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SEPSIS IN PATIENTS WITH SEVERE ACUTE RENAL INJURY

SEPSE EM PACIENTES COM LESÃO RENAL AGUDA SEVERA

SEPSE EN PACIENTES CON LESIÓN RENAL AGUDA SEVERA

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ABSTRACT

Objective: to analyze the prevalence of sepsis and mortality of patients with acute renal injury in hemodialysis renal replacement therapy. **Method:** quantitative study, cross-sectional, with 44 patients. Data were collected with questionnaires and in medical records, analyzed through descriptive measures (mean, median, standard deviation and percentages) and presented in tables. **Results:** sociodemographic variables revealed that 63.6% are males, with a mean age of 63.3 years. Sepsis was the main cause of acute renal injury in 65.9% of patients and mortality was 79.5%. The length of ICU stay was 22.45 ± 13.5 days and the total hospitalization time was 31.30 ± 21.4 days. Intermittent hemodialysis was the most used in 61.4% of the cases. **Conclusion:** despite international campaigns, sepsis and its mortality remain high. **Descriptors:** Acute Kidney Injury; Sepsis; Renal Replacement Therapy.

RESUMO

Objetivo: analisar a prevalência de sepse e mortalidade dos pacientes com lesão renal aguda em tratamento renal substitutivo hemodialítico. **Método:** estudo quantitativo, transversal, com 44 pacientes. Os dados foram coletados com questionários e em prontuários, analisados por meio de medidas descritivas (média, mediana, desvio padrão e porcentagens) e apresentados em tabelas. **Resultados:** as variáveis sociodemográficas revelaram que 63,6% são do sexo masculino, com idade média 63,3 anos. A sepse foi a principal causa de lesão renal aguda em 65,9% dos pacientes e a mortalidade foi de 79,5%. O tempo de internação na UTI foi $22,45 \pm 13,5$ dias e o tempo total de hospitalização foi $31,30 \pm 21,4$ dias. A hemodiálise intermitente foi a mais utilizada em 61,4% dos casos. **Conclusão:** apesar de campanhas internacionais, a sepse e a sua mortalidade permanecem altas. **Descritores:** Lesão Renal Aguda; Sepse; Terapia de Substituição Renal.

RESUMEN

Objetivo: analizar la prevalencia de sepsis y mortalidad de los pacientes con lesión renal aguda en tratamiento renal sustitutivo hemodialítico. **Método:** estudio cuantitativo, transversal, con 44 pacientes. Los datos fueron recolectados con cuestionarios y en prontuarios, analizados por medio de medidas descriptivas (media, mediana, desviación estándar y porcentajes) y presentados en tablas. **Resultados:** de las variables sociodemográficas, revelaron que 63,6% son del sexo masculino, con edad media 63,3 años. La sepsis fue la principal causa de lesión renal aguda en el 65,9% de los pacientes y la mortalidad fue del 79,5%. El tiempo de internación en la UTI fue de $22,45 \pm 13,5$ días y el tiempo total de hospitalización fue $31,30 \pm 21,4$ días. La hemodiálisis intermitente fue la más utilizada en el 61,4% de los casos. **Conclusión:** a pesar de las campañas internacionales, la sepsis y su mortalidad siguen siendo altas. **Descriptor:** Lesão Renal Aguda; Sepse; Terapia de Substituição Renal.

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INTRODUCTION

Severe sepsis and septic shock are the major health problems. There is an increase in its incidence, affecting millions of people every year around the world, killing one in four people, similar to polytrauma, acute myocardial infarction, or stroke. The severity of sepsis is dependent on the speed and appropriateness of the therapy administered within the first hours after its development.¹

The main causes of mortality among critical patients are severe sepsis and septic shock. They have a negative and growing impact on public health. In the last thirty years, there has been an increase in the number of deaths. The studies indicate that the incidence has increased, despite the reduction of general in-hospital mortality.²

There are international campaigns, such as Surviving Sepsis Campaign, with the objective of developing guidelines to reduce sepsis mortality by 25%, in five years, with awareness and guidance to the health professional, improving after-care in the Intensive Care Unit (ICU), with more accurate diagnosis and appropriate treatment with development of care protocols. This sepsis survival campaign began in 2002 and is already in its third edition.¹

Septic shock is one of the major factors contributing to the development of acute kidney injury (AKI) in critically ill patients. It is associated with high mortality, especially, associated with multiple organ failure.³ AKI is common during the critical phase of the disease, there is an increase in incidence in hospitalized patients, and it indicates a worsening of clinical outcome. It is associated with an increase in the use of intensive resources, mortality and an increase in hospitalization time.⁴

Renal replacement therapy (RRT) is the support of therapy in patients with acute septic kidney injury, where preventive and medical strategies have clearly failed.⁵ RRT compensates for the loss of renal function and its associated sequelae, such as, eliminating accumulation of nitrogenous products, electrolytic disturbances, uremic toxins, metabolic acidosis and volume overload. However, the extracorporeal system does not compensate for renal metabolic and endocrine function.⁶

OBJECTIVE

- To analyze the prevalence of sepsis and mortality in patients with acute kidney injury undergoing renal replacement therapy (RRT).

