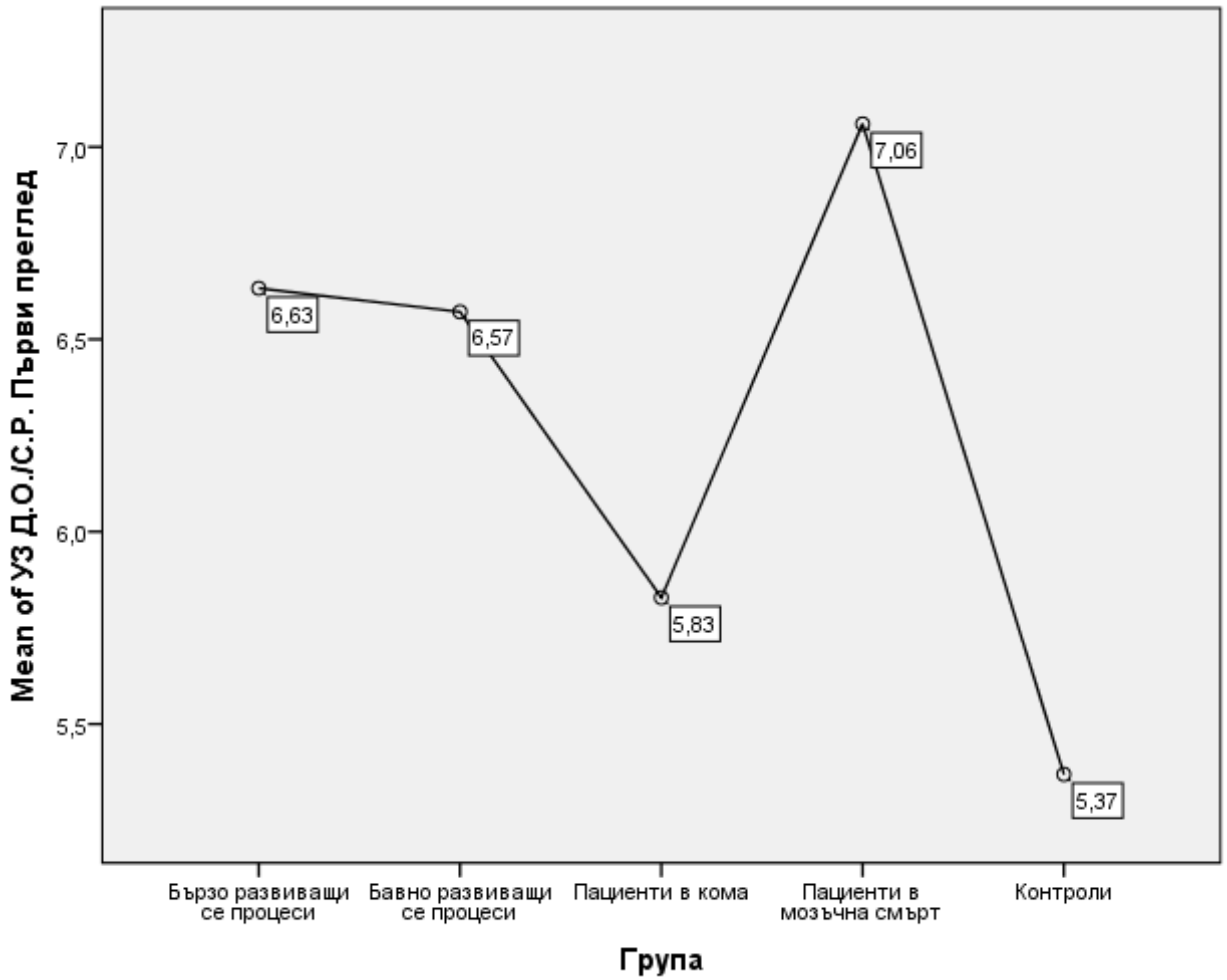

Figure 22. Diagram of the mean ONSD values of R.E./S.P. at first examination of the compared groups

5.3.4. Left eye US/Sagittal plane

The measurements of the optic nerve via US of left eye/sagittal plane for all studied groups, including the control group, followed a normal distribution (Shapiro-Wilk test: $.19 \leq p \leq .65$). Parametric tests are applied.

The measurement of the patients from the first group – rapidly developing processes leading to increased intracranial pressure (hematomas), varies between 6.0 and 7.6 mm, with a mean dimension of 6.65 (SD = 0.292) mm.

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure (tumors and hydrocephalus), varies between 6.0 and 7.1 mm, with a mean dimension of 6.62 (SD = 0.351) mm.

The measurement of patients from the third group – patients admitted to the intensive care unit, in a coma of unknown origin, varies between 4.9 and 7.6 mm, with a mean dimension of 5.81 (SD = 0.747) mm.

The measurement of patients from the fourth group – patients with proven brain death, confirmed by a 4-vessel cerebral angiography, varies between 5.9 and 8.0 mm, with a mean dimension of 7.11 (SD = 0.619) mm.

The measurement values for patients in the control group varied between 4.8 and 6.0 mm, with a mean dimension of 5.38 (SD = 0.306) mm.

The descriptive measurement statistics are outlined in Table 5 and Figure 23.

Table 5. Descriptive characteristics of ONSD measurements of L.E./S.P. at first examination in each group

US of L.E./S.P. First examination

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Mini-mum	Maxi-mum
					Lower Bound	Upper Bound		
Rapidly developing processes	43	6.647	,2922	,0446	6.557	6.736	6.0	7.5
Slowly developing processes	14	6.621	,3512	,0939	6.419	6.824	6.0	7.1
Patients in a coma	14	5.814	,7472	,1997	5.383	6.246	4.9	7.6
Brain dead patients	15	7.107	,6193	,1599	6.764	7.450	5.9	8.0
Controls	52	5.377	,3059	,0424	5.292	5.462	4.8	6.0
Total	138	6.131	,7766	,0661	6.000	6.262	4.8	8.0

