ABSTRACT

DOCTORAL THESIS

RISK FACTORS IN THE EMERGENCE OF POSTOPERATIVE RENAL FAILURE, IMPACT OF TREATMENT WITH ACE INHIBITORS

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INTRODUCTION

Acute renal failure (ARF) is an undesirable complication of major surgery which contributes to increased morbidity and mortality in the surgical field. Acute renal failure (ARF) associated with major surgery may be responsible for 18.47% of cases of acute renal failure occurring in hospitalized patients.

1. CURRENT STATUS OF KNOWLEDGE IN THE FIELD OF ACUTE RENAL FAILURE AND CONVERTING ENZYME INHIBITORS OF ANGIOTENSIN I

1.1. ACUTE RENAL FAILURE

1.1.1. Acute renal failure definition

Acute renal failure (ARF) is a syndrome characterized by postoperative rapid and sustained deterioration of glomerular filtration rate, which determines the retention of added nitrogen (urea, creatinine), changes in fluid and electrolyte and acid-base balance and manifests itself as a complication of surgery; ARF defining characteristic is that serum creatinine levels exceed 170 µmol/l or increase by 50% compared with the preoperative value, oliguria (urinary output <400 ml/24 hour or <20 ml/hour) occurs frequently (~50% of cases) but is not constant [103].

1.1.2. Epidemiology data. Incidence

Acute renal failure associated with surgical act is 18-47% of all cases of ARF occurring in hospitalized patients [32.52]. The overall incidence of ARF occurring in a context of surgery was estimated at 0.1 to 2%, but the largest groups of patients at high risk. The incidence of ARF, due to nephrotoxic damage is 20% of the total IRA postoperative [2,36,37,57].

Level of ARF in patients with postoperative mortality is alarmingly high and varies between 40-90% [52], much higher than the IRA appeared in a medical or obstetrical context.

Mortality is influenced largely by the association of other organ failure, going from 10% in case of an IRA over 90% isolated if there are three organ failures [52]. The presence of postoperative oliguria in ARF also influences mortality. In patients with postoperative oliguria ARF mortality stands at 70%, while patients with non-oliguria ARF is 45% [50,52,77].

1.1.3. Peroperator renal risk. Risk factors

Renal risk assessment is a real problem because it can influence the perioperative period the patient's vital prognosis.

Renal risk aspects:
- the patient's personal risk and
- the risk related to the surgical act itself.

1.1.4. Conclusions

IRA after surgery remains a serious complication, with a negative effect on prognosis in patients operated.
Finding groups of patients "at risk" careful perioperative management and recognition of potential nephrotoxic substances are components of the best strategy to avoid this complication [64].

Treatment of postoperative ARF has serious economic consequences, and therefore has implications not only to prevent the patient as an individual but also the general community plan.

1.2. ACE INHIBITORS

1.2.1. Definition of angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors represent a class of drugs used to treat high blood pressure, prevent pathology derived from it and decrease cardiovascular mortality. The mechanism of action of ACE is to reduce serum and local angiotensin II by competitive inhibition of angiotensin I converting enzyme to angiotensin II.

2. PERSONAL RESEARCH

2.1. Study motivation

The research project aims to identify risk factors involved in the occurrence of acute renal failure in patients who underwent radical nephrectomy for renal tumor in order to achieve a limited of the common complications with direct implications for increased morbidity and mortality of surgical patients. Among the risk factors will be analyzed include some antihypertensive drugs as ACE inhibitors.

2.2. Establishing the general characteristics of the study group and control group and working hypothesis

We conducted a prospective study of patients admitted and operated in the Clinic of Urology and Renal Transplant Fundeni, Bucharest, 2007-2010.

After management approval of the Ethics Commission and the clinic, patients were informed about the study. The study included a total of 184 patients divided into two groups depending on progress on the development of postoperative ARF (group with the ARF - the study and control group).