METHOD

A quantitative, cross-sectional study carried out at the intensive care unit of a large tertiary hospital, a reference in the macro-region of the Triângulo-norte region of the state of Minas Gerais, Brazil. Hospital belonging to the network of University Hospitals of the Ministry of Education and academically linked to the Federal University of Uberlândia/FUU. Cross-sectional study of prevalence in the adult Intensive Care Unit (ICU). This unit consists of 30 beds divided into nine surgical, nine clinical, nine neurological and three isolation.

Each member of the Nursing team is responsible for one or two critical patients per term of service. There was an analysis of the data in the patient records and in the Hospital Information System (HIS), such as age, gender, date of hospital stay, date of ICU stay, hospitalization diagnosis, biochemical and hematological parameters and preexisting infections. The type of hemodialysis therapy, noradrenaline use, date of hospital discharge or death, biochemical and hematological parameters and infections presented after the onset of hemodialysis were also collected. The data collection was obtained through the completion of a questionnaire elaborated from the objectives proposed by the researchers. All patients who started hemodialysis treatment for acute kidney injury, were analyzed for a period of six months, in the first half of 2015.

Participants were all patients aged 18 years and over evaluated by nephrologist physicians and found the diagnosis of acute kidney injury and the need for hemodialysis renal replacement therapy initiated at the hospital. The signature of the patient's consent term or legal guardian was a necessary factor. Patients with exogenous intoxication, patients with AKI transferred from other hospitals in RRT, end-stage renal disease on a hemodialysis program, renal transplant patients or patients with suspected brain death were excluded. Characterized the population as age, gender, comorbidities, type of hospitalization, time of hospitalization, use of noradrenaline and mechanical ventilation.

The AKI was stratified according to the RIFLE criterion (Risk, injury, failure, loss or end-stage renal disease). In the absence of a baseline (creatinine) value, glomerular filtration rate (GFR) was calculated in relation to serum creatinine based on age, race, and sex by the simplified MDRD (Modification of Diet in Renal Disease) formula.⁷

For the definition of SIRS, sepsis and septic shock, the 1991 Consensus Conference Definitions, of the American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference Committee were used. The ACCP / SCCM Consensus Conference (ACCP / SCCM, 1992) ⁸, in agreement with SCCM / ESICM / ACCP / ATS / SIS International Sepsis Definitions Conference of 2001.⁹ If there were any doubts about the type of infection, the ICU attending physician was consulted.

The SOFA prognostic score (Sequential Organ Failure Assesment), formed from the sum of changes in six different systems, makes it possible to measure organ dysfunction separately, as well as to note the efficacy of therapies directed to that organ system, as well as individually assess patients,¹⁰ being used as a predictor of death.

Routine infectious parameters in the ICU were analyzed as blood count, C Reactive Protein (CRP), Procalcitonin and cultures. There was no interference of the researcher regarding the requests for medical examinations, being an expectant participation. The patient was followed until its clinical outcome (hospital discharge or death). The inclusion or suspension of the patient in the TRS was an exclusive decision of the nephrologist.

Data were initially, described through descriptive measures (mean, median, standard deviation and percentages) and tables. Quantitative variables were evaluated if they followed the normal probability,

distribution using the Shapiro-Wilk test. For the quantitative variables that follow normal distribution, the Pearson correlation coefficient was calculated and, those variables that do not follow normal distribution, were obtained Spearman correlation coefficient.

The association of qualitative variables was assessed by the chi-square test. The variables were still evaluated using Student's t-test or Kruskal-Wallis test. All tests were conducted, considering a significance of 5% (p <0.05) and using Sigmaplot v.

The study obtained a favorable opinion from the Research Ethics Committee under number 862.802.

RESULTS

During the study period, the sample consisted of 44 patients. In Table 1, we observed that the mean age of participants was 63.3 ± 16.9 years, ranging from 19 to 89 years, with a predominance of males, 63.6% (28/44) and 36.4%. The majority of patients required invasive ventilatory support (90.9%) and noradrenaline (68.2%), both of which were correlated with mortality (p = 0.023 and p = 0.007, respectively).

