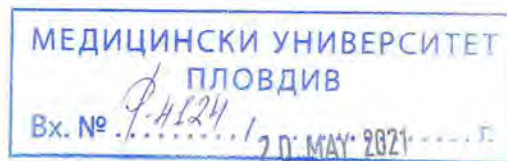


To the Chairman of the Scientific
Jury designated by Order No. P-496/07.04.2021
of the Rector of the Medical University of
Plovdiv.



REVIEW

by Prof. Petya Filipova Pechalova - Petrova, DMD, DDS, MD, PhD
Medical University – Plovdiv,
Faculty of Dental Medicine,
Department of Oral Surgery

of a dissertation for receiving a doctoral degree

Sphere of higher education: 7. Healthcare and sports

Professional field: 7.2. Dental medicine

Doctoral programme: Oral Surgery

Author: Dr. Tanya Ivanova Sbirikova, self-training PhD student

Department: Oral Surgery

Theme:

Control of postoperative pain – psychological, fMRI and immunological studies

Academic supervisor: Assoc. Prof. Dr. Deyan: Zdravkov Neychev, PhD, Medical
University of Plovdiv, Faculty of Dental Medicine, Department of Oral Surgery

1. General presentation of the procedure and the doctoral candidate

This review was prepared on the basis of Order of the Rector of the Medical University of Plovdiv No. **P-496/07.04.2021**, with appointed Scientific Jury under the procedure for public defense of the dissertation above mentioned.

The presented set of materials in both paper and electronic form is in accordance with Art. 115 (I) of the Procedure for Awarding Doctoral Degrees at the Medical University of Plovdiv, set in the Regulations of the Medical University of Plovdiv of 06 Nov 2014, and was provided to me within the legal deadline.

The doctoral candidate has enclosed 3 scientific publications printed in scientific journals and 2 participations in scientific forums related to the theme of the dissertation.

2. Biographical notes of the doctoral candidate

Dr. **Tanya Ivanova Sbirkova** was born on 04 December 1981.

In 2000 she graduated from the French Language School "Antoine de Saint-Exupery", Plovdiv.

In 2000 she was admitted to the Faculty of Dentistry of the Medical University of Plovdiv. Graduated in dentistry in 2006. In 2011, she acquired a specialty in Oral Surgery.

Since 2007 and until now Dr. Sbirkova is an assistant at the Department of Oral Surgery of the FDM, MU – Plovdiv and has a total work experience of 14 years as a lecturer. She conducts practicals and seminars in oral surgery for Bulgarian speaking and English-speaking dental students. Since 2012 and until now Dr. Sbirkova has been working in AGPPPDM "Charisma" Ltd.

Dr. Sbirkova is a member of Bulgarian Dental Association and Union of Scientists in Bulgaria.

3. Significance of the theme and appropriateness of the objectives and tasks set

The theme of the dissertation addresses a significant and important problem for the dental science and practice. The objective is clearly stated – *“to study the possibilities for influencing the pain symptoms after surgical removal of impacted third mandibular molars using various drugs, using fMRI, immunological and psychological tests.”*, and the tasks are defined correctly and implemented using modern research methods.

4. Knowledge on the problem

Pain is a complex biological phenomenon - an indicator of a violation of the patient's homeostasis and the most common reason for visiting a doctor. Pain is at the root of impaired quality of life. Of particular interest is postoperative pain. With improper treatment, it could become chronic and progress to chronic pain. In these cases, treatment is difficult, the quality of life - deteriorated, and the cost of its impact increases many times over. Therefore, any study of this biological phenomenon is of great interest to medical science and practice.

The doctoral candidate has made a thorough critical analysis of the literature, formulating unsolved problems on the theme, namely:

- Objectification of postoperative pain through the use of modern technologies such as fMRI
- Assessment of the influence of certain factors on the intensity of postoperative pain
- Determination of the relationship between the size of postoperative edema and the intensity of postoperative pain by examining the change in serum levels of CGRP and Procalcitonin
- Evaluation of the drugs used Placebo, Ibuprofen and Ibuprofen in combination with Gabapentin for the control of postoperative pain by reporting changes in serum levels of CGRP and Procalcitonin
- Investigation of the possibilities of using CGRP and Procalcitonin as diagnostic markers for a general inflammatory process in the body
- Assessment of the impact of anxiety and the presence of negative / positive previous experience on postoperative pain.

