

**UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA**

**DOCTORAL SCHOOL**



**PhD THESIS  
ABSTRACT**

**The antioxidants in the preventive therapy of postsurgical complications**

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## Table of Contents

<b>INTRODUCTION</b> .....	3
<b>THE KNOWLEDGE STAGE</b> .....	4
<b>OWN CONTRIBUTION</b> .....	4
Premise and objectives .....	4
Material and method.....	5
Results.....	6
Discussions.....	7
<b>FINAL CONCLUSIONS</b> .....	8
<b>BIBLIOGRAPHY</b> .....	9

**KEY WORDS:** antioxidants, oxidative stress, surgical wounds, posttraumatic stress.

## INTRODUCTION

After the surgery, the oxidative stress induced in the cells of the traumatized vasculo-tissular unities is generated by the accumulation of the species reactive of oxygen (SRO) and nitrogen (SRN), together with the reduction of the antioxidant capacity of the serum. (Vrabete M. 2001)

Traumatic wounds, such as: cut wound, crush, puncture, infected, shoots, etc. Represent about 33-41% of diseases affecting the upper limbs (hand, forearm) in patients hospitalized in the department of plastic and reconstructive surgery, for recovery of the lack of substance and functional recovery of the affected segment. In reconstructive plastic surgery, the direct or indirect involvement (neighborhood) of the component muscles of the dermatome from the operated area causes the installation of some phenotypic and structural modifications, not just functional, which can be reversible, in acute, sub-acute phase but also irreversible chronic ones that determine the defective healing. (H. Eikermann, et al 2006)

The efficient defectless healing, within maximum three weeks from the immobilisation of the muscle in the operative wound, appears at about 55% of cases. There is, however, a considerable percent of defective healing that causes the discomfort characteristic to posttraumatic condition, in which the associated psychic disturbance maintains the neuro-motor handicap, the mental state being very hard to treat, in time. (Deac C. 1999)

The unfavorable evolution of the functional status of the muscles in the late postsurgical period (over six weeks) requests the application of some helping recovery kinotherapeutic methods, including: neuro-musculo-cutaneous electric stimulation, the exercises to maintain the activity of the proprioceptive sensitivity, the ultrasound therapy, etc. (Dubay D.A. 2003)

The phenotypic modifications from the striated muscle fibre level sum the elements of the processes of inactivation/activation of the specific genes and of the structures (proteins) encoded and transcribed in the genetic code, in accordance with the O<sub>2</sub> supply from the mitochondria level and the rapport between the oxidants-antioxidants established at this level. It is considered that the hipoxia starts mechanisms involved in the remodelling (plasticity) of the striated muscle, through reactions triggered and controlled by mitochondrial enzymes and functional proteins, activated by the reduction of the O<sub>2</sub> level. The increase of the capillaries number for the increase of the O<sub>2</sub> supply and the increase of the oxidative capacity at the mitochondrial level are few elements controlled by the enzymes from the respiratory chain and the rapport endo and exogenic oxidants-antioxidants. (Hoppeler, 2003)

## **THE KNOWLEDGE STAGE**

**CHAPTER 1** – makes a review of the general data about surgical wounds and their healing (Steed D.L.2003)

**CHAPTER 2** – emphasizes the modern concepts of recognizing the oxidative stress, by detecting the most sensitive parameters of its reflection. The antioxidant capacity of the serum, the free O<sub>2</sub> radicals and/or the species reactive of O<sub>2</sub>, the antioxidant enzymes (superoxiddismutaze, catalaze), the reduced glutathione, the metals with antioxidant effect: Zn, Cu and malondialdehyde, as argument of lipoperoxidation.

**CHAPTER 3** – displays the considerations over the plasticity of the striated muscle and its manifestations, in posttraumatic period.

There are presented mechanisms of miocellular adaptation to training through endurance as well as the integration of the signal in the tissue activity.

## **CONTRIBUTIONS**

**The premise** of the study is to highlight the mechanisms of adaptation of the organisms that assure the healing of the surgical wounds, per primam, allowing a quick social reinstatement of the subject.

### **Objectives**

- The selection of the clinic-laboratory parameters that express the ratio oxidants/ antioxidants correlated with the healing process;
- To establish the correlation between the redox disequilibrium and the type of the reported pain.
- The highlighting of the postsurgical complications, consequences of the oxidative stress (OxS) and the effects that the auxiliary therapy with exogenic antioxidants has.
- To establish the clinic-laboratory indicators (markers) (functional and biochemical) and their expression in the form of scores.
- The recording of types of therapies, with favourable effect over the redox ratio in the postsurgical reaction.

## Material and method

With the approval of the Ethics Committee of PMU and the Emergency County Hospital No.1 from Craiova I observed the clinical and paraclinic evolution of a 60 people batch, hospitalized in the Plastics and Reparatory Surgery section, having their approval and the approval of the Manager of the Plastics and Reparatory Surgery Clinic. The patients have suffered hand injuries which required non-functional reconstruction (structural) of the thumb with autologous graft application through: cleft free skin plasty (CFSP), time of the intervention:  $120 \pm 60$  minutes, under general anesthesia (the risk of the anesthesia third degree).