Patients enrolled in the study have hypertension personal history of pathologic being treated chronically (> 6 months) with ACE inhibitors, β-blockers, channel blockers Ca2+ or diuretics and underwent surgery for renal tumor (nephrectomy radical previous track). Depending on the appearance as complication in the postoperative period, the ARF has divided patients into two groups:
- Study group (Group I) - 115 patients who developed postoperative ARF
- control group (Group II) - 68 patients without postoperative ARF.

Considering that the parameter type of antihypertensive treatment, which followed in the preoperative patient, we subdivided the patients in group I subgroups:
- Group - ACE: 61 hypertensive patients treated with ACE
- Group - beta-blockers: 27 hypertensive patients treated with beta-blockers
- Group - Ca2+ channel blockers: 18 hypertensive patients chronically treated with the Ca2+ channel blockers

\[\text{Group non-IECA}\]
- **Group - diuretics**: 9 hypertensive patients treated with diuretics.

### 2.3. Conclusions

The descriptive analysis comparing the group with acute renal failure compared to the control group after surgery for renal tumors following general conclusions can be drawn:

1. Old age is a predictor of ARF in the study given the relatively high proportion of patients > 71 years (23.5%) who developed ARF, which reinforces the fact that old age is reduced nephron capital, and comorbidities associated are multiple.

2. The statistically significant differences observed in the group of sex between the ages IRA average, meaning a higher average age in men (63.2 years), while in women the average age is 58.3 years.

3. Analyzing the results obtained by classifying patients by severity score ASA (American Society of Anesthesiologists) shows that most patients were classified as ASA III in the two groups; it is consistent with the high percentage of patients with advanced age-associated pathology history.

4. Patients with diabetes in the group who have progressed to postoperative ARF was a 35% higher than in the group of postoperative patients who have not evolved to the IRA. The increased incidence of ARF occurrence is explained in the study group because patients with diabetes, insulin-dependent or not, multifocal vascular abnormalities and particularly in the kidney.

5. The average intraoperative blood pressure (mBP) was regarded as an independent risk factor with age factor.

6. The presence of higher proportion of cardiovascular risk factors (angina, myocardial infarction, stroke) in the group with ARF to control group stresses the importance of confounding factors in the onset and development of postoperative ARF.

7. In terms of antihypertensive treatment in both groups the proportion of patients treated with ACE inhibitors for hypertension is 53.04% and 51.47% in the IRA group in the control group. Since the difference between these values is small, we found that treatment with ACE inhibitors is not a single factor in determining risk postoperative ARF.

8. The group finds that in factors perioperative bleeding ARF group was higher than in the controls, but the difference was not statistically significant.

### 2.4. MATHEMATICAL MODELS FOR PREDICTION OF POSTOPERATIVE ARF OCCURRENCE

#### 2.4.1. General definitions

#### 2.4.1.1. Hypothesis

To determine perioperative risk factors involved in the occurrence of postoperative ARF after intervention by unilateral nephrectomy for renal tumor before we built a logistic model "naive", which contains various types of antihypertensive drugs as in preoperative treatment of these patients.
2.4.1.2. Presentation logistic models:

Model 1 = diabetes treated with ACE + EF <30% + substances intraoperative contrast + mBP <80 mmHg + age

Model 2 = non-ACEI treatment + diabetes + EF <30% + mBP intraoperative contrast agent <80 mmHg + age

Model 3 = diabetes + EF <30% + mBP intraoperative contrast agent <80 mmHg + age

Model 4 = patients without risk factors (diabetes, LVEF <30%, mBP, age).

Combining variables in each model was achieved by applying Hosmer-Lemeshow Test of goodness fit.

2.4.2. UNIVARIATE ANALYSIS

2.4.2.1. Hypothesis

Univariate analysis takes into account risk factors involved in the occurrence of postoperative acute renal failure (age, ASA score of severity, diabetes mellitus, congestive heart failure, administration of nephrotoxic substances in the preoperative period, mean arterial pressure, myocardial infarction, hemoglobin).

