UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA

INTRAVENOUSLY ANESTHETICS EFFECT ON THE NEUROPSYCHOLOGICAL STATUS AT SURGICAL PATIENTS DURING EARLY POSTOPERATIVE

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1. Introduction:

In the last years there were proposed several monitoring tools, as scores or scales, to quantify the intensity of pain, sedation or agitation. To the surgical patients, in early postoperative period, it was recorded: impaired memory and concentration, mild personality changes, cognitive changes, and emotional instability. All these changes, are included in the category of: PostOperative Cognitive Dysfunctions (POCD), which can increase patient length of stay and hospital costs [Ahlgren E, 2003]. Recently, it is trying to observe and to describe the clinical features and possible pathology of POCD, risk factors, and strategies for prevention or treatment of altered clinico-functional and metabolical changes appearing in postoperative period to prevent several complications [Morimoto Y, 2009]. The largest POCD studies for surgical patients to date were undertaken by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) [Mafra F, Fodale V. 2008.][Fodale V, 2006]. The changes in mental function after anesthesia and surgery have been categorized into two distinct syndromes:

- Postoperative delirium, a transient fluctuating disturbance of consciousness that occurs shortly after surgery.
- POCD: a change in cognitive performance, categorized according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as personality disorders, such as: schizoid, paranoid, histrionic, and depressive. These personality disorders are the support for psychiatric complications, which may install as disease

2. **The aim of our study:**

- To evidentiate the psychiatric changes in early period of arousal from anesthesia in surgical patients using the newest tools of evaluation such as scales and EEG exploration, associated to the clinical and functional manifestations.

**Objectives:**

1. To monitor and control the level of pain and sedation in early postanesthetic period and to observe the dynamic evolution of this ones, from 4 hours until 72 hours after surgical intervention

2. To select the management and to elaborate an individual protocol of medical management and strategy, for every patient, depending on his neuropsychological status.

3. To correlate several parameters, reflecting the neuro-psychological status, the biochemical changes (oxidant/antioxidant balance) reffered to the quality of his/her diet (alimentation), the specificity of treatment and the duration of wound healing

3. **Materials and methods.**

3.1. **Materials.**

We observed and noted clinical symptoms, and used screenig tests as tools for evaluating the values of pain and neuropsychological, prospective pathophysiological, prospective randomised, clinical study was approved by Ethic Commission of UMF and of Hospital nr.1 Craiova. We selected 100 patients from Plastic and Reconstructive Surgery Department with the agreement of Head of this section and having the patientshiatric changes. We introduced as instrument of measurements: the rating numerologic scale of pain, Ramsay Sedation Scale (RSS), the criteria of delirium diagnose applied in early period of arousal (20 minutes- 4 hours) at the moment T1, at 4-7 hours: complete arousal (T2) and at 72 hours (T3). We tried to correlate the results of answers to tese questionnaires to EEG aspects, auditory evoked potentials (AEP), with morphopathologic and biochemical aspects characteristic for the evolution toward the wounds healing.

We associated those moments to the functional values: arterial pressure, central pulse, diuresis, respiratory frequency, ( to evaluate the autonomic nervous sistem implication), and laboratory parameters oxidants/antioxidant values ( free O2 radicals, as peroxides,
NO, capacity antioxidant of plasma (CAO) and superoxide dismutase (SOD), for evaluating the implication of oxidative stress in postoperative evolution. All values were compared among them and correlate them with morphopathological aspects evidentiated with an optic microscop, from biopsies prelevated immediate to the postoperative period and at the end of the postoperative wounds healing.

3.2. Methods and techniques.

We applied the same kind of general anesthesia with oro-tracheal intubation. The general anesthesia or programmed coma, could induce deep unconscious state, and provides a “quiet” operating field by reducing organ activity and muscle movement. During the period of maintaining the anesthesia, we combined sleep-inducing agents (hypnotics) with analgesics (relieve pain, but don’t block other sensations), muscle relaxants, and medication to relieve anxiety (commonly used drug is midazolam), which causes drowsiness, relieves anxiety, and acts on the brain to help block any memory of the procedure. Propofol (Diprivan) is given to induce unconsciousness. We used continuous infusion with poropol because its activity is a short installation of this one si rapid (usually within 40 seconds) and wears off quickly; thereafter during surgery analgesics blunt the body’s response to pain, helping steady the heart rate and blood pressure. While the patient is unconscious, the anesthesiologist monitors their vital functions and level of sedation and adjusts medications as needed. Following surgery, she may receive drugs to reverse the anesthesia or simply wake up as the medications wear off.