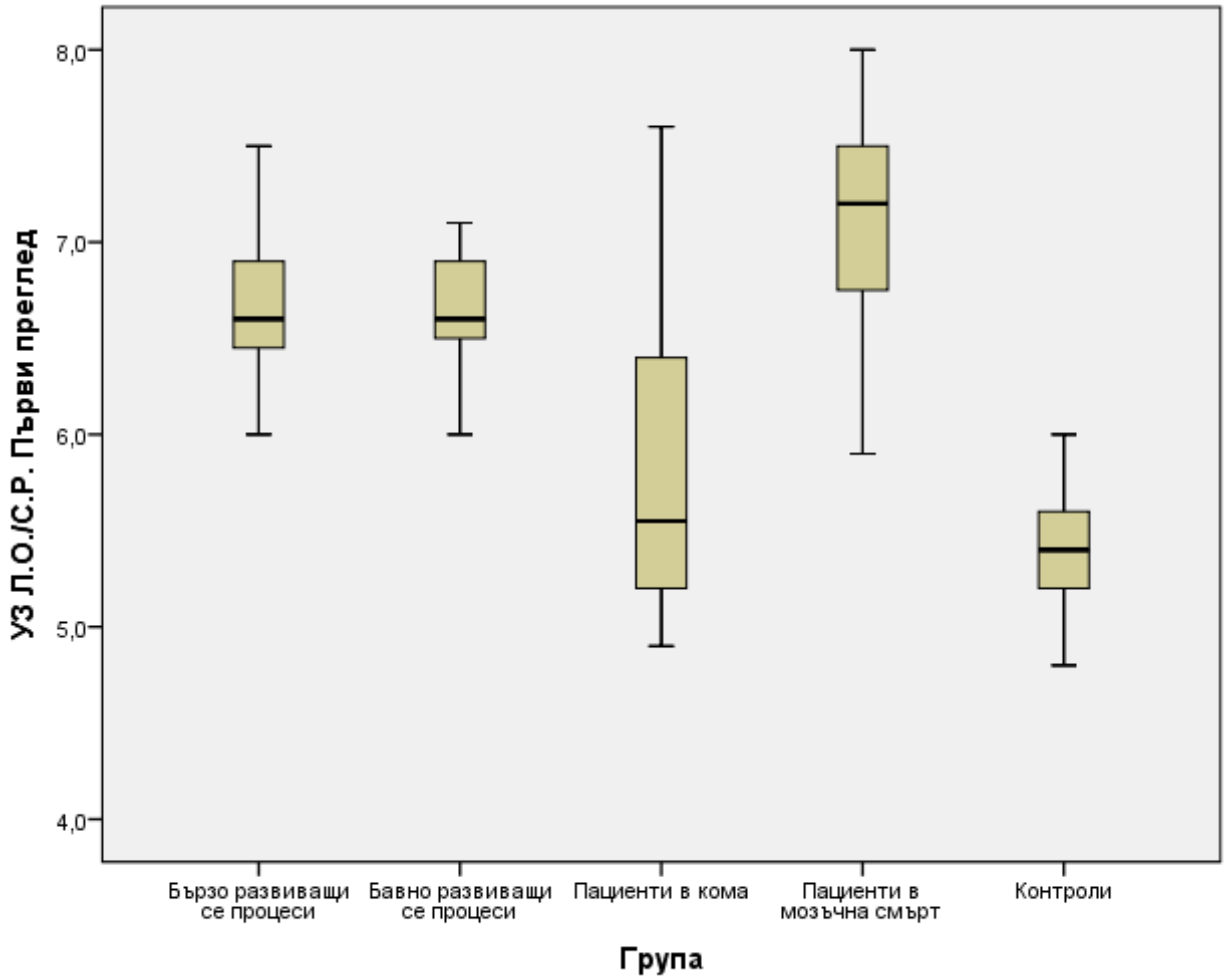

Figure 23. Descriptive statistics of ONSD measurements of L.E./S.P. at first examination in each group

A statistically significant difference was established when measuring the optic nerve among the observed groups ($F = 88.385$; $p = .001$). After a post-hoc test, that difference turned out to be statistically significant ($.001 \leq p \leq .019$) for all comparisons between the groups, except for the measurements between the first and second group ($p = 1.0$).

Figure 24 shows a diagram of the ONSD dimensions mean values of the L.E./S.P. at first examination, for each examined group.

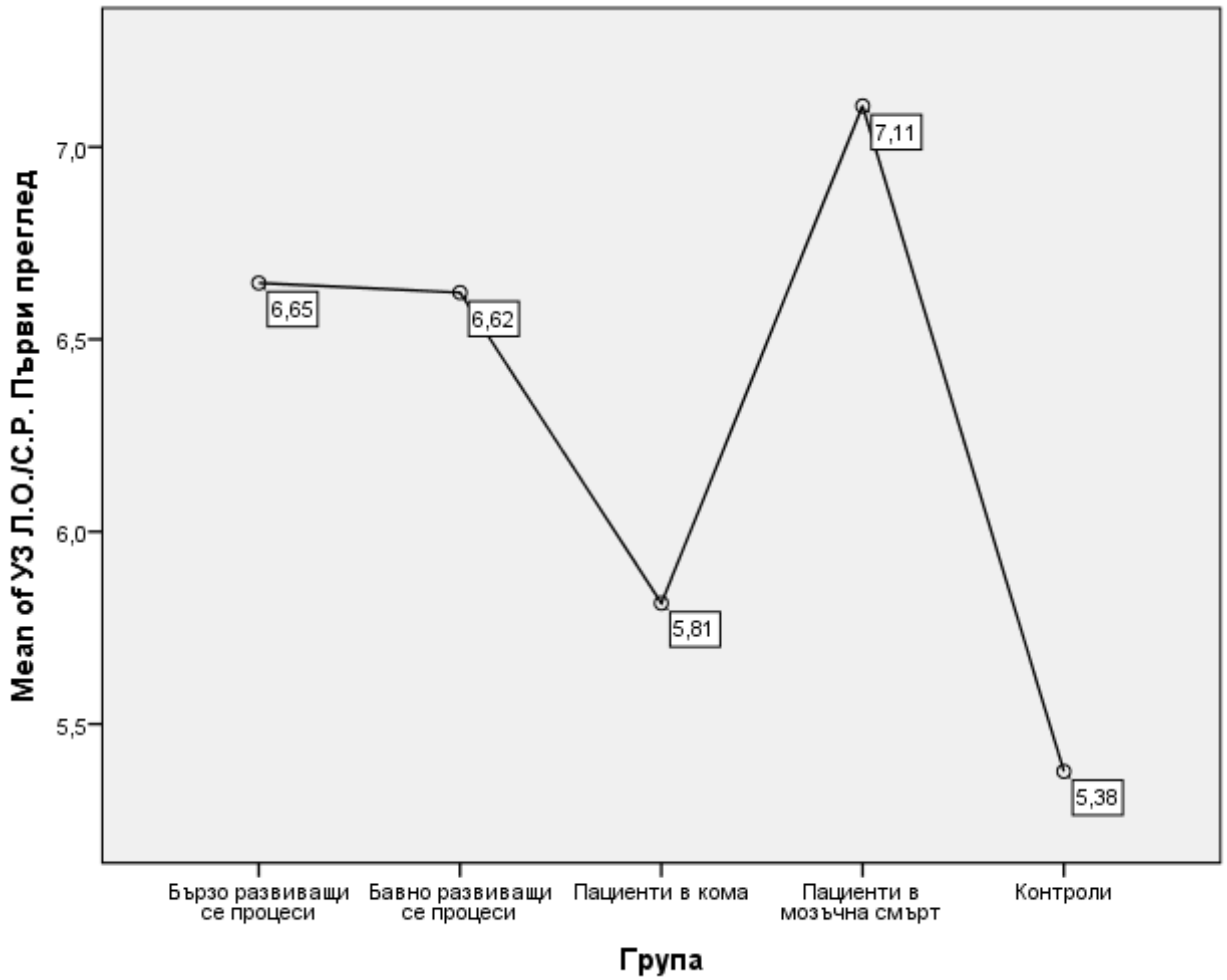

Figure 24. Diagram of the mean ONSD values of R.E./S.P. at first examination of the compared groups

No statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the first group and the patients in the second group. For all comparisons p > ,05.

A statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the first group and the patients in the second group (coma). The measurements values from the patients in the third group are statistically significantly lower than those of the patients in the first group, as follows:

- Right eye / transverse plane – with 0,78 mm on average (t = 3,801; p = .002)
- Left eye / transverse plane – with 0,76 mm on average (t = 3,612; p = .003)
- Right eye / sagittal plane – with 0,82 mm on average (t = 3,934; p = .001)

- Left eye / sagittal plane – with 0,83 mm on average (t = 4.068; p = .001)

A statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the first group and the patients in the fourth group (brain dead). The measurements values from the patients in the fourth group are statistically significantly higher than those of the patients in the first group, as follows:

- Right eye / transverse plane – with 0,41 mm on average (t = 2.321; p = .033)
- Left eye / transverse plane – with 0,46 mm on average (t = 2.710; p = .015)
- Right eye / sagittal plane – with 0,41 mm on average (t = 2,405; p = .028)
- Left eye / sagittal plane – with 0,46 mm on average (t = 2,772; p = .013)

A statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the second group and the patients in the third group (coma). The measurements values from the patients in the second group are statistically significantly higher than those of the patients in the third group, as follows:

- Right eye / transverse plane – with 0,68 mm on average (t = 2.978; p = .007)
- Left eye / transverse plane – with 0,79 mm on average (t = 3,447; p = .003)
- Right eye / sagittal plane – with 0,74 mm on average (t = 3,252; p = .004)
- Left eye / sagittal plane – with 0,81 mm on average (t = 3,658; p = .002)

A statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the second group and the patients in the fourth group (brain dead). The measurements values from the patients in the fourth group are statistically significantly higher than those of the patients in the first second group, as follows:

- Right eye / transverse plane – with 0,51 mm on average (t = 2.519; p = .019)
- Left eye / transverse plane – with 0,43 mm on average (t = 2,205; p = .0.38)
- Right eye / sagittal plane – with 0,49 mm on average (t = 2,528; p = .018)
- Left eye / sagittal plane – with 0,49 mm on average (t = 2,617; p = .016)

A statistically significant difference was found between the values of the initial measurements of the optic nerve of the patients in the third group (coma) and the patients in the fourth group (brain dead). The measurements values from the patients in the fourth group are statistically significantly higher than those of the patients in the third group, as follows:

- Right eye / transverse plane – with 0.18 mm on average (t = 4,618; p = .001)

- Left eye / transverse plane – with 1,22 mm on average (t = 4,678; p = .001)
- Right eye / sagittal plane – with 1,23 mm on average (t = 4,804; p = .001)
- Left eye / sagittal plane – with 1,29 mm on average (t = 5,086; p = .001)

Figure 25 shows a comparison of the initial measurements of the optic nerve in the different groups.

