To the Scientific Jury

Established by Order No. P-3012/18.10.2023

To the Rector

Medical University

Plovdiv

RECENTIONS

On the dissertation thesis of Dr. Angel Petrov Prodanov entitled "LIFE-CONSUMING HYPERGLYCEMIC DISORDERS IN PATIENTS WITH DIABETES IN THE INTENSIVE CARE WARD" for the award of the educational and scientific degree "DOCTOR" in the specialty "Anaesthesiology and Intensive Care", with scientific supervisor Prof. Dr. Chavdar Stefanov, MD, PhD, DMS.

Reviewer: Professor dr Viliyan Platikanov, MD, PhD, head of ICU clinics at the University Hospital "St. Marina", Varna.

Dear members of the Scientific Jury,

At the first meeting of the scientific jury I was appointed to prepare a review, which I am presenting below.

Biographical and educational data of the dissertant:

Dr. Angel Prodanov was born in 1985. He graduated in 2011 in Plovdiv with a Master's degree, diploma № 8668, specialty "Medicine". In 2017, after a successful state examination, he received recognition of a specialty in "Anesthesiology and Intensive Care" - diploma № 2464. In 2020 he graduated from the second higher education at the Medical University of Plovdiv, with a recognized Master's degree in the specialty "Public Health", diploma No. 859. In 2021 he was enrolled as an independent doctoral student at CASIM of Medical University Plovdiv, and in 2023 he was discharged with the right to formal defense. Currently he is an anesthesiologist at the Department of Anesthesiology of the University Hospital "St. George". He is also a teacher in the same specialty at department CASIM of MU Plovdiv and a procurator of Uni Hospital in Panagyurishte.

Evaluation of the dissertation

"Hyperglycemia" is a medical term denoting a condition in emergency medicine in which the blood sugar level is above the normal range. Hyperglycemia can severely damage the body. Ignoring hyperglycemia is dangerous to the body and leads to complications and permanent damage to blood vessels and nerve cells. Blood glucose values above 6.7 mmol/l (before a meal) or above 8.9 mmol/l (two hours after a meal) are considered risky. Lack of or reduced sensitivity to the very important insulin for glucose metabolism, leads to the conversion of fatty acids into ketones, resulting in excess acidity in the body (diabetic ketoacidosis). The most common cause of chronic hyperglycemia is diabetes. Hyperglycemia can also occur in the case of infectious or liver diseases or diverse inflammatory syndromes. Hyperglycemia is common in the acute phase of a number of serious diseases. The presence of hyperglycaemia and ketoacidosis in the course of their treatment in the intensive care unit is particularly problematic for patients, either because of another disease or because of decompensation of diabetes. The incidence of fasting hyperglycaemia increased steadily with age - 1.5% in 18-29 year olds, 5.2% in 30-54 year olds and 9.5% in 55-74 year olds and was approximately twice as high in men as in women - 7.9% versus 3.4%.

The dissertation thesis of Dr. Angel Petrov Prodanov on "LIFE-CONSUMING HYPERGLYCEMIC DISORDERS IN PATIENTS WITH DIABETES IN THE INTENSIVE CARE WARD" is written in 148 standard typewritten pages plus 22 pages of references. Includes 25 tables and 27 figures.

It is written in clear and correct Bulgarian, in high style, is relatively easy to read, and is arranged as required.

It contains 10 main sections:

- list of figures and tables

- literature review

- aim and objectives

- material and methods

- results

- comprehensive therapeutic approach and discussion

- protocol for the treatment of life-threatening hyperglycaemia conditions
- conclusion
- conclusions
- contributions
- literature used

There is no **"introduction"** section presented. The first page of the following "Literature Review" has quite comprehensive information, which in my view is quite sufficient to be distinguished in such a section introducing the topic.

The **"literature review"** section is written in 40 pages. It includes data from 246 scientific sources, all in Latin. More than 60% of the authors consulted are from the last 20 years, and the oldest article is from 1947, indicating a fairly extensive acquaintance of the author with the movement of knowledge on the subject. The survey is divided into 7 subsections, each of which is also structured into other subsections. It ends with subsection 2.7, entitled as "Conclusion". It synthesizes the information from the literature review. The main thought of this conclusion is that there is currently no protocol that can be defined as a universal one. Hyperglycaemia in the intensive care unit is an important morbidity parameter and is relevant to the final outcome of intensive care patients.

As a recommendation, I reflect my opinion that there has been a lot written on this issue from Bulgarian authors in Bulgarian language, both as monographs and as guidelines for the management of patients with hyperglycaemia in Society of Endocrinology documents and as articles, besides abroad and at home, and the author should familiarise himself with them and reflect them in the literature review.

