STUDY ON RENAL CHANGES AFTER GENERAL ANESTHESIA WITH SEVOFLURANE, LOW FLOW

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INTRODUCTION.
Proteinuria is the most common laboratory manifestation of renal disease; in the absence of clinical symptoms, it consists of a urinary excretion of more than 150 mg/day of protein. [1] Most often proteinuria is asymptomatic, being detected by screening or in patients with hypertension and diabetes during their examination. Proteinuria is the result of protein combinations, which have been filtered by the glomerulus and which have not been resorbed, filtered by the glomerular proximal tubules and by secreted protein by the renal tubules or other accessory glands [2]. Physiologically the glomerular membrane filters only the proteins with low molecular weight, which are subsequently absorbed by the renal tubules. Glomerular membrane damage, decreased tubular reabsorption or destruction of kidney tissue causes proteinuria [3].

The presence of increased amounts of protein in the urine can be an important indicator of kidney dysfunction. Widespread introduction of Sevoflurane, as induction and maintenance agent of volatile general anesthesia, showed an increased safety profile [4,5]. Among the side effects of Sevoflurane, is mentioned the glomerular toxicity effect, as a result of the contact of Sevoflurane with CO2 absorbents, that give rise to toxic compounds: Compound A, B, C, D. [6] Experience in repeated exposure to Sevoflurane is little known, which is why the use of Sevoflurane in patients with renal disease, diabetes and hypertension is not restrictive. In this study we aimed to analyze changes in serum urea and creatinine, post anesthesia in relation to glomerular permeability modification for proteins.

MATERIAL AND METHOD. We performed medium and long-term anesthesia, with low flow (2l / min) Sevoflurane, to a total of 155 patients of the Department of Anesthesiology, from the Mures County Hospital in the period 01.10.2009-01.11.2014. We collected demographic data, biological samples of serum and urine preoperatively, 24 and 72 hours postoperatively.

RESULTS
By applying statistical analysis tests GraphPad Prisma 6 for repetitive data from the 3 intervals, we get the following results:

- For serum creatinine by Anova table operatively to 24 and 72 hours postoperatively, we obtained a value P = 0.054 by Bartlett test, and a P <0.0001 value. After analyzing serum urea operatively, at 24 and 72 hours postoperatively by Anova table we obtain a P = 0.0521 value, and by applying Bartlet’s test a P = 0.0037 value. Through statistical analysis of blood glucose, preanesthetic, postanesthesia 24 and 72 hours, we obtained the following statistics: by Anova table a P value <0.0001, and by Bartlett’s test application a P value <0.0001. Analyzing preanesthetic plasma and 24 and 72 hours for total protein/24 hours, we have the following data: by applying the Anova test, P <0.0001, by applying Bartlett’s test P <0.0001.

CONCLUSIONS
Determination of serum creatinine and urea, is inadequate for monitoring renal injury produced by A compound. Analyzing the partial and final data of this study, we observed a significant presence of proteins and carbohydrates in urine after surgery, with a maximum at 24 hours and postanesthesia regression trend for 72 hours, but without return to initial values, preanesthetic. Maintaining high levels of protein and carbohydrates in urine, at 72 hours in patients with Sepsis, Diabetes, is an important sign, which highlights once again the undesirable effect that Sevoflurane has on kidney

Keywords: sevoflurane, proteinuria, creatinine, serum urea.
risk over ASA III, the refusal of patients to use biological samples for research; preoperative proteinuria.

The anesthesia complied with the following protocol:

**Standard Monitoring:** ECG, noninvasive TA, SpO2, AV, breathing, ETCO2, MAC, ET Sevo, Temperature, Diuresis.

Anesthetic induction: Midazolam, Propofol, Fentanyl, Rocuronium.

**Maintenance of Anesthesia:** Sevoflurane, Fentanyl and Rocuronium.

In order to maintain anesthesia it was used a low flow of fresh gas (low flow fresh gas) FGF-2 l/min at a MAC (minimum alveolar concentrator) between 0.8-1.2 for Sevoflurane. The CO2 absorber used in the study was Soda lime, which contains Sodium, calcium hydroxide, Violet ethyl, and water. For volume replacement balance we used crystalloid fluids: Ringer and saline 0.9%, with an administration rate of 500 ml/hour, respectively postoperatively 35 ml/kg/body weight/24 hours. Blood losses were replaced by blood and blood products to maintain a homeostatic balance. No plasmexpander type (Hydroxyethyl starch, dextran) colloid fluids were administered.

We collected 155 urine samples preoperatively, 122 urine samples 24 hours after surgery and 122 samples from 72 hours before surgery, the samples were analyzed without being preserved in advance to avoid possible conservation errors. Quantitative determination of urine protein was performed by spectrophotometry at 600 nm, with Konelab 30i autoanalyzer in a specialized Laboratory of the Mures County Hospital.

We collected 366 blood samples, pre and postoperative, in which we analyzed serum urea, serum creatinine and serum glucose preoperative, postoperative 24 hours and 72 hours postoperatively. We excluded 32 patients from the study due to changes in preanesthetic glomerular proteins. We collected data such as: age, gender, ASA risk, BMI, main diagnosis, anesthetic duration, associated pathology (hypertension, diabetes, sepsis), anesthetic history. The results were statistically analyzed by using the software, GraphPad Prisma 6 by which we analyzed demographic data, anesthetics peculiarities, p-value, which we considered significant below 0.05.