We administered our patients: analgetics (fentanyl, meperidine, ketamine, isolated or in combinations, depending on the duration of the intervention and the psychological and mental status of the patients, noted in preoperative interview). Also we administered hypnotics (propofol, midazolam), barbiturates (thiopenthal), sevorhane and curarisation with: pancuronium. The anesthetic patrulater was obtained by means of association realised by anesthesiologist namely: analgesia, hypnosis, antishock effect and relaxation. The adequacy of anesthesia could be observed in: hemodynamic stability, good oxygenation, maintenance of hydro-ionic and oxidant/antioxidant balances (redox).

4. Results

Pain Rating Scale
Table no.8 The subjective responses to evaluate pain (p<0,005)

<table>
<thead>
<tr>
<th>Moments</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2± 2    7 ± 2    7 ± 7
B: 13 cases  B:0 cases  B:0 cases
C: 24 cases  C: 5 cases  C: 2 cases
1± 1     5 ± 1     5 ± 5
B: 15 cases  B:13 cases  B:3 cases
C: 12 cases  C:12 cases  C 5 cases
1±1      3±1      3±  3
B: 12 cases  B: 27 cases  B:37 cases
C: 4 cases  C: 23 cases  C:33 cases.

Table no.9
Medicines given for algosedation.

<table>
<thead>
<tr>
<th>Medicines</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>36 cases</td>
<td>5 cases</td>
<td>4 cases</td>
</tr>
<tr>
<td>Midazolam</td>
<td>27 cases</td>
<td>4 cases</td>
<td>3 cases</td>
</tr>
<tr>
<td>Propofol</td>
<td>15 cases</td>
<td>2 cases</td>
<td>3 cases</td>
</tr>
</tbody>
</table>

Men had much higher TAC than women did. Sex differences in TAC level in males could paradoxically reflect a high oxidative stress level in male subjects that has stimulated the compensatory upregulation of antioxidants.

Because plasma antioxidants are directly stressed by cigarette smoke–derived free radicals, cigarette smoking could have triggered biological antioxidant responses that are largely under genetic control.

We have measured the TAC of 20 samples (from control group), receiving antioxidant nutrition. Their diet, usually, was rich in fruits and vegetables. The results of TAC assay for normal individuals (mean values ± SEM 2.48 ± 0.10 as compared to 1.20 ± 0.01 mmol/L, t-value 12.8, p < 0.0001). obtained from the group of 20 smokers, selected from the two groups (B,C)

The values of malondialdehyde, marker for lipo-peroxidation and intensity of oxidative stress .

Table no.10. MDA values in T1 (p<.05)

<table>
<thead>
<tr>
<th></th>
<th>Control gr.</th>
<th>Gr.b</th>
<th>Gr.c</th>
</tr>
</thead>
</table>

Table no.11. SOD values in T1 (p<0.05)

<table>
<thead>
<tr>
<th>SOD (U/ml)</th>
<th>Variatia %</th>
<th>Table no.12. The values of ROS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.71±0.67</td>
<td>-</td>
<td>0.02±0.002</td>
</tr>
<tr>
<td>5.57±0.75</td>
<td>52.8*</td>
<td>0.24±0.002</td>
</tr>
<tr>
<td>3.56±0.25</td>
<td>49±8*</td>
<td>0.43±0.002</td>
</tr>
</tbody>
</table>

Increasing of SOD in T1 evidentiates the ability of cells to remove the oxidative stress.
In the both groups B and C, the antioxidant endogenous capacity was increased.

The values of ROS increase progressively from T1 to T3, inducing the excessive consum of endogenous antioxidants. NO production decrease, so vasoconstriction, hypoperfusion and hypercoagulability of plasma can appear. Amplification of these events influence in a nefavourable manner the evolution of wound healing.
Discussions.

There are several reasons why patients could manifest psychological disturbances during postoperative period, and their stay in hospital. There are many reports sustaining this aspect, so, beginning from the year 1965 when it was described the appearance of psychiatric complications in postoperative period, classified as: hospital psychosis or “hospital syndrome”. Blacher showed that in apparently normal patients appeared psychiatric disturbances, named by him: “hidden psychosis”. Recent data make an attention, mentioning that these findings were based on the patients reports, only.