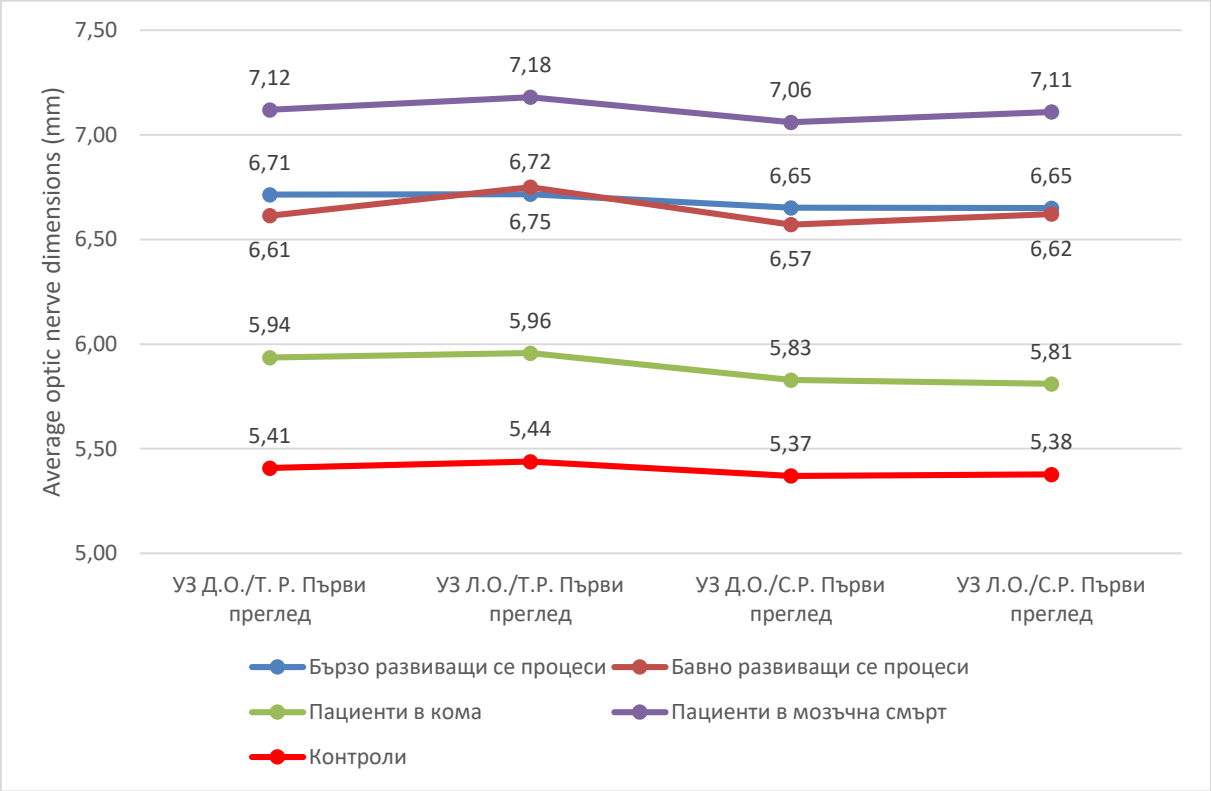

Figure 25 Comparison of the initial measurements of the optic nerve in the studied groups

5.3.5. Patients in a coma without established cause, admitted in the intensive care unit.

There are 14 patients from the third group, admitted in a coma (16.3%). Of them 8 (57,1%) are males and the other 6 are females. Their age varies between 22 and 87 years, with an average age of 68.4 years (SD = 18.02).

From the patients in the group, just 4 (figure 26) had a pathological finding from the head CT scan. One of them had a brain tumor, one had a subdural hematoma, and two of them had ischemic cerebral infarctions. In all four individuals, in all planes, the ONSD had dimensions above 6,5 mm.

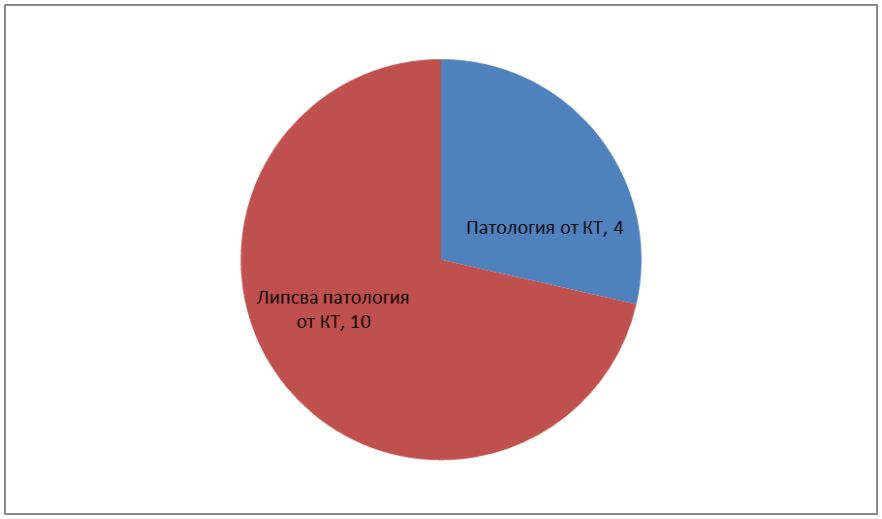

Figure 26 Distribution of third group patients according to the findings from the head CT scan.

The dimension of the optic nerve in ultrasound of the right eye / transverse plane varies from 5.0 to 7.5 mm, with the mean dimension being 5.94 (SD = .738) mm.

The dimensions of the optic nerve in ultrasound of the left eye / transverse plane varies from 5.0 to 7.8 mm, the mean dimension is 5.96 (SD = .768) mm.

The dimension of the optic nerve in ultrasound of the right eye / sagittal plane varies from 4.9 to 7.5 mm, with the mean dimension being 5.83 (SD = .755) mm.

The dimension of the optic nerve in ultrasound of the left eye / sagittal plane varies from 4.9 to 7.6 mm, with the mean dimension being 5.81 (SD = .747) mm.

Figure 27 shows the mean dimensions in both planes.

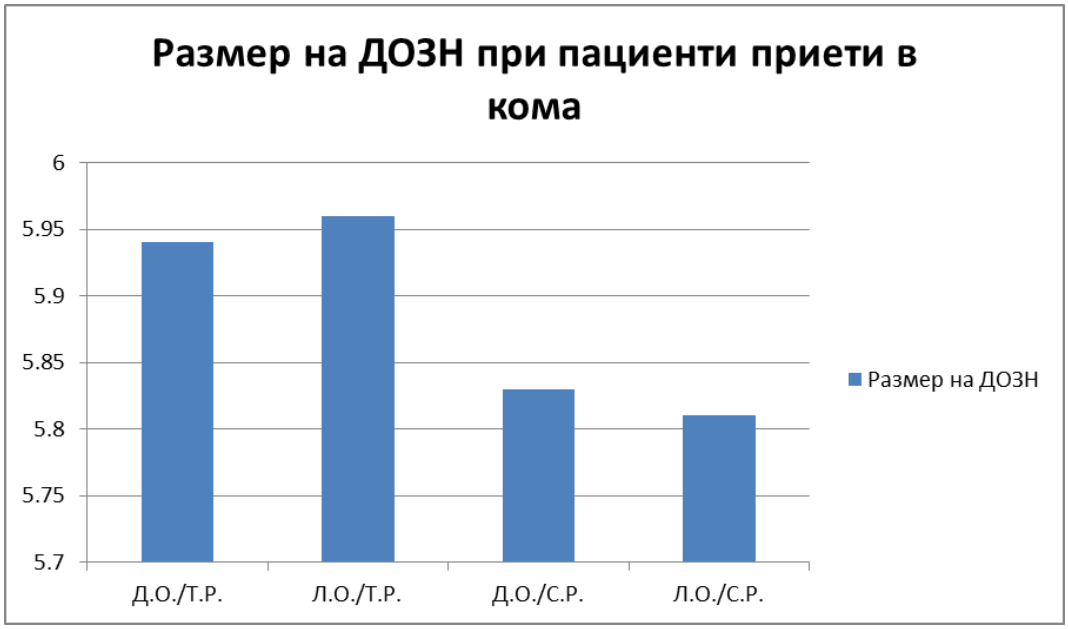

Figure 27 Average dimensions of ONSD in patients, admitted in a coma

The descriptive measurement statistics are outlined in Figure 28.