**RESULTS**

Demographic data and surgical and anesthetic particularities are presented in Table No.1

By applying statistical analysis tests Graph Pad Prisma 6 for repetitive data from the 3 intervals, we get the following results:

For serum creatinine by Anova table operatively to 24 and 72 hours postoperatively, we obtained a value $P = 0.054$ by Bartlett test, and a $P < 0.0001$ value, which are graphically presented in Figure No. 1.

After analyzing serum urea operatively, at 24 and 72 hours postoperatively by Anova table we obtain a $P = 0.0521$ value, and by applying Bartlet’s test a $P = 0.0037$ value graphically presented in Figure No. 2.

Through statistical analysis of blood glucose, preanesthetic, postanesthesia 24 and 72 hours, we have the following data: by applying the Anova test, $P < 0.0001$, by applying Bartlett’s test $P < 0.0001$, data expressed graphically in Figure No. 4.

<table>
<thead>
<tr>
<th>Table 1 - Preoperative and demographic data</th>
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<tbody>
<tr>
<td><strong>Sevoflurane</strong></td>
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<tr>
<td><strong>n = 122</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>59</td>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>Average</td>
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<tr>
<td>22.000</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>B/F</td>
</tr>
<tr>
<td>40/82</td>
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<tr>
<td><strong>Anesthetic duration (min)</strong></td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>191.8</td>
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<tr>
<td><strong>MAC</strong></td>
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<tr>
<td>Average</td>
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<tr>
<td>1.6%</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>38</td>
</tr>
<tr>
<td><strong>General</strong></td>
</tr>
<tr>
<td>84</td>
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</tbody>
</table>

**Figure 1 - Serum creatinin mg%**

![Creatinine Graph](image1.png)

**Figure 2 - Serum urea mg%**

![Urea Graph](image2.png)
78.94% of the subjects with a history of anesthesia, have proteinuria over 150 mg/24 hours to 72 hours postanesthesia. 100% of patients who had been anesthetized and had various diseases, which required surgery, have persistent proteinuria over 150 mg%/24 hours, after 72 hours postanesthesia.

DISCUSSIONS:

Determination of proteins removed glomerular, is a screening test in diabetics, hypertensive persons and in lupus disease, this being considered an early sign of kidney disease in diabetics, patients with lupus and patients with cardiovascular risk factor, and in hypertensive persons. [7,8]

In the clinical studies, with reference to the affection of the renal function, data from literature are inconsistent. Maze RA. argues that glomerular integrity may be compromised outside damage of glomerular filtration rate by increasing the passage for albumin. [9] Serum creatinine is not a direct measure of tubular integrit, at which A compound causes injury. Higuchi H and many other experts believe that albuminuria, glycosuria and enzymuria are markers of nephrotoxicity of A compound, but are not implemented as the "gold standard" in pre- and postoperative surgical patients due to high cost compared to the cost of serum creatinine determination. [10,11]

For example, the dose of A compound that produces necrosis to 25% of corticomedullar cell junction histologically detected, is not associated with increased serum urea and with maximum serum creatinine increase with 0.5 mg%. Necrosis produced by A compound, histologically demonstrated does not associate with changes in serum creatinine. [12] It should also be considered careful monitoring of calca sodate because lack of color change, does not necessarily represent optimal functionality. [13,14]

In previous studies, performed by our team, we did not find significant changes in the urea and serum creatinine after exposure to Sevoflurane anesthesia, but glomerular permeability to proteins was severely affected after Sevoflurane anesthesia. [15] The data obtained through extension of the study highlight the significant changes for glomerular permeability to proteins (P <0.0001), and carbohydrates (P = 0.0001), while changes in serum creatinine and urea, which were insignificant at first glance, are statistically significantly modified. (P = 0.054 for serum creatinine, namely P = 0.0052). Noteworthy is the large number of patients with proteinuria, among those without a history of kidney disease, so persistent proteinuria over 72 hours in patients with sepsis (100% with proteinuria) in those with a history of anesthesia (78.94% with proteinuria). Interesting is the persistence of proteinuria in diabetic and hypertensive patients, given the prognostic role proteinuria has in the evolution of these diseases.
Series determination of urea and serum creatinine, is irrelevant in the perioperative renal toxicity, which is why we recommend determining other markers of kidney disease, such as urinary protein, albuminuria, due to reduced costs and simple determination. Widely routine use of Sevoflurane, without taking into account the possible renal toxic effect, without a rigorous monitoring of renal function is dangerous, which is why we recommend caution in the use of high concentrations of Sevoflurane, over 1.5 MAC at low flow of fresh gas (FGF) below 2 l/min.

“This paper was published under the frame of European Social Found. Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/133377”.

**Conclusions**

Determination of serum creatinine and urea, is inadequate for monitoring renal injury produced by a compound. Analyzing the partial and final data of this study, we observed a significant presence of proteins and carbohydrates in urine after surgery, with a maximum at 24 hours and postanesthesia regression trend for 72 hours, but without return to initial values, pre-anesthetic. Maintaining high levels of protein and carbohydrates in urine, at 72 hours in patients with Sepsis, Diabetes, is an important sign, which highlights once again the undesirable effect that Sevoflurane has on kidney. Patients with Sepsis, Diabetes, Hipertensive patients, should be considered from the start with glomerular disease even if preoperative serum and urine are normal.

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