EPIDEMIOLOGY OF ACUTE KIDNEY INJURY IN HUNGARIAN INTENSIVE CARE UNITS

PhD thesis

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INTRODUCTION

The incidence of the acute kidney injury (AKI) has been continuously increased over the years. This is a difficult burden for the staff and cost of the intensive care units. In the previous years epidemiological survey about the AKI was not carried out in Hungary. We have no controlled data about the epidemiology of AKI in critically ill patients. We have no standardized protocol for the treatment of kidney injury. There are no consistent methods for acute renal replacement therapy in intensive care units. There is not a specified and secured condition system for the management of acute kidney injury in Hungarian intensive care units. The lack of adequate financial refund for the renal replacement therapies is also a major problem.

AIMS OF THE STUDY

The aims of our study were to examine the incidence of AKI in Hungarian ICU's, to evaluate its impact on the outcomes (mortality, hospital- and ICU stay) in the context of other risk factors.

To examine the underlying factors that may be risk factors for acute kidney injury in Hungary.

To assess the daily practice of the renal replacement therapy in the treatment of AKI.

To define the tasks, which would improve the effectiveness of the treatment of AKI in the near future.

METHODS

Patients and Methods

This study is a national, multicenter, prospective, epidemiological survey of AKI in 7 ICUs in Hungary. The participant centres represent the spectrum of Hungarian ICUs (each of them were multidisciplinary non-cardiac ICU, representing the occurrence ratio of ICU patients in Hungary): two university centres (University of Debrecen, University of Szeged), three regional hospitals (Petz Aladar County Hospital Gyor, Javorszky Odon Hospital Vac, Hetenyi Geza County Hospital Szolnok,) and two city hospital (Dr. Kenessey Albert Hospital Balassagyarmat, Szent Lukacs Hospital Dombovar). During the two months of the study, every newly admitted patient was registered in the survey and was followed up until hospital discharge or death in hospital.

We analysed demographic, morbidity and outcome data of 459 adult patients admitted to ICUs between 10/01/2009 and 11/30/2009.

AKI was defined and classified by the AKIN criteria, which has only three stages. Stage 1 is defined as an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 μmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours). Stage 2 is defined as doubling of serum creatinine or a urinary output lower than 0.5 ml/kg/h for 12 h. Stage 3 is defined as tripling of serum creatinine or a serum creatinine higher than 4 mg/dl if there is an acute rise in serum creatinine of at least 0.5mg/dl, or a urinary output lower than

0.3 ml/kg/h for 24 h, or anuria for 12 h. Stage 3 also includes patients who need renal replacement therapy, irrespectively of the stage they are in, at the time of renal replacement therapy.

Chronic kidney disease patients on dialysis (n=3) and theoretically the renal transplant patients (n=0) were excluded from the analysis.

Data collection

Multiple data were collected on the day of ICU admission, including: demographics, co-morbidities, hospital and ICU admission, presumed aetiologies of AKI, urea and serum-creatinine level, Simplified Acute Physiology Score version II (SAPS II) and the Sepsis-related Organ Failure Assessment Score (SOFA).

The aetiologies of AKI were identified from a group of seven possible choices (septic shock, hypovolemia, cardiogenic shock (these definitions were based on international guidelines), surgical procedure, obstructive nephropathies, drug-induced and others).

If the patient required renal replacement therapy during the stay of intensive care unit, it was selected from a menu: continuous or intermittent technique. Within we fixed the fact of haemodialysis, hemofiltration, or a combination of both, hemodiafiltration. Subsequently, the renal replacement dose (treatment rate, ultrafiltration rate) was taken up.

The data were collected using an Excel-based data collection file. This was available to each participating centre with instructions.

We analyzed our prospectively collected database also with respect to surgical interventions. Medical patients (164), chronic kidney disease patients on dialysis (n=3), theoretically the renal transplant patients (n=0), polytraumatic patients (n=17) and the patients, who were after several body cavities affecting surgical intervention (n=10) were excluded from the analysis. The included patients (n=265) were categorized by serum creatinine and/or urine output into the AKIN stages, and the highest AKIN stage during ICU staying was evaluated.

RESULTS

Altogether 459 patients (aged 59.6±16.2 years, male/female ratio 258/201) were entered into the study. Because there were no significant differences among the examined variables in respect of the gender, in the following analyses the data were drawn together.