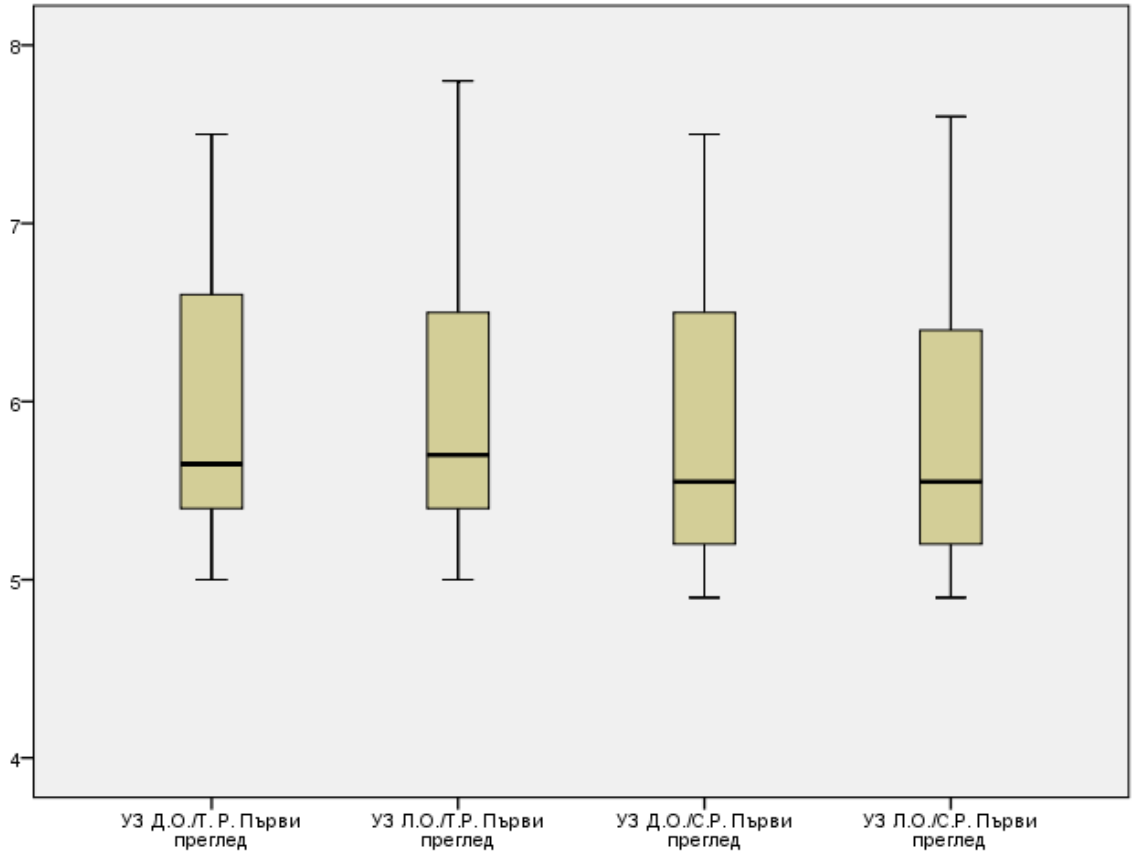

Figure 28 Descriptive measurement statistics of the optic nerve in patients admitted in a coma.

Measurements follow a normal distribution (Shapiro-Wilk test, for all, 214> p>, 179. Parametric tests are applied.

5.3.6. Brain dead patients

The brain dead patients are 15 (17,4%). Seven (46,7%) of them are males and the other 8 are females. Their age varies between 21 and 64 years, with an average age of 47 years (SD = 12.12).

The dimension of the optic nerve in ultrasound of the right eye / transverse plane varies from 5.9 to 8.1 mm, with the mean dimension being 7.12 (SD = .643) mm.

The dimensions of the optic nerve in ultrasound of the left eye / transverse plane varies from 5.9 to 8.1 mm, the mean dimension is 7.18 (SD = .638) mm.

The dimension of the optic nerve in ultrasound of the right eye / sagittal plane varies from 5.8 to 8.0 mm, with the mean dimension being 7.06 (SD = .623) mm.

The dimension of the optic nerve in ultrasound of the left eye / sagittal plane varies from 5.9 to 8.0 mm, with the mean dimension being 7.11 (SD = .619) mm.

The descriptive measurement statistics are outlined in Figure 29.

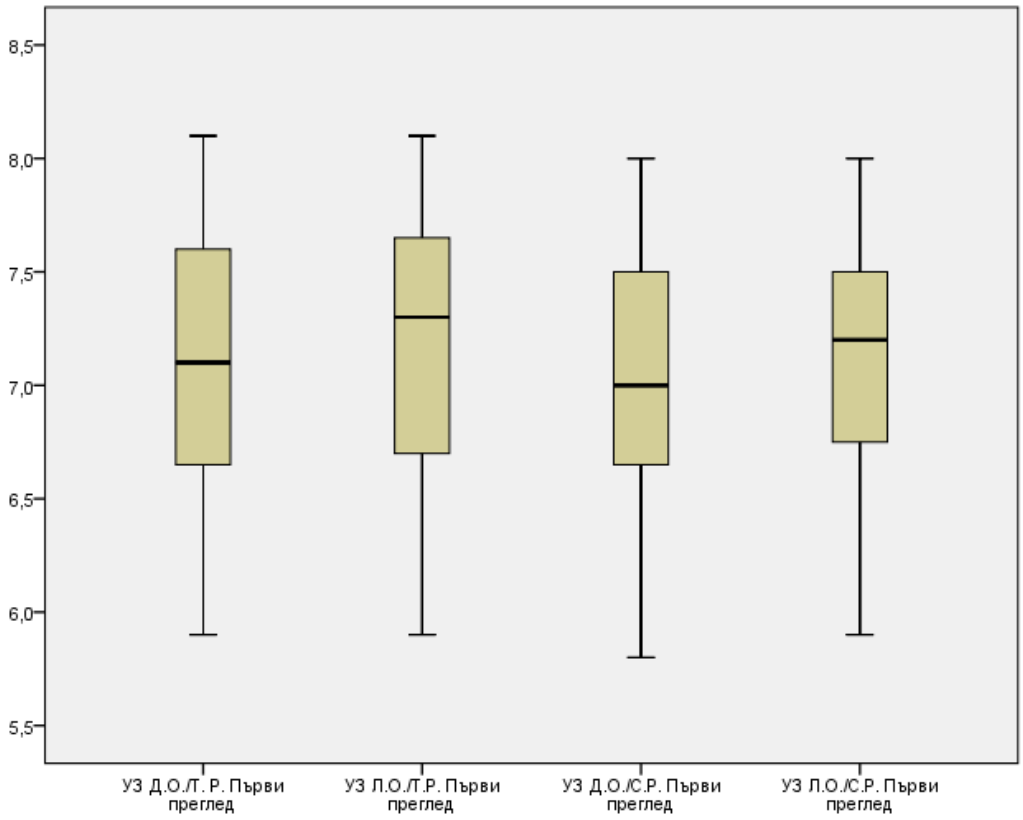

Figure 29 Descriptive measurement statistics of the optic nerve in patients admitted brain dead.

Measurements follow a normal distribution (Shapiro-Wilk test, for all, 731> p>, 448. Parametric tests are applied.

5.4. Comparison between the measurements in the studied groups and the control group

The following dimensions (Figure 30) of the optic nerve were found in the patients from the control group:

The dimension of the optic nerve in ultrasound of the right eye / transverse plane varies from 4.8 to 6.1 mm, with the mean dimension being 5.41 (SD = .310) mm.

The dimensions of the optic nerve in ultrasound of the left eye/transverse plane varies from 4.8 to 6.1 mm, the mean dimension is 5.44 (SD = .329) mm.

The dimension of the optic nerve in ultrasound of the right eye / sagittal plane varies from 4.8 to 6.0 mm, with the mean dimension being 5.37 (SD = .293) mm.

The dimension of the optic nerve in ultrasound of the left eye / sagittal plane varies from 4.8 to 6.0 mm, with the mean dimension being 5.38 (SD = .306) mm.