2.4.2.4. Opinion univariate analysis

In the study I performed, risk factors significantly impact the onset of postoperative ARF by applying Student's t test were represented:
- Diabetes mellitus
- Congestive heart failure with LVEF <30%
- Preoperative administration of contrast agent, correlates with data from literature publications.

2.4.3. BIVARIATE ANALYSIS

2.4.3.1. Hypothesis

Because we found that some important factors in triggering the ARF, which were included in univariate analysis, no statistical significance or were "borderline", I decided to carry out a bivariate analysis.

Results of univariate analysis, performed by logistic regression, supplemented by the bivariate probit model that we have made combining two variables in the univariate analysis.

2.4.3.4. Opinion bivariate analysis

- Combination therapy with ACE inhibitors with any of the risk factors shown in univariate analysis enhances statistical significance of that risk factor.
- Combination therapy with beta-blocker with any risk factors in univariate analysis is not statistically significant.
- The combination of two risk factors statistically significant in univariate analysis does not reach the threshold of statistical significance in the bivariate model, which suggests that the practice of medicine is not enough presence of two risk factors in the history of the patient to trigger pathological ARF.
### 2.4.4. MULTIVARIATE ANALYSIS

#### 2.4.4.1. Method

Multivariate analysis is the advanced method of simultaneous analysis of multiple variables in this study are the risk factors in the onset of postoperative ARF. We aimed to evaluate several combinations of risk factors (multivariate model) to estimate as accurately predictive ability postoperative evolution toward an ARF (with Limpdep 9.0 Econometric Software Inc., Plainview, NY).

For each model it was calculated loglikelihood ratio - Chi-squared test, prediction of success and failure prediction.

The choice of combinations of risk factors in the model above was such that the coefficient selection bias is positive, and fit-area model test was carried out using Hosmer-Lemeshow goodness of fit. Collinearity tolerance was tested using variables and their inflation factor.

#### 2.4.4.3. Conclusions on the prediction of occurrence of postoperative ARF

By comparing Model 1 with Model 2 we see a possible collinearity between therapy with ACE inhibitors and \( \beta \)-blocker, as both have statistical significance in the base model. Adding other variables (DM, CHF with LVEF <30\%, administration of contrast agent) enhances the power of the model, but individually they can not generate the ARF.

By comparing Model 1 with Model 3 shows that the only difference between these models is given by the ACE, noting that treatment with ACEI is a negative prognostic factor in generating the ARF.

Comparing Model 2 with Model 3 we see that non-medication treatment with ACE inhibitors (\( \beta \)-blockers, calcium channel blockers) is associated with an increased risk of developing the ARF, but only in the presence of other variables in the model.

Fourth multivariate model refers to patients operated for renal tumor, which history has not chosen any of comorbidity for other models, no drug treatment with ACE inhibitors and \( \beta \)-blockers, but developed ARF in the postoperative period.

### 2.5. MATHEMATICAL MODELS FOR THE PREDICTION OF SEVERITY OF POSTOPERATIVE ARF

#### 2.5.1. Multivariate analysis

##### 2.5.1.1. Hypothesis

We defined postoperative ARF as a 20% decrease in glomerular filtration rate, assessed by creatinine clearance (Cockroft formula).

To determine the severity of ARF in patients operated for renal tumors, we constructed a "naive", logistic model, the same formula as the leading risk factors for ARF.

### 2.11. CONCLUSIONS

Comparing the descriptive analysis results of the group with acute renal failure against the control group after surgery for renal tumors the following general conclusions can be drawn:
1. Old age is a predictor of ARF in the study given the relatively high proportion of patients > 71 years (23.5%) who developed ARF, which supports the idea that old age is reduced nephron capital, and comorbidities associates are multiple.

2. The statistically significant differences observed in the group of sex between the ages ARF average, meaning a higher average age in men (63.2 years), while in women the average age is 58.3 years.

3. Analyzing the results obtained by classifying patients by severity score ASA (American Society of Anesthesiologists) shows that most patients were classified as ASA III in the two groups, it is consistent with the high percentage of patients of advanced age, associated pathology history.