Table 1. Demographic and clinical characteristics of critically ill patients in RRT. Uberlândia (MG), Brazil, 2017.

n	44	p-value
Age (years) (± SD)	63.3 ± 16.9	
Sex (%)		0.3086
Male	63.6	
Female	36.4	
Reason for hospitalization (%)		
Surgical	50	
Trauma	29.5	
Clinical	20.5	
Patients on MV (%)	90.9*	0.023
Patients on Noradrenaline (%)	68.2*	0.007
Co-morbidity (%)		
SAH	59.1	
DM	27.3	
Cardiopathy	20.9	
Smoking	54.4	
RIFLE rating (%)		0.1168
R	2.3	
I	22.7	
F	75	
Cause of AKI (%)		
Sepsis	65.9	
Nephrotoxic drugs / contrast	11.4	
Hepatorenal	6.8	

Large surgery	6.8	
Cardiogenic shock	4.5	
Urinary Tract Obstruction	2.3	
Hypovolemia	2.3	
Mortality (%)	79.5	
Renal function recovery of survivors (%)	66.6	
Dependents of TRS after hospital discharge (%)	33.3	
SOFA (± SD)	15.4(±2.5)	
Length of ICU stay (days) (± SD)	22.45(±13.5)	
Total hospitalization time (days) (± SD)	31.3(±21.4)	
Dialytic mode (%)		
Intermittent Hemodialysis	61.4	0.8586
SLED	11.4	
Both	27.3	

Source: Medical Records and Intra-Hospital Information System of HC-UFU.DP-Standard deviation; MV- Mechanical ventilation; SAH- Systemic Arterial Hypertension; DM-Diabetes Mellitus; R-Risk; I-Injury; F-Failure; AKI- Acute Kidney Injury; SOFA- Sequential Organ Failure Assesment; UTI - Intensive Care Unit; SLED- Sustained low-efficiency extended dialysis. * p <0.05 in relation to death. Uberlândia (MG), Brazil, 2015.

Sepsis was the main cause of AKI, according to table 3. Using the SOFA score for death, on the first day of initial hemodialysis, an average of 15.4 ± 2.5 was found, with a mortality greater than 90 %, according to table 1. There was an association between SOFA score and death with p = 0.0021,

according to table 2. In this study, septic shock and severe sepsis were present in 54.5% and 13.6% of the population studied when starting renal replacement therapy, as shown in table 3. The main focus of primary infection was pulmonary (41.1%), according to table 4.

Table 2. Clinical and laboratory characteristics related to the mortality of critically ill patients in renal replacement therapy -Uberlândia (MG), Brazil, 2017.

Variables	Death(35)	Non Death	p-value
Age	65.29±15.08	55.56±22.05	0.2052
Urinary volume	2.03±0.86	2.44±1.01	0.2324
Creatinine admission	1.18±0.48	1.92±1.06	0.0061
Creatinine pre HD	3.72±2.05	4.41±2.67	0.5124
Urea admission	48.20±20.27	83.67±28.08	0.0039
Urea Pre HD	150.74±57.02	163.22±78.96	0.8272
Procalcitonin	14.54±28.47	15.47±34.87	0.3238
MAP pre HD	61.77±12.55	78.78±10.69	0.0006
CRP	17.32±11.69	18.96±14.38	0.7257
Admission / HD days	12.31±14.27	7.56±7.38	0.3193
Length of hospital stay	30.34±19.13	35±30.01	0.9304
SOFA	15.40±2.56	12.22±2.73	0.0021

Source: Medical Records and Intra-Hospital Information System of HC-UFU.HD- hemodialysis, MAP- Mean arterial pressure, CRP-Reactive Protein, SOFA-Sequential Organ Failure Assesment. Uberlândia (MG), Brazil, 2015.

Table 3. Classification of infection at the start of TRS and its relation with the mortality of critically ill patients in renal replacement therapy - Uberlândia (MG), Brazil, 2017.

Classification of infection when starting TRS(%)	p-value	
No infection		
SIRS	18.2	0.2118
Sepsis	9.1	0.8172
Severe sepsis	13.6	0.8004
Septic shock	54.5	0.0266

Source: Medical Records and Intra-Hospital Information System of HC-UFU.TRS- Renal replacement therapy, SIRS- Inflammatory Response Syndrome. Uberlândia (MG), Brazil, 2015.

Table 4. Main sepsis infection outbreaks of critically ill patients in renal replacement therapy - Uberlândia (MG), Brazil, 2017.