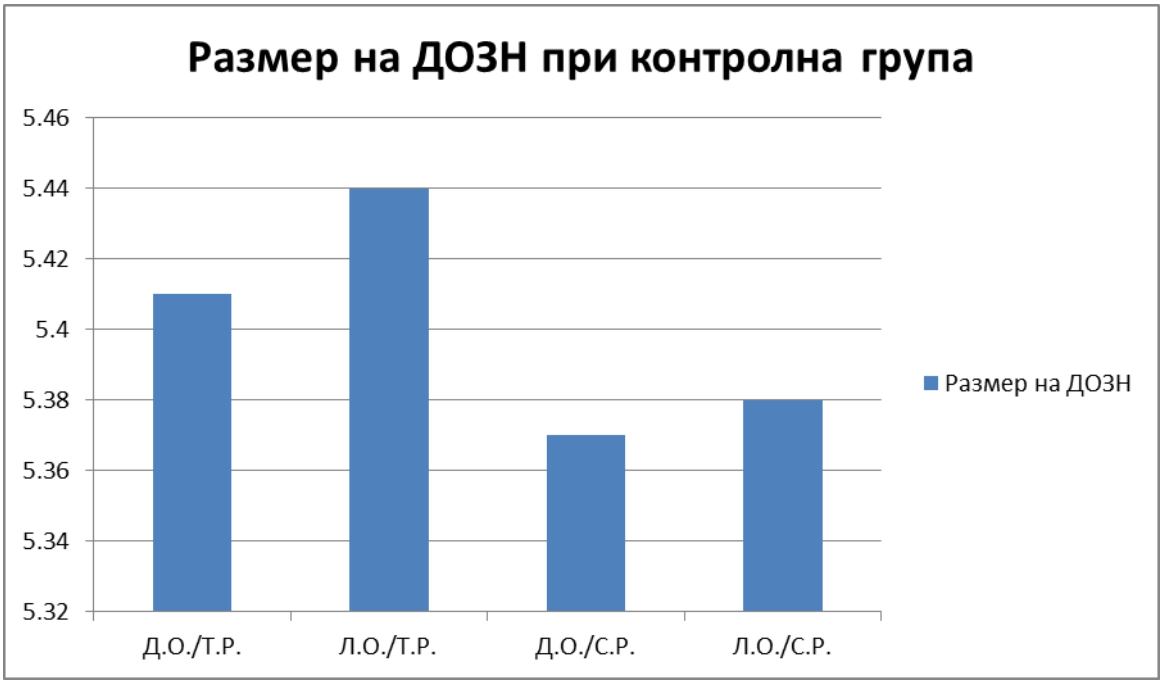

Figure 30 Mean ONSD dimensions in the control group

A statistically significant difference was found between the primary measurements of the optic nerve in the first group of patients – rapidly developing processes, leading to increased intracranial pressure, and the control group patients. The measurements values from the patients in the control group are lower than those of the patients in the first group, as follows:

- Right eye / transverse plane – with 1.3 mm on average ($t = 18,907$; $p < .001$)

- Left eye / transverse plane – with 1,28 mm on average ($t = 19,560$; $p < .001$)

- Right eye / sagittal plane – with 1,28 mm on average ($t = 19,161$; $p < .001$)

- Left eye / sagittal plane – with 1,27 mm on average ($t = 20,544$; $p < .001$)

A statistically significant difference was found between the primary measurements of the optic nerve in the second group of patients – slowly developing processes, leading to increased intracranial pressure, and the control group patients. The measurements values from the patients in the control group are lower than those of the patients in the second group, as follows:

- Right eye / transverse plane – with 1.2 mm on average ($t = 9,88$; $p < .001$)

- Left eye / transverse plane – with 1,31 mm on average ($t = 12,726$; $p < .001$)

- Right eye / sagittal plane – with 1,2 mm on average ($t = 10,494$; $p < .001$)

- Left eye / sagittal plane – with 1,24 mm on average ($t = 13,095$; $p < .001$)

A statistically significant difference was found between the optic nerve measurement values of patients in the third group – patients admitted to the ICU in a coma, without a clear cause, and the patients from the control group. The measurements values from the patients in the control group are lower than those of the patients in the third group, as follows:

- Right eye / transverse plane – with 0.53 mm on average ($t = 2,617$; $p = .02$)

- Left eye / transverse plane – with 0.52 mm on average ($t = 2,469$; $p = .027$)

- Right eye / sagittal plane – with 0.46 mm on average ($t = 2,232$; $p = .042$)

- Left eye / sagittal plane – with 0.44 mm on average ($t = 2,142$; $p = ,049$)

A statistically significant difference was found between the primary measurements of the optic nerve in the fourth group of patients –patients with proven brain death, confirmed by a 4-vessel cerebral angiography, and the control group patients. The measurements values from the patients in the control group are lower than those of the patients in the fourth group, as follows:

- Right eye / transverse plane – with 1.71 mm on average ($t = 9,987$; $p < .001$)

- Left eye / transverse plane – with 1,74 mm on average ($t = 10,184$; $p < .001$)

- Right eye / sagittal plane – with 1,69 mm on average ($t = 10,189$; $p < .001$)

- Left eye / sagittal plane – with 1,73 mm on average ($t = 10,456$; $p < .001$)

When comparing the measured dimensions of the optic nerve to the reference values of 5.5 – 5.9, which are the ones most frequently cited in the world literature and studies, we found a statistically significant difference between the measured dimensions of the optic nerve in the transverse plane and their reference values –5.4 mm ($t = 2,718$; $p =, 018$ for the right eye, and $t = 2,717$; $p =, 018$ for the left eye). No such difference was found in the sagittal plane measurements. The result is similar when comparing to the reference value of 5.5. The lowest reference value at which no statistically significant difference was found between the measured optic nerve dimensions and the reference value, is 5.6 mm ($,303 > p > ,105$ for all measurements).

5.5 Dimensions before and after craniectomy

Craniectomy was performed on 27 (62.8%) patients from the first examined group (rapidly developing processes, leading to increased intracranial pressure /hematomas/), and in all patients (14) from the second examined group (slowly developing processes, leading to increased intracranial pressure). Measurements of the optic nerve were performed prior to applying anesthesia (for group 2 those examinations coincided with the first examination) and immediately prior to extubation.

The measurements of the optic nerve via US for both studied groups, do not follow a normal distribution (Shapiro-Wilk test: $p < .05$). Non-parametric tests are applied – Wilcoxon Signed Ranks Test, for both dependent samples. A non-parametric coefficient for rank correlation of Spearman rank (rho) was used to establish the correlation dependence.

5.5.1. First group (rapidly developing processes, leading to increased intracranial pressure /hematomas/)

5.5.1.1. US of Right eye/Transverse plane

The optic nerve measurements of the patients from the first group – rapidly developing processes leading to increased intracranial pressure (hematomas), prior to application of anaesthesia, varies between 5.9 and 7.1 mm, with a mean dimension of 6.73 years (SD = 0.331). Immediately after extubation, the measurements varied between 5.9 and 6.7 mm, with a mean dimension of 6.29 (SD = 0.216) mm.

A statistically significant high correlation was found between the measurements of the optic nerve of the patients from the first group before and after the craniectomy and decompression (rho = 0.697; p <0.001), as well as a statistically significant difference in the measurements before and after surgery (z = -4,396 ; p <.001). The optic nerve dimensions were decreased by 0.45 mm on average.

5.5.1.2. US left eye/Transverse plane

The optic nerve measurements of the patients from the first group – rapidly developing processes leading to increased intracranial pressure (hematomas), prior to application of anaesthesia, varies between 6.2 and 7.3 mm, with a mean dimension of 6.73 years (SD = 0.288). Immediately prior to extubation, the measurements varied between 5.9 and 6.5 mm, with a mean dimension of 6.28 (SD = 0.204) mm.

A statistically significant moderate correlation was found between the measurements of the optic nerve of the patients from the first group before and after the craniectomy and decompression (rho = 0.530; p = 0.004), as well as a statistically significant difference in the measurements before and after surgery (z = -4,390 ; p <.001). The optic nerve dimensions were decreased by 0.45 mm on average.