Parameters	*All patient*	*AKI*	*nonAKI*	*p = AKI vs. nonAKI*
Patient number (%)	459	112 (24,4)	347 (75,6)	
Age (year), mean±SD	59,6 ± 16,2	64,9 ± 14,4	57,6 ± 16,3	p<0,001
SAPS II. score, median	28 (16, 46)	47,5 (33, 59)	22 (14, 38)	p<0,001
SOFA score, median	4 (1, 7)	6 (4, 9.25)	2 (1, 5.5)	p<0,001
$SOFA_{non\ renalis}$, median		6 (3, 9)		
Sea-creatinin at ICU admission (umol/L), median	76 (59, 103)	117,5 (81, 205)	70 (57, 86.75)	p<0,001
Se-creatinin peak-concentration (umol/L), median	80 (61, 111.75)	165,5 (111.75, 274)	71 (58, 89)	p<0,001
Mechanical ventilation n (%)	200 (43,6)	84 (75)	116 (33,4)	p<0,001
Ventilator days, median	3 (1, 7)	3,5 (2, 11)	2 (1, 7)	0,177
Vasopressor, n (%)	100 (21,8)	58 (51,8)	42 812,1)	0,0018
Vasopressor hours, median	49 (24, 96)	48 (24, 99)	63 (18, 92)	0,619

One-hundred-twelve patients (24.4%) had AKI during their ICU stay. By AKIN criteria 53 patients (11.5%) were in Stage 1, 25 patients (5.5%) in Stage 2 and 34 patients (7.4 %) in Stage 3. Seventeen patients (15.2% of the AKI cases) had received renal replacement therapy. AKI patients tended to be older (64.9 vs. 57.6 years, $p<0.001$) and usually had more severe underlying diseases (SAPS II. 47.5 vs. 22. $p<0.001$, SOFA 6 vs. 2, $p<0.001$). The proportion of patients who needed mechanical ventilation during their ICU stay differed significantly in patients without or with AKI (75.0% and 33.4, $p<0.001$). A similar difference was also observed in the vasopressor needs (51.8% vs. 12.1% in patients without and with AKI, respectively, $p=0.0018$).

The major reason for ICU admission was surgical in 64.3% (gastrointestinal tract surgery was the most common), followed by neurological, cardiovascular, pulmonary diseases and trauma cases.

In 44.0% of patients, AKI was associated with septic shock. Sixteen percent of AKI was associated with major surgery, 20% was related to cardiogenic shock, 39% was related to hypovolemia, and 2% of AKI was potentially drug-related.

A logistic regression analysis was performed to analyse the predisposing factors for the incidence of AKI. Among the analysed parameters vasopressor treatment, SAPS II score, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stages of AKI. The same distribution was found when the independent predisposing factors for AKI Stage 3 were evaluated.

Among AKI Stage 3 patients 50% (17/34) received renal replacement therapy RRT). The overall utilization of

intermittent renal replacement therapy (IRRT) was high, with 64.8% (among all patients with RRT). All patients were treated with a veno-venous technique. The most common mode in the IRRT group was intermittent haemodialysis (88%) and in the continuous RRT group continuous veno-venous haemodiafiltration (94%). The median filtration dose was a regimen of 20 mL/kg/h.

The overall in-hospital mortality rate of AKI was 49% (55/112). The ICU mortality rate was 39.3% (44/112). Any degree of AKI was associated with a significantly increased all-cause ICU (9.5% vs. 29.3%, p<0.001) and hospital mortality (16.1% vs. 39.3%, p<0.001) compared with not having AKI. For patients admitted with AKI to the ICU, the median length of stay at the ICU increased by 120% (2 vs. 4.5 day, p<0.0001) and the median length of hospitalization by 35% (10 vs. 13.5 day, p=0.005), compared to patient without AKI.

Parameters	All patients	nonAKI	Acute kidney Injury				p= AKIall vs. nonAKI
			Stage 1	Stage 2	Stage 3	AKI all	
ICU-s stay (day), median	2 (2,5)	2 (2,4)	4 (2,8)	5 (3,14)	6 (2,18)	4.5 (2,13)	< 0,001
In-hospital stay (day), median	11 (7,16)	10 (7,14)	14 (5,18)	12 (7,24)	14 (4,29)	13.5 (5,20)	0,015
Overall mortality, n (%)	111 (24,2)	56 (16,1)	19 (35,9)	11 (44)	25 (73,5)	55 (49,1)	< 0,001
ICU-s mortality, n (%)	77 (16,8)	33 (9,5)	14 (26,4)	10 (40)	20 (58,8)	44 (39,3)	< 0,001
In-hospital mortality, n (%)	34 (7,4)	23 (6,6)	5 (9,4)	1 (4)	5 (14,7)	11 (9,8)	0,301

According to the logistic regression analysis age, mechanical ventilation, SOFA score and AKI Stage 3 were found as independent risk factors for ICU mortality. In respect of the hospital mortality only the higher age, the need of vasopressor treatment and the neurological diseases were the independent risk factors for the mortality.