4. Patients with diabetes in the group who have progressed to postoperative ARF was a 35% higher than in the group of postoperative patients who have not evolved to the IRA. The increased incidence of ARF occurrence is explained in the study group because patients with diabetes, insulin-dependent or not, multifocal vascular abnormalities, particularly in the kidney.

5. In the group with the ARF 67% of patients underwent more than 72 hours preoperative computer tomography examination with injection of a contrast substance, and the remaining 33% had a magnetic resonance imaging exam or computer tomography examination of more than 72 hours preoperatively and 72% in the control group of patients underwent a computer tomography examination with injection of a contrast substance, and the remaining 28% had a magnetic resonance imaging exam. Relatively small difference between the groups is probably due to contraindications for this exam by the higher number of diabetic patients.

6. The average intraoperative blood pressure (mBP) was regarded as an independent risk factor with age factor.

7. The presence of higher proportion of cardiovascular risk factors (angina, myocardial infarction, stroke) in the group with ARF to control group stresses the importance of confounding factors in the onset and development of postoperative ARF.

8. In terms of antihypertensive treatment in both groups the proportion of patients treated with ACE inhibitors for hypertension is 53.04% and 51.47% in the ARF control group. Since the difference between these values is small, we found that treatment with ACE inhibitors is not a single factor in determining risk postoperative ARF.

9. S-type mathematical analysis were performed: univariate analysis, bivariate analysis and multivariate analysis.

10. Univariate analysis, performed by logistic regression took into account risk factors involved in the occurrence of postoperative acute renal failure (age, ASA score of severity, diabetes mellitus, congestive heart failure, administration of nephrotoxic substances in the preoperative period, Tam, myocardial infarction, hemoglobin) being found that three of these factors were statistically significant (p <0.5, confidence interval = 95%), namely diabetes mellitus, congestive heart failure with EF <30%, administration of contrast agent or other nephrotoxic substances.
11. In bivariate analysis have been considered important factors in triggering the ARF, which in univariate analysis were not significant or were limited statistically significant, and have used bivariate probit models combining two variables in the univariate analysis (models containing variable as the first treatment of hypertension with ACE inhibitors or beta-adrenoblocant combined with one of the statistically significant variables in univariate analysis or statistical value limit or combining two risk factors statistically significant in univariate analysis.

12. Combination therapy with ACE inhibitors with any present risk factors in univariate analysis enhances statistical significance of that risk factor.

13. Combination therapy with beta-blocker with any risk factors in univariate analysis is not statistically significant.

14. The combination of two risk factors statistically significant in univariate analysis does not reach the threshold of statistical significance in the bivariate model, which suggests that the practice of medicine is not enough presence of two risk factors in the history of the patient to trigger pathological ARF.

15. By comparing Model 1 with Model 2 we see a possible collinearity between treatment with ACE inhibitors and beta-blocker, as both have statistical significance in the base model. Adding other variables (DM, CHF with LVEF <30%, administration of contrast agent) enhances the power of the model, but individually they can not generate the IRA.

16. By comparing Model 1 with Model 3 shows that the only difference between these models is given by the ACE, noting that treatment with ACEI is a negative prognostic factor in generating the ARF.

17. Comparing Model 2 with Model 3 shows that treatment with non-ACE inhibitor medication (beta blockers, calcium channel blockers) is associated with an increased risk of developing the ARF, but only in the presence of other variables in the model.

18. Fourth multivariate model refers to patients operated for renal tumor, which history has not chosen any of comorbidity for other models, no drug treatment with ACE inhibitors or beta-blockers, but developed ARF in the postoperative period. To determine the severity of ARF in patients operated for kidney tumors has devised a mathematical model using the same steps as in mathematical analysis predicting ARF in these patients.

19. The prediction of severity of an ARF. Pair of pathology factors: treatment with ACE inhibitors, diabetes mellitus, congestive heart failure with LVEF <30%, administration of contrast agent causes a severe impairment of renal function (assessed by Cl.creat.) Regardless of patient age.