5.5.1.3. Right eye US/Sagittal plane

The optic nerve measurements of the patients from the first group – rapidly developing processes leading to increased intracranial pressure, prior to application of anaesthesia, varies between 5.9 and 7.0 mm, with a mean dimension of 6.64 (SD = 0.326) mm. Immediately prior

to extubation, the measurements varied between 5.7 and 6.6 mm, with a mean dimension of 6.19 (SD = 0.224) mm.

A statistically significant high correlation was found between the measurements of the optic nerve of the patients from the first group before and after the craniectomy (rho = 0.623; p = 0.001), as well as a statistically significant difference in the measurements before and after surgery (z = -4,410; p <.001). The optic nerve dimensions were decreased by 0.45 mm on average.

5.5.1.4. Left eye US/Sagittal plane

The optic nerve measurements of the patients from the first group – rapidly developing processes leading to increased intracranial pressure, prior to application of anaesthesia, varies between 6.1 and 7.0 mm, with a mean dimension of 6.67 (SD = 0.283) mm. Immediately prior to extubation, the measurements varied between 5.8 and 6.6 mm, with a mean dimension of 6.19 (SD = 0.220) mm.

A statistically significant moderate correlation was found between the measurements of the optic nerve of the patients from the first group before and after the craniectomy and decompression (rho = 0.408; p = 0.035), as well as a statistically significant difference in the measurements before and after surgery (z = -4,326; p <.001). The optic nerve dimensions were decreased by 0.48 mm on average.

Figure 31 shows the changes in the optic nerve dimensions before and after neurosurgery to decompress and evacuate a pathological process and alleviate high ICP for patients in the first group.

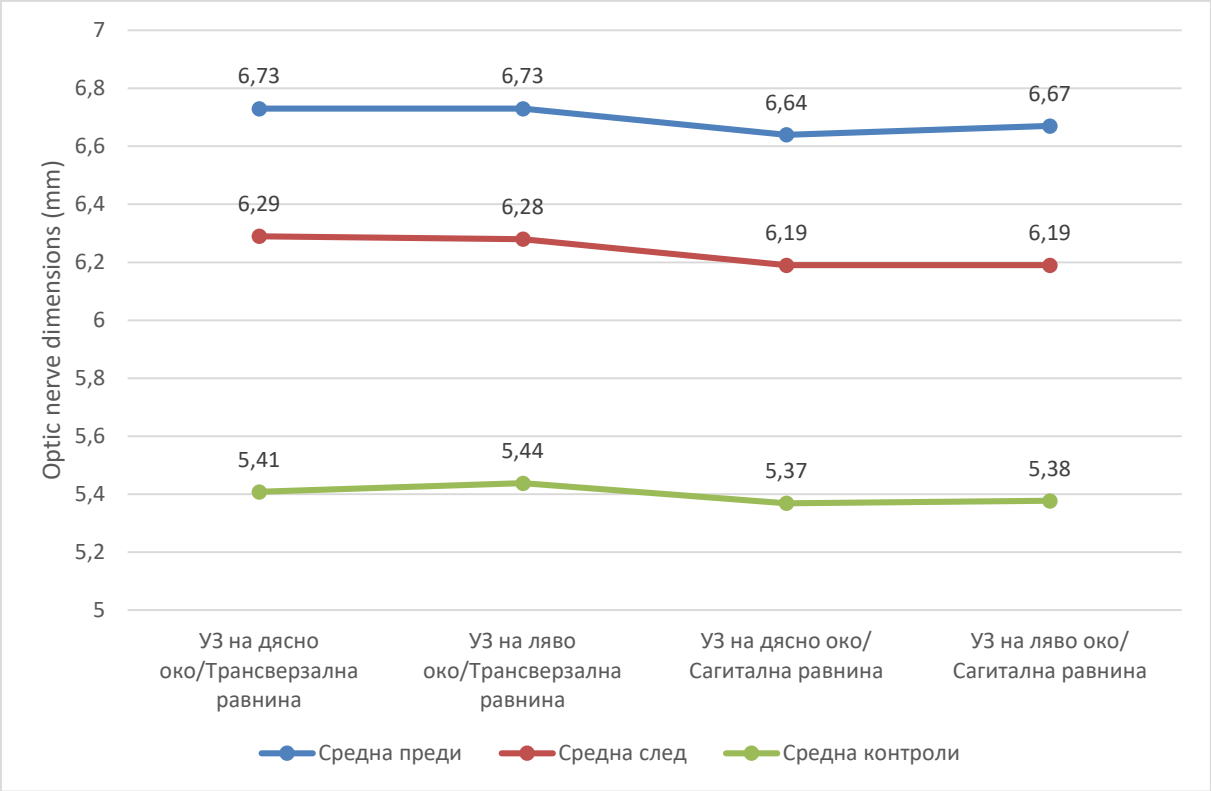

Figure 31. Changes in the dimension of the optic nerve before and after surgery for patients in the first group

5.5.2. Second group – slowly developing processes leading to increased intracranial pressure.

5.5.2.1. US of Right eye/Transverse plane

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure prior to applying anaesthesia varies between 6.0 and 7.2 mm, with a mean dimension of 6.61 mm (SD = 0.428). Immediately prior to extubation, the measurements varied between 5.9 and 6.3 mm, with a mean dimension of 6.14 (SD = 0.134) mm.

A statistically significant, extremely high correlation was found between the measurements of the optic nerve of the patients from the second group, before and after the craniectomy (rho = 0.623; p = 0.001), as well as a statistically significant difference in the measurements before and after surgery (z = - 3,088; p = .002). The optic nerve dimensions were decreased by 0.47 mm on average.

5.5.2.2. US left eye/Transverse plane

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure prior to applying anaesthesia varies between 6.2 and 7.7 mm, with a mean dimension of 6.75 mm (SD = 0.390). Immediately prior to extubation, the measurements varied between 5.9 and 6.4 mm, with a mean dimension of 6.16 (SD = 0.122) mm.

A statistically significant, high correlation was found between the measurements of the optic nerve of the patients from the second group, before and after the craniectomy (rho = 0.634; p = 0.015), as well as a statistically significant difference in the measurements before and after surgery (z = - 3,304; p = .001). The optic nerve dimensions were decreased by 0.59 mm on average.

5.5.2.3. Right eye US/Sagittal plane

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure prior to applying anaesthesia varies between 6.0 and 7.1 mm, with a mean dimension of 6.57 mm (SD = 0.401). Immediately prior to extubation, the measurements varied between 5.8 and 6.2 mm, with a mean dimension of 6.08 (SD = 0.133) mm.

A statistically significant, extremely high correlation was found between the measurements of the optic nerve of the patients from the second group, before and after the craniectomy (rho = 0.970; p < 0.001), as well as a statistically significant difference in the measurements before and after surgery (z = - 3,187; p = .001). The optic nerve dimension was decreased with 0.5 mm on average.

5.5.2.4. Left eye US/Sagittal plane

The measurement of patients from the second group – slowly developing processes leading to increased intracranial pressure prior to applying anaesthesia varies between 6.0 and 7.1 mm, with a mean dimension of 6.62 mm (SD = 0.351). Immediately prior to extubation, the measurements varied between 5.9 and 6.4 mm, with a mean dimension of 6.14 (SD = 0.139) mm.

A statistically significant, extremely high correlation was found between the measurements of the optic nerve of the patients from the second group, before and after the craniectomy (rho = 0.908; p < 0.001), as well as a statistically significant difference in the

measurements before and after surgery (z = - 3,186; p = .001). The optic nerve dimensions were decreased by 0.48 mm on average.