Postoperative acute kidney injury

265 patients met the inclusion criteria and were followed for the development of AKI after ICU admission. In forty-eight cases (18.1%) developed AKI.

Patients with AKI were older (median age 67 vs. 61 years, p=0.002) with higher serum-creatinine level at ICU-admission (110 vs. 67 µmol/L, p <0.001) than patients without AKI: AKI patients were more severely ill (median SAPS II 40 vs. 18, p<0.001, SOFA 5 vs. 2 p<0.001) and have higher ratio of respiratory support (60.4% vs. 18%, p=0.002) and catecholamine-needs (50% vs. 6.5%, p<0.001). Sepsis occurred more frequently in the AKI-group (45.8% vs. 2.3%, p<0.001).

Forty-eight patients (18.1%) had AKI during their ICU stay. By AKIN criteria 27 patients (10.2%) were in Stage 1, 11 patients (4.2%) in Stage 2 and 10 patients (3.8 %) in Stage 3. Among AKI Stage 3 patients 40 % (4/10) received renal replacement therapy.

	All patients	AKI	non-AKI	p value
Patient number (n)	265	48%)	217	
Age (year),median	63 (52, 71)	67 (58, 77)	61 (50, 70)	0.002
SAPS II. score, median	21 (12, 34)	40 (29, 57)	18 (12, 28)	<0.001
SOFA score, median	2 (1, 5)	5 (3, 9)	2 (1, 4)	<0.001
Se-creatinine at ICU admission (µmol/L), median	72 (57, 89)	110 (78, 156)	67 (56, 84)	<0.001
Se-creatinine peak-concentr. (µmol/L), median	74 (59, 96)	148 (111, 225)	67 (57, 85)	<0.001
Mechanical ventilation, n (%)	68 (25.7%)	29 (60.4%)	39 (18%)	0.002
Vasopressor treatment, n (%)	38 (14.3%)	24 (50%)	14 (6.5%)	<0.001
Number of septic patient , n (%)	27 (10.1%)	22 (45.8%)	5 (2.3%)	<0.001

The overall mortality rate of AKI was 39.6% (AKI 1: 25.9%, AKI 2: 40%, AKI 3: 54.5%) and the ICU mortality rate was 33.3% (AKI 1: 18.5%, AKI 2: 10%, AKI 3: 54.5%). Any degree of AKI was associated with a significantly increased all-cause ICU (6.9% vs. 33.3%, p<0.001) and overall in-hospital mortality (8.8% vs. 39.6%, p<0.001) compared with not having AKI. For patients admitted with AKI to the ICU, the median length of stay at the ICU increased by 200% (2 vs. 6 days, p<0.0001) and the median length of hospitalization by 80% (10 vs. 18 days, p<0.001), compared to patient without AKI.

Parameters	AKI	non-AKI	p value
ICU-s stay (days), median (IQR)	6 (3, 17)	2 (2, 3)	<0.001
In-hospital stay (days), median (IQR)	18 (12, 24)	10 (8, 14)	<0.001
ICU-s mortality, n (%)	16 (33.3%)	15 (63.9%)	<0.001
In-hospital mortality, n (%)	2 (4.2%)	4 (1.8%)	<0.001
Overall mortality, n (%)	19 (39.6%)	19 (8.8%)	<0.001

We analyzed the incidence of acute kidney injury according to different types of surgery. The incidence of AKI occurred more frequently in the abdominal surgery group (53.9%, p<0.001), than in intracranial- (12.9%), thoracic-surgery (2.0%) or surgery outside the cavities (10%) groups.

A logistic regression analysis was performed to analyze the predisposing factors for the incidence of AKI. Among the analyzed parameters vasopressor treatment, serum creatinine on ICU admission and sepsis were the independent risk factors for development of any stage of AKI. Multivariate analysis in respect of the different types of surgery for the determinants of AKI identified the intra-abdominal surgery as an independent predictor (OR: 2.558; CI: 1.75 – 3.366;

p=0.020). According to the logistic regression analysis, age, vasopressor treatment, SAPS II. score and serum-creatinine peak-concentration were found to be independent risk factors for ICU mortality.