On page 31 of the dissertation there is a backlog of recommended text from a previous review that should be removed when the manuscript is submitted for formal review.

Aim and objectives section - 1 page. On the basis of the author's views and the extensive literature review, a clear aim is formulated, in close connection with the title of the thesis, and 4 specific tasks to be performed, which I find clear and

precise. Particularly valuable is task 4 which describes the activities necessary to form a comprehensive therapeutic approach in patients with diabetes mellitus and life-threatening hyperglycemic conditions.

Material and methods section - 10 pages. The study is retrospective, on 123 intensive care patients from the ICU of St. George's University Hospital for the period January 2019 - January 2022. Inclusion and exclusion criteria are tabulated and the study itself goes through three stages - preparatory, screening and analytical. All methodologies used during the observation periods are described in great detail. Two main types of glycaemic control are structured for comparison, respectively the numerical values from the glycaemic analysis - "Strong" and "Liberal" glycaemic control.

Different highly informative indicators were used to assess patient outcomes, and a relationship between these and glycaemic control type was sought. For clarity of expression, each indicator has a specific definition in the text.

Well-standardized and state-of-the-art statistical methods were used to provide reliable information and relevant conclusions.

The results section, presented in 55 pages, is the largest section of the dissertation, as it should be. It describes the results obtained, which meet the set objectives. The majority of the patients included in the observation were male, the mean age of the participants was 49, and obesity was recorded among half of the subjects, statistically confirmed. In general, I believe that the results solve the set objectives. The presentation of the figures, supported by tables, figures and brief commentary, gives a very good impression of clarity and lucidity. Comorbidities were more common and less common ones in intensive care units. It is clear that they cannot be grouped in detail exactically, but they are still grouped by some common feature - for example, trauma patients, septic patients, patients with CHD, etc.

Subsection 5.2.1 is very interesting and important, as it describes and justifies the incidence and general characteristics of the observed complications related to glycaemic control - one of the thesis repers. On average, patients less admitted 16 +/- 8 days in the ICU and averaged 42 +/- 12 hours free from ICU. There were no statistically significant differences in complication rates when grouped by gender. A significantly higher proportion of infusions were received by males compared to females.

Subsection 5.2.4 records the result that patients with a body mass index defining obesity received 15 E more insulin in the first 24 hours of their treatment.

An interesting subsection is 5.2.7.8. It is the one that describes the correlation between laboratory parameters and therapeutic strategy, which has been statistically confirmed.

Too important for final conclusions and analysis are the data in subsection 5.3.3, namely the determination of survival and mortality according to the type of glycemic control. According to the data of the present study, an increased mortality and a decreased relative proportion of dehospitalizations were observed in patients in whom "liberal" glycaemic control was implemented.

Section 6 describes in detail the complex therapeutic approach in the patient groups that participated in this retrospective study, as well as a discussion of the results obtained. Based on these and refracted through the literature review, a clinical approach for critically ill surgical and non-surgical patients presenting to the clinic with life-threatening hyperglycaemic conditions is proposed in the form of a 'protocol', which I adopt. The protocol includes volemic control, electrolyte control and insulin treatment.

Section 7, **'conclusion'**, is a synopsis of the reflections in the operational part of the thesis

The 'conclusions' section extrapolates **6 conclusions** with which I agree. I believe that the information in the conclusions could have been presented in a more synthesized manner. In conclusion #3, its main idea is up for discussion, as it is known that cerebral edema itself leads to arterial hypertension, which is a compensatory mechanism to maintain cerebral perfusion pressure and cerebral blood flow.

As a side note here, I would like to say that in a scientific publication, terms like "....not categorically associated", "...possible to use" have no place, as here conclusions should only be based on statistically supported or unsupported data that define categoricity one way or the other. There is no room for conjecture or equivocation.

In the section **"contributions"** two main groups are formed, namely scientific-theoretical and scientific-practical ones, which I accept.

Scientific output - The dissertant has submitted 3 scientific publications published in full text.

Critical remarks:

1. Reflected specifically to each section.

2. Single grammatical errors.

CONCLUSION

The dissertation "LIFE-CONSUMING HYPERGLYCEMICAL DISORDERS IN PATIENTS WITH DIABETES IN THE INTENSIVA CARE WARD" meets all the methodological and scientometric requirements for the degree of Doctor of Medicine.

Therefore, in spite of the few critical remarks, I propose to the esteemed Scientific Jury to vote positively and to grant to Dr. Angel Petrov Prodanov the scientific and educational degree "DOCTOR" in the specialty "Anesthesiology and Intensive Care".

He prepared the review

Professor. V Platikanov, MD

15.11.2023.

Varna