Dr. Tanya Sbirikova demonstrates in-depth knowledge of the topic she is developing and her ability to conduct research independently.

5. Research methodology

The objective was achieved through the completion of four main tasks and two subtasks, namely:

1. *Registration of pain intensity after surgical removal of impacted third mandibular molars:*

- *To study the intensity of pain using the Visual analog scale (VAS) and the factors (age, sex, smoking, difficulty and duration of surgical intervention, preemptive analgesia, postoperative complications) affecting the sensation of pain.*
 - *Activation of areas in the brain after surgical removal of impacted third mandibular molars.*
2. *To find the relationship between the intensity of postoperative pain and reactive inflammatory process by examining Procalcitonin and CGRP.*
 3. *To examine the serum levels of neurotransmitters and inflammatory pain mediators - Procalcitonin and CGRP (calcitonin-gene related peptide), and their response to the drugs administered.*
 4. *To study the influence of anxiety on the intensity of postoperative pain and on the physiological parameters – blood pressure, pulse rate and saturation in young adults.*

Study design

The study is randomized, double-blind, placebo-controlled in order to avoid the subjective moment when including patients in a particular group, as well as to ensure that the results of various drugs are as accurate and objective as possible.

The clinical material examined for the dissertation tasks is as follows:

Forty patients with impacted third mandibular molars bilaterally, with indications for extraction. At random, patients were divided into three groups, taking respectively:

- ✓ Placebo - 10 patients
- ✓ Ibuprofen (400 mg) - 15 patients
- ✓ Ibuprofen (400 mg) with Gabapentin (300 mg) - 15 patients

Subject of observation:

Forty patients with impacted third mandibular molars bilaterally, with indications for extraction, selected by inclusion and exclusion criteria.

Units of observation:

Adults who accidentally or were referred to the Department of Oral Surgery for removal of impacted third mandibular molars.

Signs of observation:

Age, sex, smoking, changes in saturation, pulse rate and blood pressure during surgery, postoperative pain, pain intensity, swelling - different localizations, changes in the activity of certain brain structures due to postoperative pain, study change in levels of procalcitonin and CGRP.

Time of observation:

The research was conducted in the period September 2017 - May 2018.

Place of observation:

Department of Oral Surgery, Faculty of Dental Medicine, Medical University of Plovdiv; Immunology Research Centre, Medical University of Plovdiv; Translational Neuroscience Complex, Medical University - Plovdiv

Surveillance authorities:

The observations were made by the study leader in collaboration with pre-trained teachers.

The clinical material selected for the implementation of the main goal and tasks is sufficient for the development of a dissertation.

Patients participating in the study met inclusion and exclusion criteria, namely:

Inclusion criteria:

1. Clinically healthy patients aged between 17 and 40 years with indications for extraction of the third mandibular molar, bilateral
2. No evidence of pain associated with the extracted third mandibular molar

Exclusion criteria:

1. Patients not included in the studied age group
2. Pregnancy and lactation
3. Patients with aneurysmal clips and pacemakers
4. Patients with tattoos and piercings
5. Patients with a history of head trauma or seizures
6. Patients with neurological or mental illness
7. Systemic alcohol intake and drug use

8. Taking drugs that affect brain function (including aspirin) in the last two weeks before the fMRI
9. Women, 5 days before and 5 days after their menstrual cycle (in order to exclude the influence of hormonal factors on pain)
10. Anamnestic data for drug allergy
11. Acute inflammation in the area of the tooth to be extracted
12. Systemic lupus erythematosus or other disease to connective tissue
13. Diseases of the stomach or intestines, incl. Crohn's disease
14. Liver, kidney or cardiovascular diseases, incl. Hypertension
15. Chronic lung diseases
16. Intake of NSAIDs, anticoagulants, antiplatelets, digoxin, antihypertensives, phenytoin, cholestyramine, aminoglycosides, quinolones, immunosuppressants, bisphosphonates, pentoxifylline, baclofen, drugs for the treatment of diabetes and depressive drugs.