We elaborated the different types of major abdominal procedures according to the occurrence of AKI and did not find significant differences among the different types of surgery. The most frequent diagnosis was cancer, and this illness associated with significantly lower rate of AKI than was observed in the mechanical obstruction and perforation groups.

In the abdominal surgery group, we analyzed the incidence of AKI on the basis of serum creatinine level at ICU admission (under and above the normal laboratory limit values). About 110 patients had serum creatinine under the normal laboratory level and, during the ICU stay, AKI developed in 16 (14.5%) patients. The serum creatinine level during admission was above the normal limits in 39 patients and among them significantly higher ratio of AKI (n=23; 58.9%) was observed ($p < 0.005$).

The ICU and hospital stay and mortality did not differ significantly in respect of the creatinine level at admission.

CONCLUSIONS

We have conducted a national, multicenter, prospective, epidemiological study on AKI, occurring at representative Hungarian ICUs. For the first time, we have established the incidence of AKI using the AKIN criteria in Hungarian ICUs. The value of our study was confirmed, by the "BioMed Central Nephrology" on-line professional surface

where our summarizing article was classified, as "Highly accessed" (1 year >1300 views). Our results raised a number of problems in relation to diagnostic and therapeutic approach of acute kidney injury in the intensive care units.

AKI occurs in similar incidence in Hungarian ICU-s compared to international data. In contrast, the mortality is much more favourable when compared to intensive care units in Europe. We have to think about this fact. A possible solution would be the demand for early diagnosis, timely to begin the causal treatment opposite to the late symptomatic therapies. Although these data were not analyzed in our study, but from the high mortality rate we can conclude that it would be appropriate to introduce the measurement of biomarkers in early diagnosis and closely use with the clinical status, as a monitor of our treatment's success or failure. The early detection of biomarkers for acute renal failure (ARF) could predict the development of AKI, the need of RRT and also the ICU's and in hospital stay and mortality. Most markers for early detection of ARF require prospective evaluations in large populations. Thus, future studies will be needed to determine how can be utilized the biomarkers of AKI to guide prognosis, resource use, and enrolment into trials of therapeutic intervention above and beyond our current clinical measures. Since the assessment is an important element not only for early diagnosis but also in the differential diagnosis of prerenal renal failure, we consider their availability for routine intensive care and perioperative medicine.

In 50% of AKI stage 3 we missed to apply any form of RRT. This ratio is too far from the international rate that may also contribute to our higher mortality. The reason of this low frequency of RRT in the stage 3 of AKI is not obvious from the data of the study. Perhaps, these patients were in advanced/irreversible stadium of the multi-organ failure

therefore there was no reason for RTT. Perhaps, these patients died before the introduction of RRT. Perhaps, the material and personal conditions were not provided and the patients were not transportable. Perhaps, ... I do not want an other "perhaps" issue to start my thoughts. One thing is certain, something is not right, something is wrong.

We need to ensure for the intensive care units the financial background of the dialysis treatments.

Parallel with the financing support it is necessary to ensure adequate equipments that are suitable for carrying out the different treatment modalities.

We have to ensure special trainings for intensive care physicians and nurses. We have to integrate the education of the theoretical and practical foundations of renal replacement therapy into the teaching. We should organize post-graduate education courses for both physicians and intensive care nurses to be able to perform RTT efficiently.

We have to think about the high incidence of AKI after abdominal surgery. Because there are very few epidemiological data in international literature in this field, we have not thought the monitoring intra-abdominal pressure (IAP) before the start of our study. IAP monitoring is an important factor in the prevention of acute kidney injury. We can expect higher IAP not only in abdominal surgery, but there are several factors which may influence its value, especially, in patients with severe sepsis. Fluid resuscitation to correct hypovolemia and avoid organ failure remains a cornerstone of critical care management. Similarly to the concept of “early goal-directed therapy”, originally described for the treatment of severe sepsis, it is reasonable to control the high IAP as soon as possible. Although, adequate intravascular volume is

also especially important in the treatment of intraabdominal hypertension (IAH)/abdominal compartment syndrome (ACS), the excessive fluid resuscitation is an independent risk factor of both IAH and ACS, and worsens the survival. To avoid this complication IAP monitoring is essential.

We need to complete the “Clinical Practice Guideline of Hungarian Society of Anaesthesiology and Intensive Care for the renal replacement therapy” with the treatment protocol of acute kidney injury.

After the first steps, we may go on our road to prevent the occurrence and to establish the adequate management of AKI. In this case we have the chance that not only the morbidity ratio but also the mortality ratio will approach to the international high standard.

LIST OF PUBLICATIONS

List of publications related to the dissertation

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