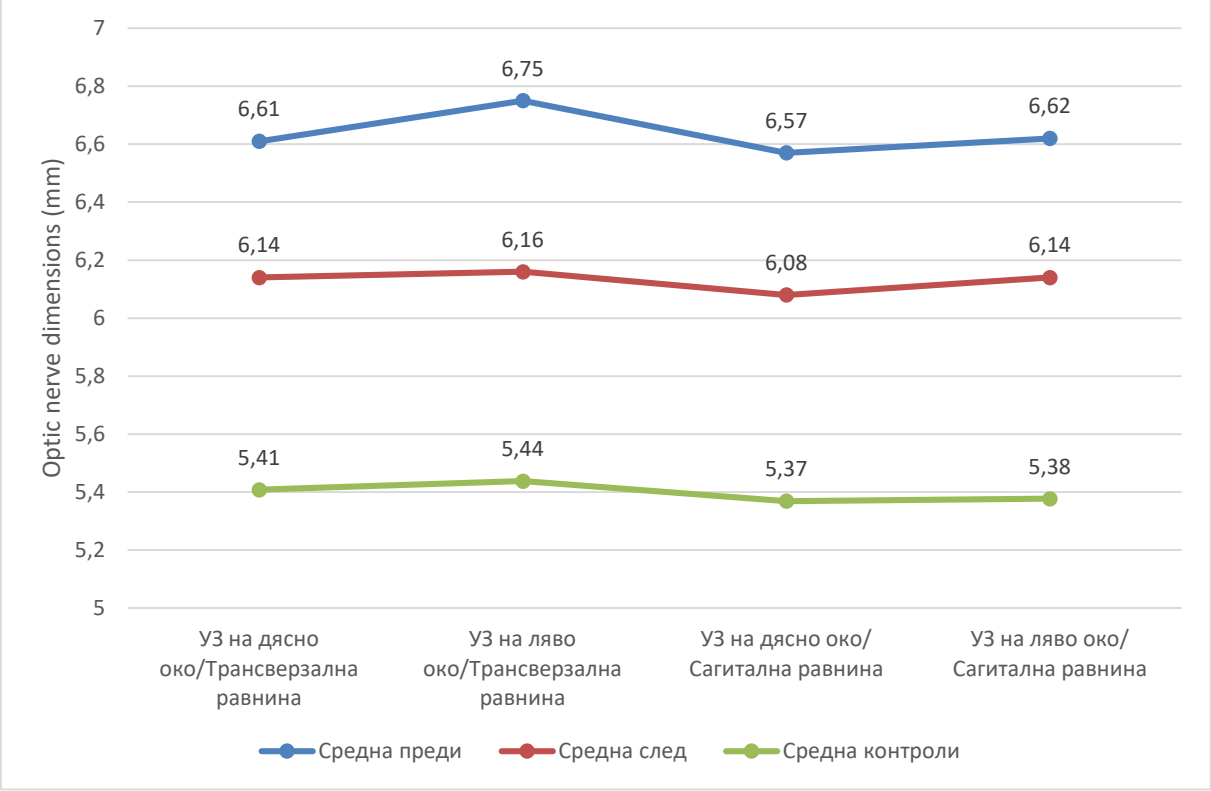

Figure 32. Changes in the dimension of the optic nerve before and after surgery for patients in the second group

5.6. Use of mannitol and hyperventilation.

Mannitol was applied in 10 (23.2%) patients from the first group (rapidly developing processes, leading to increased intracranial pressure /hematomas/).
There was no statistically significant difference in the dimensions of the optic nerve (for both eyes and both planes) after administration of mannitol (p> 0.05 for all comparisons).

Therapeutic hyperventilation was applied in just 7 (16.3%) patients from the first group (rapidly developing processes, leading to increased intracranial pressure /hematomas/).

There was no statistically significant difference in the dimensions of the optic nerve (for both eyes and both planes) after administration of therapeutic hyperventilation ($p > 0.05$ for all comparisons).

6. DISCUSSION

6.1. Patients characteristics

The 138 individuals included in the study, distributed among the different groups, are characterized by an irregular distribution of data by age, with a difference reported as statistically significant ($F = 5{,}869$, $p < .001$) (*Table* 1), but we did not find a statistically significant difference in the age of the patients from the first and the control group ($t = 1{,}562$; $p = .124$), as well as between the second and control group ($t = 0{,}189$; $p = .853$). It is notable that the age in the fourth group is the lowest, while the age in the third – the highest. *(Fig. 15)* Our team believes that this is due to the fact that the patients in group 4 were potential donors who were conditioned in the ICU and it is understandable that they are not elderly. Group 3 included patients admitted to the intensive care unit in a relatively urgent state, without prior diagnostic clarification, and in most of them (10 out of 14), the cause of the quantitative changes in consciousness was not related to a pathological finding from a brain CT scan. Often times the patients were very old, with vascular dementia, with some motor deficits, bed-bound and dehydrated, as evidenced by the results obtained. Similarly to the opinion of Jochen Bauerle et al. (74) we did not find any statistically significant difference in the ONSD dimensions of the measured optic nerves between men and women (for all groups $.122 \leq p \leq .229$) and so we believe there is not any.

6.2. First US examination

Some authors measure ONSD by an US in two planes – transverse and sagittal and to obtain the final dimension they calculate the mean value (45, 52, 92). Other authors measure the ONSD by US only in the transverse plane. (20, 47, 83, 113). Our team decided to study and analyze the data obtained from the two planes for right and left nerve, in order to increase the accuracy and reliability of the results, due to the fact that the structure of the subarachnoid space of the nerve is not the same in all parts and according to Killer He et al. is a complex septate, trabecular system with changes in diameter along the nerve (82).

We did not find any statistically significant difference between the values of the initial measurements of the optic nerve of the patients in the first group and the patients in the second group. For all comparisons $p > ,05$. From the obtained results it is evident that between the mean values of the ONSD dimensions in the two planes in the first and second group, there is no significant difference and the values are very close – 6.71 (SD = 0.363 mm) for the right nerve in the transverse plane in the first group, and 6.61 (SD = 0.428) mm for the second group (Table 2 and Fig. 18) Our team believes that this is due to the fact that both groups include patients with verified pathology of the CNS, leading to similar effects on the ICP and, in parallel, to similar changes in ONSD. From the above we can conclude that the measurement of ONSD by US is a good method for detection of increased ICP, but it does not offer possibility to differentiate the etiology.

After statistical processing, we established that the ONSD dimension values in the first and second groups, in both planes, are markedly higher than those measured in the third group. For all comparisons $p < ,007$. The patients in the third group were in a coma, without a diagnosis. Of the 14 patients subject to US examination and brain CT scan, only 4 had pathological CT scan results, indicating IICP. In all 4 patients the ONSD in both planes was > 6.5 mm and indicated a diagnosis leading to IICP. One of the patients, who subsequently fell into group 4 (brain death), was admitted with prolonged, generalized, tonic-clonic seizures and with GCS – 8 points. During the first US examination, the following ONSD dimensions were measured – 6.1 mm for right nerve and 6.0 mm for the left nerve in the transverse plane, and 6.0 mm for right nerve and 6.0 mm for the left nerve in the sagittal plane. The brain CT scan showed no indications of pathological changes. Due to the deteriorated condition, persistent coma and seizures, on the following day we carried out a second US examination, and measured the following ONSD dimensions – 8.1 mm for right nerve and 8.0 mm for the left nerve in the transverse plane, and 8.0 mm for right nerve and 8.0 mm for the left nerve in the sagittal plane. We decided to transport the patient to the imaging department and perform a new brain CT scan, which showed an extensive ischemic area, general cerebral edema and a 14 mm dislocation from the mid-line. In the following 2 days the patient fulfilled the criteria for brain death; was excluded from group 3 and included in group 4. In the remaining 10 patients who showed no pathological findings from the CT scan, the ONSD in both planes had lower values, which led to lower mean values of the dimensions we measured in the third group. For objectification, one can consider the mean values in the transverse plane for the right nerve, with the following values – 5.94 (SD = 0.738) mm for the third group, compared

to those for the first group – 6.71 (SD = 0.363) mm and for the second – 6.61 (SD = 0.428) mm. (Table 2 and Figure 18) The values of the other planes, for the right and left nerves, followed a similar pattern. Despite the small number of patients in the group limiting the significance of the results, and based on our clinical observations, we believe that the ultrasound of ONSD is an adequate method for detection of IICP and is definitely a useful method for guidance and orientation for differential diagnosis in patients with quantitative deviations in consciousness without a clear diagnosis.

After performing statistical processing of the results, we obtained the highest values of ONSD in the fourth group (brain death). The values for the transverse plane are 7.12 (SD = 0.643) mm for the right nerve and 7.18 (SD = 0.638) mm – for the left (Table 2 and Table 3), whereas these coincide with the values from other research – 7.2 ± 0.5 mm (95) According to Topcuoglu et al dimensions above 7.1 mm correlates with brain death diagnosis with sensitivity of 98.3% (95% CI: 90.7-99.7%), and specificity – 84.2% (95% CI: 77.5-89.5%) (163). We agree and support the latter statement, and according to our team, an increase in the ONSD of over 7.1 mm in comatose patients on invasive mechanical ventilation (IMV) is suspected for developing brain death. The difference in the results compared to the first, second and third groups is obvious, and said difference was statistically significant for all comparisons $p < ,05$.