Statistical methods for data analysis:

The systematization, processing and analysis of the primary data in the form of quantitative and qualitative variables was realized with the statistical package of the social science software IBM SPSS Statistics v. 25. The fMRI data were analyzed using SPM 12 (Statistics Parametric Mapping, <http://www.fil.ion.ucl.ac.uk/spm/>) on the MATLAB R2015a platform for Windows. The results of all tests are considered statistically significant at p-value <0.05. The graphical analysis was performed in an MS Office 365 environment using Excel. Variation analysis of quantitative variables, frequency analysis of qualitative variables, parametric analysis, t-test - to prove the difference between two variables, ANOVA, z-test for comparison of relative shares with Bonferoni correction were used to objectify the results of the performed analyzes, Shapiro-Wilk test, Wilcoxon sign rank test, Pearson and Spearman correlation coefficient, regression analysis. The fMRI images were regrouped, co-recorded with structural images normalized in the space of the Montreal Neurological Institute (MNI) and smoothed with a 6 mm full width at half the maximum Gaussian function. Graphical analysis includes box-type diagrams, pie charts, bar charts, digital imaging.

6. Characteristics and evaluation of the dissertation

The dissertation was written on 175 pages, and contains 20 tables, 18 figures, 33 diagrams and 7 appendices. The bibliography includes 271 references, 5 of which are in Cyrillic and 266 in Latin. It contains all sections necessary for a dissertation.

The results are comprehensively and correctly described, analyzed and interpreted.

The dissertation finishes with conclusions based on the results, the discussion and the summaries of the study.

7. Contributions and significance of the dissertation for the science and practice

As a result of the study, the following conclusions were made:

1. Postoperative pain after surgical removal of impacted third mandibular molars has the highest intensity at the 6th postoperative hour and has a significantly lower intensity after the second, compared to the first surgical intervention.
2. The difficulty of the surgical intervention is the factor that most strongly affects the postoperative pain
3. A local inflammatory reaction, most pronounced in the 24th and 48th postoperative hours, and a mild or insignificant systemic inflammatory response were found.
4. There is no association between the intensity of postoperative pain and the administered drug after surgical removal of impacted third mandibular molars
5. Preemptive analgesia reduces pain in the early postoperative period.
6. Preoperative anxiety leads to an increase in the intensity of postoperative pain and to a change in physiological cardiac parameters.
7. Familiarizing the patient with the nature of surgical manipulation leads to a reduction in anxiety and the intensity of postoperative pain.
8. The presence of previous experience in surgical intervention to remove an impacted third mandibular molar leads to a reduction in anxiety and no change in CGRP values.

The dissertation outlines the following contributions of theoretical and scientific-applied nature, as follows:

Theoretical contributions:

1. For the first time in Bulgaria fMRI is applied in order to objectify the postoperative pain in Oral Surgery

2. For the first time in Bulgaria the serum levels of CGRP and Procalcitonin are examined on the occasion of operative interventions in Oral surgery.
3. The change in physiological cardiac parameters due to anxiety accompanying surgical interventions in Oral Surgery is examined
4. It has been proven that patients' awareness before surgical interventions in Oral Surgery leads to a reduction in anxiety and easier toleration of surgical manipulation.

Scientific and applied contributions:

1. The intensity of postoperative pain is found to be strongest at the 6th postoperative hour
2. Difficulty is defined as a leading factor that affects the intensity of postoperative pain.
3. It was confirmed that postoperative administration of anti-inflammatory drugs is necessary in order to control the inflammatory component of postoperative pain
4. The need for pre-operative analgesia to treat postoperative pain in the early postoperative period was confirmed.
5. The reduction of anxiety after thorough acquaintance of the patient with the forthcoming procedure determines the weaker feeling of postoperative pain after surgical removal of affected third mandibular molars.