I analyzed the anatomo-clinical and morphopathological aspects of the wounds and I requested the prediction of the surgeon on the capacity of the patients to heal "per primam".

The selected batch has been homogeneous as a result of establishing some strict criteria of selection of the patients, demographical as well as of monitoring during the postsurgical period of the observed parameters.

**Work techniques** – usual techniques: the number of leukocytes, the leukocitary formula, the state of plasma coagulation (INR) and those made with the ELSA technique: the determination of SOD, CAT, of MDA, Copper, Zinc, GSH in dynamic evolution, at 24-48 hours postsurgical, at 3-7 days and at hospital discharge and the automated technique of measuring the free O<sub>2</sub> radicals TBARS and CAO, Oczan Erel.

The histo-pathological examination of the wound in the postsurgical period has been interpreted, through optic microscopy, through smears stained with HE.

All the obtained data were processed and entered into a scoring system (scales or indicators) that were used to assess the general postsurgical condition.

<b>The general condition of the organism</b>	<b>Score</b>
Very good	1-3
Good	4-6
Medium	7-9
Bad	10-14

Table no.1 The general condition of the organism

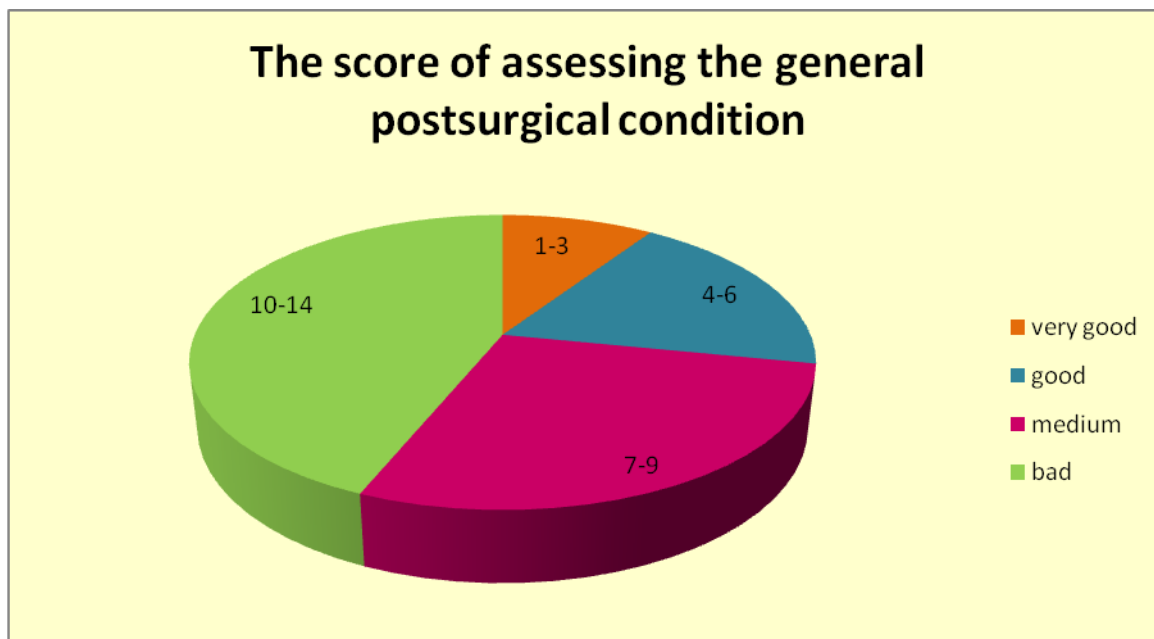


Figure no.1 The score of assessing the general postsurgical condition

Of the calculated scores and the indicators there can be cited: the assessment of the central pain, the assessment of the peripheral pain, based on the anatomic-pathologic modifications, the installation of the postsurgical physiopathologic complication, the code of the organic dysfunctions etc.

### Results

All the obtained data have been entered in tables and graphics made in Microsoft Excel and submitted to a study of **statistic analysis**. Calculating the coefficients of the correlation between the administration of the SOD, Zn and the redox profile of the plasma I obtained the following:

The value CAO correlates with the SOD value, at 48 hours after administration ( $r:0.85$ ) and less with the Zn values ( $r:0.75$ ). After 72 hours from administration of the SOD, the SOD and CAO evolution has taken a steady state, until the seventh day when the level returned to marto values and stabilized. I considered that this is the moment when, the administration of the medicines is no longer necessary, the antioxidant endogen mechanisms being restored.

The administration of Zn was accompanied with the return of its serum values after five days from the beginning of the administration. The small increases, but progressive have

not modified the CAO values, which proves that Zn, like the other oligoelements, does not modify the redox potential, but it serves to cicatrization.

