

**TO THE CHAIRMAN OF THE SCIENTIFIC JURY
DESIGNATED BY A WRITTEN ORDER Nr. R-109-169/22.05.2024
OF THE RECTOR OF MEDICAL UNIVERSITY OF VARNA**

STATEMENT OF OPINION

**By Assoc. Prof. Georgi Angelov Pavlov, MD, PhD
Department of Anesthesiology, Emergency and Intensive Care Medicine
Medical Faculty, Medical University of Plovdiv**

On doctoral thesis "**CHANGES IN WATER-ELECTROLYTE BALANCE IN ORGAN DONORS WITH BRAIN DEATH AND THEIR CORRECTION IN THE INTENSIVE CARE UNIT**" for awarding educational and scientific degree "Doctor of Philosophy" in doctoral program in Anesthesiology and Intensive Care.

Doctoral candidate: Dr. Boryana Ivanova Georgieva- Assistant Professor, Department of Anesthesiology, Emergency and Intensive Care Medicine, Medical Faculty, Medical University of Varna

Scientific Supervisor: Assoc. Prof. Boryana Ivanova Naydenova-Sabeva, MD, PhD- Head of Department of Anesthesiology, Emergency and Intensive Care Medicine, Medical Faculty, Medical University of Varna

1. General presentation of the procedure and the doctoral student.

The presented set of documents and materials is in accordance with the Inner Regulations of Medical University of Varna and Art. 69 of the Regulations for the Development of the Academic Staff of Medical University of Varna.

Dr. Boryana Ivanova Georgieva was born in 1993 in Chirpan. She graduated his Master's degree in Medicine from Medical University of Varna in 2018. In 2019 she started his medical practice as a resident in the Department of Anesthesiology and Intensive Care at University Hospital "St. Marina"- Varna, where she is still working so far. Since 2020 she has been a full-time doctoral student and an assistant professor at the Department of Anesthesiology, Emergency and Intensive Medicine at the Faculty of Medicine of Medical University of Varna. She is fluent in English and French.

2. Relevance of the topic

The dissertation work of Dr. Boryana Georgieva is dedicated to disturbances in fluid and electrolyte balance and the methods for their assessment and correction in patients with severe brain damage and brain death. In my view, the topic is a contemporary and practically significant problem which has not yet been the subject of scientific research in Bulgaria.

3. Characteristics and evaluation of the doctoral thesis

The thesis represents a completed scientific work. It is properly constructed and includes all the relevant sections following the established specific form. The following sections are included in the thesis: Contents - 4 pages; Abbreviations - 1 page; Introduction - 1 page; Literature Review - 35 pages; Aim and Tasks - 1 page; Materials and Methods - 8 pages; Results and Discussion - 58 pages; Conclusions - 1 page; Contributions- 1 page; Appendices - 10 pages; Scientific Publications in Connection with the Dissertation - 1 page; References- 10 pages. The doctoral thesis is written on a total of 132 pages. It is well illustrated with 45 figures and 52 tables.

The bibliographic reference covers 124 titles of which 5 in Cyrillic and 119 in Latin. It is in alphabetical order.

The title is clearly formulated and sufficiently informative. It reflects adequately the content of the research and corresponds to the presented data and conclusions.

Literature review – it covers 35 pages. About 23% of its volume represents a detailed description of the etiology, general mechanisms of brain death and the criteria and diagnostic tests, which is not directly related to the topic of the dissertation. The rest of the literature review includes a detailed description of the physiological role of the major electrolytes, their physiological regulatory mechanisms, and the pathophysiological mechanisms of the relevant electrolyte disorders. It is noticeable the presence of a number of unclear, contradictory and incorrect formulations that create confusion and are unacceptable for the strictly scientific nature of a dissertation work, for example:

- In section 5.1.2.1. it is inaccurately stated that one of the mechanisms for the occurrence of hypernatremia is hypotonic water losses. It is correct to talk about hypotonic body fluids losses.
- In the next section 5.1.2.2. it is stated that "hypotonic water losses do not greatly alter the plasma volume, since the loss of pure water increases the colloid-osmotic pressure in the plasma...", which creates contradiction and confusion. This same section states that "Mannitol inhibits water reabsorption in the loop of Henle and proximal tubule." Mannitol does not inhibit any of the physiological mechanisms of water reabsorption in the segments of the nephron, but creates an osmotic gradient, resulting in increased loss of hypotonic urine relative to plasma.
- In section 5.1.2.3. it is stated that "ECT volume in diabetes insipidus is normal due to pure water loss", which is incorrect. It remains relatively normal if at least one of the following two conditions is present
 - the patient compensates for the loss of free water by adequate oral intake of water, which cannot be achieved in patients with severe brain damage and brain death, or with adequate volume resuscitation from the treating team. Otherwise, left without adequate substitution (oral or parenteral), the loss of free water in central diabetes insipidus will lead to severe hypovolemia and hypovolemic hypernatremia.
- In the section on the treatment of hypovolemic hypernatremia (item 5.1.2.5.1.) an equation for water deficit assessment is proposed, which is stated to "not be applied to hypotonic losses", making it completely redundant for assessment of deficit in hypovolemic hypernatremia. The same section also discusses the correction of isovolemic and hypervolemic hypernatremia, which creates confusion, ambiguity, and unnecessary repetition in subsequent sections devoted specifically to the correction of iso- and hypervolemic hypernatremia.
- It is incorrect (based mainly on the topic of the dissertation) to talk about an "isotonic" or "physiological" solution of NaCl. Despite these common and widely used names, 0.9% NaCl solution is neither physiological nor isotonic. This solution has an osmolarity of 308 mOsm/l and is effectively hypertonic with respect to plasma. It is also incorrect to talk about 0.45% physiological serum.
- It would be appropriate in the literature review to consider the mechanisms of hyponatremia occurrence, especially in the earlier stages of brain damage before the occurrence of brain death, such as the syndrome of inadequate ADH secretion and the cerebral salt-wasting syndrome.
- In section 5.2.2.2. it is incorrectly stated that "When chlorine-containing preparations are administered, they interact with bicarbonate in an attempt to buffer the pH." Hyperchloremic metabolic acidosis with increased intake of chlorine-containing preparations is the result of compensatory increased renal bicarbonate excretion but not of an interaction between these ions.
- In the sections on disorders in chlorine homeostasis, some causes and mechanisms that do not apply to patients with severe brain damage and brain death were commented, such as proximal and distal renal tubular acidosis, which has no connection with the topic of the dissertation work and is completely unnecessary.