8. Assessment of publications related to the dissertation

Three publications related to the dissertation are presented, as Dr. Sbirikova is the first author in two of the publications and the second in one of them, namely:

1. **Sbirikova TI**, Neychev DZ, Raycheva RD, Atanasov DT. *Factors which Influence Postoperative Pain Intensity after Surgical Removal of Impacted Mandibular Third Molars. J of IMAB 2019 Oct-Dec;25(4):2793-9.*
2. Neychev D, **Sbirikova T**, Ivanovska M, Raycheva R, Murdjeva M, Atanasov D. *Correlation between CGRP levels and the neuropathic and inflammatory component of postoperative pain. Folia Med (Plovdiv) 2020;62(2):365-71.*
3. **Sbirikova T**, Massaldjieva R, Neychev D, Raycheva R. *Anxiety and changes in physiological parameters during surgical procedures for removal of impacted mandibular third molars in young adults J Int Dent Med Res 2021;14(1):221-7*

Participations in scientific events related to the dissertation

1. *Сбиркова Т, Нейчев Д. Съвременни аспекти на контрола на постоперативната болка чрез използване на фЯМР за отчитане на ефективността на направената аналгетична интервенция. VII Международна Конференция на Младите Учени, 15-16 Юни 2017, Дом на Учените, Пловдив.*
2. *Сбиркова Т, Атанасов Д. Обективизиране на контрола на постоперативната болка след екстракция на импактирани трети долночелюстни молари. Дни на медицинската наука. Проектна сесия. Пловдив 30.03.2019г.*

Dr. Sbirkova's scientific articles have been published in prestigious English-language journals. The presented scientific reports presented at scientific forums are in Bulgarian. The results obtained in them satisfy quantitatively and qualitatively the legal requirements for dissertation work.

9. Personal involvement of the doctoral candidate

I consider that the research and observations of patients and the resulting conclusions and contributions of the dissertation are personal work of the author.

10. Author's summary

The author's summary contains 63 pages, illustrated with 15 figures, 26 diagrams and 20 tables. It correctly reflects the nature of the study and the results achieved in the dissertation. The conclusions are included in it.

It has been prepared in accordance with the requirements of the Act for the Development of the Academic Staff in the Republic of Bulgaria and the regulations of the Medical University of Plovdiv. It reflects the content of the dissertation.

11. Critical comments and recommendations

The set of materials related to the dissertation, which was submitted to me, is complete and is in accordance with the Act for the Development of the Academic Staff and its Implementation Rules as well as with the regulations of the Medical University of Plovdiv.

CONCLUSION

The theme of the dissertation chosen by Dr. Tanya Sbirikova, namely “Control of postoperative pain – psychological, fMRI and immunological studies”, addresses a significant problem in the dental science and practice.

The literature review is comprehensive and gives a clear idea of the current state of the issue under consideration. It ends with a critical analysis, which is a good basis for the research carried out.

The clinical material and the research carried out are of interest for dental practice and science. I consider that the results obtained in the dissertation, their interpretation, and the presented publications related to it are the author's personal work.

The dissertation shows that the doctoral candidate Dr. Sbirikova **possesses** in-depth theoretical knowledge and professional skills in the specialty Oral Surgery, and **demonstrates** competences and skills for conducting independent research.

Based on the above stated, I consider that the requirements set in the Act for the Development of the Academic Staff and its Implementation Rules as well as in the regulations of the Medical University of Plovdiv are met. The presented materials and dissertation results are in **full compliance** with the specific requirements of the Medical University of Plovdiv.

In conclusion: I confidently give my positive opinion of the dissertation themed “Control of postoperative pain – psychological, fMRI and immunological studies” and I will vote “**YES**” for awarding doctoral degree in the scientific specialty **Oral Surgery** to **Dr. Tanya Ivanova Sbirikova**.

07.05.2021

Reviewer: 

(Prof. Petya Filipova Pechalova – Petrova, DMD, DDS, MD, PhD)