The pain, as a dual manifestation: periferic and central. is presented in postoperative period, usually associated with sympathetic hyperactivity reflected in increasing of heart rate, arterial pressure, myocardial oxygen consumption, all of these ones, leading to myocardial ischaemia. Phillips-Bute B, Mathew JP, et al, 2006] The reducing of the movements of the chest wall and diaphragma causes the postoperative atelectasis, which could be installed, frequently. Because of these manifestations, analgesia is necessary not only to ameliorate the amplitude of respiration. but also, for extubation, when patient is weanned from mechanical ventilation to spontaneous respiration and endotracheal tube is removed. The continuing of the sedation can attenuate the cardiovascular stress response, over extubation[Laalou FZ, 2008]. The benefits of algosedation are reffered to the favourable effects upon the neuroendocrine stress response , including: release of adrenocorticotropic hormone (ACTH), prolactin, growth hormone, vasopressin (from the pituitary gland), cortisol, aldosterone and cathecolamines, from adrenals associated with glucagon secretion and insulin suppression. This endocrine axis increases the inflammatory response, that means cytokines, prostaglandines, and P substance eliberation, creating a vicious circle, amplifying pain and conditions for infectiouse complications apperance. The degree of traumatic or postoperative injuries is obtained evaluating the periferic pain, (clinical local aspect, morpho-pathologic, biochemical parameters) s senszitivity to pain is very complex from each to other, and because of this characteristic analgetic’and the psycho-affective colour of this one, as central pain. The patient strategies have to be individualised. Usually it is recomendated to asociate: opioids, with non steroidal anti inflammatory drugs and may be with local anesthetics.

The pain is associated with sympathetic hyperactivity , and for that, deacreasing sympathetic tone and oxygen consumption, could stabilise the haemmodynamics and treat agitation and motor activity. The sedation and the analgesia correctly administered in postoperative period, protect patient against stressfull stimuli and provide anxiolyis, nocturnal sleep and amnesia. Propofol approaches the ideal sedative drug, having favourable effects on intracranial...
haemmodynamics, but hypotension, primarily appeared because of systemic vascular resistance reduction, may compromise cerebral perfusion pressure and negate its benefits.[Laalou FZ, 2008]

Delirium is poorly present in posthanesthetic period and is manifested as an acute reversible state with following the diagnostic criteria, proposed by DSM[Kagansky N, 2004]. The correct diagnostic of delirium is only those elaborated after a psychiatric consult, which could discriminate it from schizophrenia, dementia or depression[.Gauthier S, 2002] [Yocum GT, 2009] After recording the results, obtained by two observers, it is necessary to make the complete analysis, determining the levels of sensitivity (sn) and specificity(sp) of ROR image. This curve could clarify the trw diagnostic.

The aethiology for delirium and sleep disturbances is multifactorial, iatrogenic risk factors is not removed, also sedative and analgesic medications. The development of delirium is associated with prolonged hospital stay and increased costs.

Antioxidant molecules, which scavenge free radical species to prevent or delay oxidative damage of important macromolecules, membrane lipids and lipoproteins, are prevalent in plasma and other biological fluids. Among them, bilirubin, uric acid and protein thiols are the major endogenous antioxidants, while vitamins C and E, as well as a number of food-derived (poly)aromatic substances, belonging to stilbens, flavonoids and phenolic acids, are the main classes of nutritional antioxidants. Assays for total antioxidant capacity in plasma differ in their type of oxidation source, target and measurement used to detect the oxidized product. Reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) are produced as a consequence of normal aerobic metabolism in animal species[ A. C. Maritim,R. A. Sanders, 2003] [Evans JL, 2002 ]. These "free radicals" are removed and/or inactivated in vivo by a battery of antioxidants [[Evans JL, 2002]. A biological antioxidant is defined as a substance, which, at low concentrations compared to that of the oxidisable substrate, significantly delays or prevents this oxidation [Evans JL, 2002]. Individual members of the antioxidant defense team are employed to prevent the generation of free ROS and RNS.

About 85% of TAC, in normal subjects, is due to endogenous antioxidants, and only about 15%, under normal circumstances is due to exogenously (dietary provided) antioxidant substances: as an effect of diet suggesting that exogenously provided antioxidants might modify the TAC of human plasma. TAC is a complex trait reflecting homeostasis of redox metabolism, which is highly relevant to nearly all pathological processes, including neurodegenerative disorders inflammatory and immunological reactions. The production and the consumption (by free radicals) of each
antioxidant affect the total antioxidant capacity. TAC is considered not only the indicator of redox homeostasis but a marker of genetic control. On the basis of a dietary questionnaire it was underlined that the capture of 85% of total macronutrient intake is no significant on TAC levels for any of the dietary components (protein, carbohydrate, fat, and alcohol). Many authors sustain the importance of investigating the genetic mechanisms responsible for variation in TAC. There is a significant gene-by-smoking effect, in which additive effects of genes explain as much as 83% of phenotypic variance in TAC levels in smokers, whereas the genetic contributions are significantly reduced to only 49% in nonsmokers. Theses values do not sustain clinical trials using of various antioxidants to prevent or treat "presumed oxidative stress."