20. In model 2 prediction of severity of ARF is observed that the combination of the following factors cause a decrease Cl. created. to the value of 46.64 ± 0.13: non-ACEI antihypertensive therapy, diabetes mellitus, congestive heart failure EF<30%, administration of contrast agent, TAM <80 mmHg and any age.

21. Model 3 for prediction of severity of ARF. The presence of risk factors (diabetes, congestive heart failure with LVEF <30%, administration of contrast agent and any age) triggering the ARF in the postoperative period. Cl. created. drops to an average of 53.5345. The specificity of this model is low despite a high sensitivity, and these factors have additive effect in generating the ARF.
22. Model 4 for prediction of severity of ARF. It was achieved by combining the following variables: non-diabetic, without administration of contrast agent, non-CHF and any age (LVEF ≥ 50%). Cl. creat. level is around 86. The specificity of this model with a low sensitivity shows that age and Tam are not the only random variables involved in the decrease of Cl. creat.

23. Comparing Model 1 with Model 2 we see a possible collinearity between ACE inhibitors and beta-blockers compared with impaired renal function. The presence of other variables (DM, CHF with LVEF < 30% and administration of contrast agent) enhances the effect of each drug in part on decreasing Cl. creat.

24. Comparing Model 1 with Model 3 is observed that ACE inhibitors causes more severe impairment of renal function compared to that in the non-ACEI medication.

25. Age and mBP are independent risk factors that may cause ARF but only in combination with the above comorbidities and may worsen the prognosis of the patient postoperatively.

26. Each of the models is statistically significant. Models 3 and 4 specificity is low which confirms that the association of comorbidity in a patient operated favor the emergence ARF, but not determined.

27. The mathematical model prediction of installation and severity of postoperative ARF in patients with nephrectomy for renal tumor is an original model that can be used in medical practice in the preoperative phase, taking into account the influence of various patient risk factors that he presented in history and after clinical and laboratory factors that may cause postoperative complications.

28. Angiotensin converting enzyme inhibitors are taken into account as risk factors for postoperative ARF, with comorbidities that the patient has surgery for kidney tumors.

29. Although they could not statistically different percentages obtained with the pharmacodynamics of drugs in the ACEI group because of suspected cases is that few of these drugs captopril and lisinopril had a higher risk of being taken into account if the ARF.

30. Together with other cases cited in the literature of pathology in various other contexts in which ACE inhibitors are involved in causation installation ARF, ACE requires research to be called as preoperative risk factors especially in elderly patients.

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Key words: acute renal failure (ARF), angiotensin converting enzyme inhibitors (ACEI).

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Main parts's synthesis of Doctoral Thesis

Acute renal failure (ARF) is a syndrome characterized by postoperative rapid and sustained deterioration of glomerular filtration rate, which determines the retention of added nitrogen (urea, creatinine), changes in fluid and electrolyte and acid-base balance and manifests itself as a complication of surgery.

Angiotensin converting enzyme inhibitors represent a class of drugs used to treat high blood pressure, prevent pathology derived from it and decrease cardiovascular mortality. The mechanism of action of ACE is to reduce serum and local angiotensin II by competitive inhibition of angiotensin I converting enzyme to angiotensin II.

The research project aims to identify risk factors involved in the occurrence of acute renal failure in patients who underwent radical nephrectomy for renal tumor in order to achieve a limited of the common complications with direct implications for increased morbidity and mortality of surgical patients. Among the risk factors will be analyzed include some antihypertensive drugs as ACE inhibitors.

The mathematical model prediction of installation and severity of postoperative ARF in patients with nephrectomy for renal tumor is an original model that can be used in medical practice in the preoperative phase, taking into account the influence of various patient risk factors that he presented in history and after clinical and laboratory factors that may cause postoperative complications.

Angiotensin converting enzyme inhibitors are taken into account as risk factors for postoperative ARF, with comorbidities that the patient has surgery for kidney tumors.