- In section 5.3. too broadly, in some places with quite a lot of inaccuracies, pathophysiological mechanisms, clinical manifestations and approaches to hypokalemia were commented on, which cannot be applied to patients with severe brain damage and brain death (e.g., oral substitution, etc.), which I consider redundant.

- The statement "The occurrence of hypertonic hyperosmolarity and osmotic diuresis in brain-dead patients as a result of diabetes insipidus leads to increased magnesium losses..." in section 5.5.2.2 is wrong, since polyuria in central diabetes insipidus is not the result of osmotic diuresis.

As a significant omission from the doctoral student, I would like to point out, the lack of conclusions from the literature review about controversial and unsolved problems on the subject. This is an essential component of any scientific research and serves as a basis for deriving the purpose and tasks that the author should perform.

Main goal - it has been stated correctly, clearly and accurately formulated in harmony with the title of the dissertation and corresponds to the further development of scientific research.

Tasks - 5 tasks are set, aimed at the implementation of the set goal, describing the necessary actions.

The section "Materials and Methods" presents the subject, the object and the design of the study are. It is properly structured and presented and covers 8 pages. The research materials and methods are correctly and precisely selected to fulfill the main goal and tasks. The inclusion and exclusion criteria are carefully formulated. A wide range of modern and accurate statistical tests has been used for statistical processing which guarantees the reliability of the obtained results and the conclusions made. In my opinion, as the most important component of the dissertation work, this section should be further elaborated with a more detailed and thorough description of the study design.

As a major drawback I consider the fact that the study is entirely retrospective and descriptive without prospective evaluation of any intervention, such as evaluation of the effectiveness of the implementation of the proposed protocol for the assessment and correction of fluid and electrolyte disturbances in potential donors compared to the cohort of the retrospective analysis.

The obtained results correspond to the set tasks. Their description is supported by rich graphical and tabular material with accompanying detailed textual descriptions. In this section the doctoral student makes a discussion of the obtained results, and in some places there are comparisons with data from the literature reference.

The dissertation concludes with the formulation of **six conclusions**. I think that the first conclusion has no relation to the topic and the goals and tasks of the dissertation. The fifth and sixth conclusions are formulated too generally, which makes them inappropriate for a scientific work of a similar nature.

Contributions - Dr. Boryana Georgieva presents 4 contributions, I accept the contributions without remarks.

4. Abstract

The abstract is prepared in accordance with the requirements of the Regulations of Medical University of Varna. It is written on 68 pages. The abstract summarizes well the structure of the doctoral thesis and contains the most important studies, results, conclusions and contributions. It is illustrated with a sufficient number of figures and tables.

5. Assessment of the publications and personal contribution

Dr. Boryana Georgieva has presented two publications in reference with the PhD thesis. She is the first author in both articles. The publications are in the journal "Varna Medical Forum" which is not refereed and indexed in the world-reknown scientific information databases Scopus or Web of Science databases. I recommend that the doctoral student should prepare and publish scientific articles in

peer-reviewed scientific journals, indexed and referenced in world-renowned databases (Scopus & Web of Science).

CONCLUSION

Despite the critical remarks, I strongly believe that the doctoral thesis "**CHANGES IN WATER-ELECTROLYTE BALANCE IN ORGAN DONORS WITH BRAIN DEATH AND THEIR CORRECTION IN THE INTENSIVE CARE UNIT**" by Dr. Boryana Ivanova Georgieva meets all the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria, The Regulations for its application and the Inner Regulations of Medical University of Varna. This is the first study in Bulgaria with generalized observations and conclusions on the disturbances in fluid and electrolyte balance and their correction in organ donors with brain death in intensive care unit.

Taking into account all the abovemention facts, I grant my positive assessment of the study presented by the reviewed doctoral thesis, abstract, results and contributions by proposing to the members of the honorable Scientific Jury to give their positive vote for awarding the educational and scientific degree "Doctor of Philosophy" to Dr. Boryana Ivanova Georgieva in doctoral program in Anesthesiology and Intensive Care.

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Assoc. Prof. Georgi Pavlov, MD, PhD