TAC assay suggests that nutritional antioxidants protect against the development of chronic inflammation processes and because of these reports this kind of alimentation could be recommended in postoperative period, especially in patients with lower values of TAC, or to smokers. [Kocyigit A, Erel O, Gur S, 2001] [Kosecik M, Erel O, Sevinc E, Selek S, 2005] Benzodiazepines, used for anxiolysis and sedation, bind to receptors on macrophages and inhibit their ability to produce IL1, IL6 and TNF-alpha. [Cibelli M, et al. 2007] [Wan Y, et al. 2007] Supplementally these kind of substances, the same, like propofol, have an important antioxidant effect.

Following the aim and objectives of our study we may present several conclusions, namely: **Conclusions.**

1. The psychiatric changes in early period of arousal from anesthesia in surgical patients are: anxiety, variability of pain reactions, agitation, sleep disturbances, phobias, delirium, and others.

2. Delirium may occur secondary to alcohol withdrawal in current drinkers in the recovered alcoholic in the absence of recent use; these patients having need of supplemental nutritional support and antialcoholic medication, administered in full doses every 4-6 hours.

3. Functionally psychosis and actively suicidal individuals, manifested for the first time in surgical service, require close supervision, associated with antipsychotic agents.

4. Local morphopathological aspects of postoperative wounds, frequently, are not direct proportionally reflected in the degree of pain or agitation, but psychological disturbances induces by the intensity of these manifestatioins influence the increasing of healing and duration of hospital stay.

5. The disproportion between the intensity of pain and local morphopathological changes of
surgical wound is due to the differentiation between the peripheral segment, which need an anti-inflammatory medication and central segment, emotional one, which need sedation.

6. Sedation and analgesia protect patients from the noxious stimuli, provide anxiolysis, nocturnal sleep and amnesia and also, decrease the sympathetic tone, oxygen consumption, maintain hemodynamic stability and eliminate motor agitation.

7. Alimentation reflects social conditions, education, behaviour and could influence the wound healing, especially for those who include antioxidants elements, in their diet, represented by vegetables and fruits.

7. The tools for psychiatric disturbances evaluation are: scales, scores, EEG exploration, evoked potentials, but only associate with clinical and functional manifestations and psychiatric consult.

8. The deficiency of interviews tests results in easily manipulation of the answers to its questions, by the majority of patients.

9. Monitoring and control of the level of pain and sedation, in early postanesthetic period could be realised with RSS and numerologic rating scale of pain, by which a correct strategy of medical management could be select, from 4 hours until 72 hours after surgical intervention.

10. The evaluation of neuropsychological status, and a dialog with patients, before submitted them to the surgical-anesthetic intervention are very important for ameliorate the psychological changes, represented by negative emotions and anxiety.

11. Preoperative participation of a psychiatrist may be especially helpful in high risk procedures and when there is a critical demand for patient monitoring; whenever the surgeon suspects significant psychopathology, or when there is a prior history of postoperative psychiatric difficulty (such as amputation of one segment finger, or of hand).

12. The most important parameters for evaluation, belong to the three plans: clinical (reflecting the neuro-psychological status), biochemical (oxidant/antioxidant balance), and functional (reflecting the quality of response of neuro-vegetative system to anesthetic-surgical stress), regarding at the interface with the quality of diet (alimentation), specificity of treatment (local and central), duration of wound healing, hospital stay and costs.

13. Measurement of antioxidant status has its own limitations, which severely restricts the clinical usage of oxidative stress-related, as marker, because circulating plasma or serum antioxidant capacity, may not accurately reflect intracellular antioxidants in target areas, such as endothelial cells or vascular smooth muscle cells.

14. To select an effective medical agent, means that this one to have the ability to reduce an
make reversible the conscious level.
15. It is necessary to select a safe drug: to have no effect on the cardio-vascular, respiratory systems and metabolism, to do not exacerbate neuro-vegetative effects hypersensitivity reactions, histamine release and pain on injection at the site of venous puncture.
16. A quiet environment and a supportive reorientation is a great part of a healing conditions, realising an empathetic mental state and a good level of psychological comfort. perceptiones and shorten the duration of wound healing and and hospital stay.'17. Early mobilisation improves patient
18. The incidence of looking the hyposthasis of beeing operated, as an opportunity for enhancing the quality of life has a curative effect.
19. As a final conclusion of our study we could appreciate that to appropriate information of patients about surgery, reduces preoperative anxiety, post-operative pain, and hospital stay length.

References


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