Our control group included 52 healthy volunteers. From the comparative analyzes it is unequivocally evident that this is the group with the lowest mean values of ONSD – 5.41 (SD = 0.31) mm for the right nerve (Table 2 and fig. 18) and respectively 5,44 (SD = 0,329) mm for the left nerve (Table 3 and fig. 20), in the transverse plane, and the results are not surprising, given the fact that the control group included individuals with normal ICP. The difference between the values of the control group and the four studied groups is statistically significant for all measurements and for all comparisons $p < ,05$. The obtained values coincide with those described by other authors – 5.4 ± 0.6 mm (74). The lowest reference value at which we did not find a statistically significant difference between the measured dimensions of the optic nerve and the reference value, is 5.6 mm (.303> p> .105 for all measurements) and falls in the range 5.5 – 5.9 (8, 48, 74), which are the most frequently cited threshold values in the world literature and studies. Given the above, it is noteworthy that the ONSD, measured by US, is the highest in the group with the highest values of ICP (fourth group – brain death), the values are slightly lower in the groups with disease processes leading to IICP (first and second group), still lower values in the third group, in which the majority of patients

(71.4%) did not have pathology associated with IICP (10 out of 14), and the lowest values were measured in the control group. (Fig. 25) We attributed the mentioned regularities to the fact that the control group includes healthy volunteers, with practically normal ICP, and group 4 consists of patients who have developed brain death – a diagnosis that includes in its pathophysiology critically high values of ICP, much higher of those in other pathologies.

Our conclusion, based on statistical data and the data from our clinical observation, is that the ONSD measured via US increases in conditions associated with IICP, whereas the dimensions correlate with the values of ICP and coincide with the opinion of other authors (9, 48, 113, 114). We believe that daily monitoring of ONSD by ultrasound, in patients with severe CNS damage, could promptly direct the clinician to the presence of increasing ICP or progression to brain death. The method is fast, inexpensive, quickly adoptable, even by inexperienced clinicians, does not require potentially dangerous transportation, can be repeated many times and is not associated with ionizing radiation, which makes it safe and extremely suitable for screening, detection and monitoring of patients with elevated ICP. Based on the gained clinical experience and the obtained results, we believe that frequent monitoring of ONSD provides extremely valuable information that could lead to changes in the therapeutic plan and would be especially suitable for comatose patients for whom adequate assessment of neurological status is not possible.

What was particularly notable in the obtained results, was the fact that in all measurements, the values of the dimensions in the sagittal plane, are slightly lower than those in the transverse one. This phenomenon is clearly observed in fig. 23. Our team attributes this trend to the anatomical features of the optic nerve, as well as to the methodology of the measurement itself. In the transverse plane, we were able to direct the transducer so as to avoid the structures of the eye (front, rear eye chamber, lens). Those structures could have scattered the waves and distort the resulting image. In the sagittal plane this was not possible and we attribute the lower dimensions in this plane to the fact that the obtained image was not so clear. In conclusion, we believe that the measurement in the transverse plane alone is sufficient to get an idea ofthe state of the ONSD and the ICP, but an additional measurement in the sagittal plane reduces the chances of error, since a large difference in size between the two planes would be indicative and would require a second measurement.

6.3. Changes in the size of the ONSD after surgical decompression

Rajajee et al are of the opinion that the ONSD slowly returns to normal values when there has been a prior increase (135). In contrast to that view, Maissan et al claim the ONSD dimensions change simultaneously with the changes in the ICP during endotracheal aspiration. (101) We believe that it is appropriate here to share our observation of a patient admitted to the ward with severe SAH. At the first US examination we measured an ONSD of 7.4 mm (on both sides) for the transverse plane, and 7.3 mm for the sagittal plane. We were very impressed by the sudden increase in size to 8.1 mm. (on both sides), during tracheal aspiration, as well as by the immediate return to baseline values after its termination. Choi et al (33) and Bhandari et al (18) reported a statistically significant difference in the size of the ONSD in patients with hydrocephalus measured preoperatively, compared to those measured immediately after ventriculoperitoneal shunt placement. Steffen et al when studying 38 patients with SAH and invasive monitoring of the ICP, conclusively demonstrated that papillary edema was not an early marker of IICP. (66)

In designing the study, our team decided that it was quite appropriate to examine the pre- and postoperative dimensions of ONSD in patients from the first group (rapidly developing processes), 62.8% of whom underwent craniotomy, and the patients from second group (slowly developing processes – tumors). The dimension of the ONSD in the first group shows a mean value with 0.45 mm smaller in all measurements after the alleviating surgery, except for the left nerve in the sagittal plane, where it is smaller with about 0.48 mm. The differences found are statistically significant. Figure 31 clearly shows the downward trend in postoperative size. The graph again shows the slightly lower values of the measurements in the sagittal plane – a trend that has already been mentioned. The ONSD dimensions in the second group follow a similar pattern. The differences between the preoperative and postoperative sizes of the ONSD are visible (fig. 32) and statistically significant. The graph shows insignificantly lower values persistent in the sagittal, compared to the transverse plane. Aspide R. et al have conducted the only available similar study to date, with patients with brain tumors, subjected to elective surgical extirpation and also reported a statistically significant difference between preoperative and postoperative ONSD sizes. (13)

Based on the obtained results and the clinical observation, we can confirm the opinion of Maissan et al (101) and conclude that the US of the ONSD changes simultaneously with the changes in the ICP and this happens quickly, which makes the method suitable for monitoring and evaluation of ICP, and even to evaluate the effectiveness of surgery. However, we must take into account the fact that in our study the postoperative values were lower than the

preoperative ones, but still did not reach the values of the control group. We believe that the ONSD dimensions are definitely decreasing rapidly after the relief of ICP, but it takes more time to reach normal values.

6.4. Changes in the ONSD dimensions after the use of mannitol and hyperventilation

Mannitol was applied in 10 (23.2%) patients from the first group (rapidly developing processes, leading to increased intracranial pressure). We did not find a statistically significant difference in the size of the optic nerve (for both eyes and both planes) after the application of mannitol, unlike other authors (176), who found a clear difference between the initial dimensions and those obtained 20 minutes after the application of mannitol.

Therapeutic hyperventilation was applied in just 7 (16.3%) patients from the first group (rapidly developing processes, leading to increased intracranial pressure). We did not find a statistically significant difference in the dimension of the optic nerve (for both eyes and both planes). Klinzing S. et al reported a good correlation between moderate hyperventilation in craniocerebral trauma and the dynamic changes in the ONSD dimensions, as measured by US.

In our view the lack of changes in the ONSD dimensions at the application of the two treatment methods was due to the extremely severe pathology, and respectively, to the very high ICP under which we applied both methods. Hyperventilation is a method that we use only as a last resort, at extremely high values of ICP, due to the dangers and risks it poses. Our team takes into consideration the very small number of patients, subjected to both treatment methods, and the resulting limitations in the study.

7. CONCLUSIONS

Based on an analysis of our results, we formulated the following conclusions:

1. There is no relationship between the dimensions of the ONSD and the patients age.

2. An ultrasound measurement of the ONSD is a good method to detect high ICP, but it cannot prove the cause for high ICP.

3. US data indicating ONSD of over 7.1 mm in patients on invasive mechanical ventilation (IMV), and in a coma, is a strong indicator for the development of brain death.

4. The daily monitoring of the ONSD in patients with CNS pathology provides valuable information about the dynamics of ICP.

5. The ONSD reacts very quickly to changes in the ICP.

6. The ONSD US is a safe method, it is not associated with dangerous transportation or ionizing radiation and can be repeated many times, at the patient's bedside.

7. The ONSD US makes it possible to confirm adequate surgical decompression in cases of elevated ICP.

8. The ONSD US is a method, suitable for monitoring of patients with elevated ICP.

8. CONTRIBUTIONS

Scientific and practical contributions

1. Data provided on the benefits and safety of using US to measure ONSD in patients with suspected high ICP.
2. An analysis conducted regarding the efficiency and the type of information obtained from the application of the US method.
3. The contraindications and limitations of the method are specified.
4. For the first time in Bulgarian science and practice a study has been conducted for the measurement of the ONSD via an ultrasound.

Scientific and theoretical contributions

1. The practical and technical specifics of the US measurement of the ONSD have been outlined.
2. The advantages of the US monitoring and detection of ICP compared to the established methods have also been outlined.