Calculating the coefficients of the correlation between the scores of central pain, peripheral pain and the CAO values, I obtained: **r:0.55** for the central pain – CAO and **r:0.82** for the peripheral pain-CAO. Based on these correlations we consider that the proper evaluation of the macro and microscopic aspect of the postsurgical wound allows a prediction over the development of the local OxS, of the pain and of the time for this wound to heal, as well as whether the associations of the drug administration is necessary under the triade form: analgesics, anti-inflammatory, antioxidant. The obtained results and their statistical processing, allowed us to sustain the idea that the administration of the exogenic antioxidants reduces the level of endogen oxidants, having a preventive effect on their hiper-production and thus it prevents the stimulation of nociception, through the local biochemical mechanism of the radical excess. Through these mechanisms it is explained the reduction of the analgesic doses after the administration of the antioxidants and the increase of the tissues capacity to heal. The combination of analgesics with antioxidants, postsurgical, right after the surgery normalizes the equilibrium of oxidants/antioxidants and reduces the algogenic effect of OxS.

The slight increase of the CAO values as result of the therapy with antioxidants proves the fact that the exogenic source can participate in the growth of the blocking potential of the oxidative stress, intracellularly produced.

The state of coagulability of the plasma is a significant predictive element.

The hipercoagulability has a poor effect on the local irrigation. The 10% of cases belonged to both A and B groups. These had a difficult evolution in which the hipercoagulability generated and maintained the syndrome of compartment.

## **Discussions**

### **Remarks on the role and effects of antioxidants**

Antioxidant molecules blocks reactive O<sub>2</sub> species to prevent the effects of oxidative stress on some macromolecules, membrane lipids and lipoproteins. Of these, bilirubin, uric acid and thiol groups of proteins are important endogenous antioxidants.

Vitamina C and E and aromatic products, resulting from food ( flavonoids and phenolic acids) are the main exogenous nutritional antioxidants.

The super oxide radical stimulates SOD activation. The administration of vitamins decreases the production of superoxide or removes it, so the level of SOD is reduced.

### **Correlation of antioxidant - pain - stress**

Any pain triggers emotional stress, so it is difficult to distinguish between the proportion of participation and contribution to nociceptive pain response and/or to the stress. In posttraumatic stress, GSP<sub>x</sub>, SOD, CAT and MDA value does not change significantly compared to the control, but if they increase, that reflects the seriousness of evolution.

Pain is the result of the increase of permeability of blood-brain barrier for antioxidants. Their administration during painful stimulation is more effective than prevention.

In patients with acute posttraumatic stress, it was found that the GSP<sub>x</sub>, SOD, and MDA level is not changed compared to the control. However CISP<sub>x</sub> and SOD increase is associated with the severity of evolution. The authors reported decreases in SOD, GSP<sub>x</sub> after applying AO, analgesics and parallel combination with decreased stress-induced analgesia.

In patients with leukocyte changes I appreciated triggering an inflammatory reaction or it is pre-existence. In such situations we used non-steroidal anti-inflammatory medication type. In cases of increased plasma antioxidant capacity, we administered antioxidant medication, or food rich in antioxidants, considering that the values of this parameter must be sustained at a high level for the potentiaton of endogenous compensatory mechanism activated.

### **FINAL CONCLUSIONS**

1. Surgical stress and postoperative pain affect the psycho-emotional (anxiety) status, which together with the alteration intensity of the tissues, morph-functional preexisting deficits and surgical patient<sup>s</sup> eating habits are determinant factors of the quality of tissue healing.
2. Central pain is correlated with psycho-affective status. Peripheral pain is reduced after administration of local analgesics and anti-inflammatory drugs.
3. Analgesic effect of morphine are due to activation of the opioid system of endogenous analgesia, on which antioxidants act, a mechanism that could be potentiated by these substances, that recommends them as auxiliary medication.
4. Measurement of the effects of antioxidants on pain can be highlighted by functional indicators of pain (degree or intensity and pain tolerance) and by the dose of analgesics required by the patient.



5. The general therapy or the intravenous administration of the analgesics modifies the sensation of pain that is perceived and expressed according to the mental states, while the local application of drug associations containing: anti-inflammatory, analgesics, anesthetics and anticoagulants, even at the end of the surgery, have direct beneficial effects.
6. Recognition of complex regional pain installation, classic treated with antihistamines, anesthetics and anticoagulants, locally administered, evolving faster towards healing after the combination of antioxidants as well as therapy for SC.
7. The administration of the antioxidant medication reduces the level of TBARS, MDA, SOD, increases CAO due to the potentiation of the plasmatic antioxidant mechanisms and it reflects, at the same time, the quality of the oxygen supply.
8. The measurement and the dynamic evolution of the CAO values, related to the pre-existence of the periphery pain, registered in the memory of the cells, reflects the experience of the tissues, in correlation with the anaerobic conditions and it could be an indicator of the capacity of these tissues to resist against the oxidative injury.
9. Maintaining a constant status of antioxidant capacity in all evolutionary stages, post-surgery, minimizes the installation and the intensification of endogenous oxidative stress and thus would prevent the installation of postoperative complications.

The originality of the study and the contribution of the paper are due to the establishment of the criteria and the scores of evaluation of the elements involved in generating the postsurgical complications. These scores can be used as guide, in current practice, in order to elaborate the prognosis and the application of the adequate therapy to the surgical wounds

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