Main outbreaks of infection (%)	p-value
Pulmonary	41.10
Bloodstream infection	14.30
No definite location	14.30
Abdominal	12.5
Urinary	8.9
No defined focus	14.3
No infection	3.6
Surgical site	3.6
Cutaneous	1.8

Source: Medical Records and HC-UFU Intra-Hospital Information System. Uberlândia (MG), Brazil, 2015.

DISCUSSION

Few studies in Brazil focus on severe AKI. Usually, patients with AKI are not analyzed in a non-dialytic way, and there is a gap in this type of discussion. The population studied presented demographic characteristics similar to those described in other studies, such as age and sex,¹¹⁻³ surgical admission.¹¹

Data show that the incidence of AKI in a postoperative population generally ranges from 16.7% to 30%.¹⁴ The results of this study were above the literature (50%). In this study, the predominant comorbidities were Systemic Arterial Hypertension (SAH), Diabetes Mellitus (DM) and cardiopathy, converging with reports in the literature.^{11-2,15}

In the AKI hospital area, it affects about 5% to 7% of hospitalized patients. The number of critical patients affected can reach 3% to 25% in an ICU. When involving multiple organ failure, the mortality of critically ill patients can range from 22% to 67%. When related only to AKI, mortality reaches numbers greater than fourfold in critically ill patients. RRT is the only effective method, however, improvement is needed to reduce mortality. The mortality of patients with severe AKI, ie requiring hemodialysis, reaches high levels from 45% to 70%.^{7,16}

In this study, a mortality rate of 79.5% was found, above what is verified in the literature. This result can be explained by the profile of severe patients received in the ICU, since the SOFA mortality score presented a high index and association with mortality (p = 0.0021). Although SAPS or APACHE severity scores were not calculated, there was a high percentage of mechanical ventilation (90.9%) and noradrenaline (68.2%), both with association with death (p = 0.023 and p = 0.007, respectively)). Also, intermittent RRT (RRT-I) was used in 61.4%, although there was no association with death in this study (p = 0.8586). Continuous RRT (RRT-C) would be more appropriate for the critical patient

profile. This therapy is indicated for patients with severe hemodynamic instabilities, with continuous removal of toxins and solutes and easy handling of the hydroelectrolyte balance. However, there is a much higher cost when compared to RRT-II.¹⁷

In Brazil, the mortality of patients who are submitted to RRT, in general, is also high. In a recent study, in a retrospective cohort (death and non-death) of prolonged hemodialysis, the mortality found was superior to all studies, being 82.5%. There was recovery of renal function in 20.4% and evolution to chronic kidney disease and need for permanent RDS in 3.6% of the cases studied.¹³

Regarding other studies, in Portugal, sepsis mortality was reported in 48.8% of the patients.¹⁵ In Canada, 45.3% mortality was reported in sepsis, in a prospective study that aimed to describe the characteristics of RRT , with the use of RRT-C (70.1%), RRT-I (24.4%) and SLED (5.6%).

In Finland, mortality in RRT, found in a cohort of patients admitted to the ICU (RRT and non-RRT), was 35%. Taking into consideration only patients with severe sepsis / septic shock and SRT, mortality reached a total of 44.5 %.¹⁸

In Japan, in a retrospective cohort of sepsis and non-sepsis, the mortality of septic patients / septic shock was 48.5% with the use of RRT-C. However, there was no significant difference in this ICU mortality, since they are patients with more severe clinical conditions, alterations in vital signs and biochemical exams, in the multivariate regression analysis (odds ratio, 0.378, p = 0.12), sepsis was associated with low mortality, comparing septic and nonseptic patients.¹⁹

In this study, considering sepsis, severe sepsis and septic shock, mortality was 85.8%, an expressive value compared to the data presented previously. However, the classification criteria for AKI, indication and dialysis modality differ in each study.

Sepsis is associated with a 20% increase in absolute death rates in patients undergoing dialysis.²⁰

The length of ICU stay in this study was, on average, 22 days and total hospitalization time was 31 days. Minor ICU length of hospital stay was found in Canada (13 days), but the total length of hospital stay was 28 days.¹¹ The hospitalization time of this study was very high compared to a multicenter study, conducted in 97 centers, the length of ICU stay was six days and hospital length of 15 days.¹²

In a ICU in Finland, the mean number of days of hospitalization was 5.2 days and hospital length of 16 days.¹⁸ The time of this study, in number of days between hospital admission and the start of RRT, was 11 days. Time much higher than the one found in the literature, staying around two to three days.^{11,15}

There is a study suggesting the onset of early RRT. Potentially leading to a faster recovery of renal function, shorter hospital stay and reduced mortality. In a cohort of patients with continuous RRT with early and late onset, following KDIGO, mortality within 90 days was lower in the early RRT group, compared to the late group (39.3% and 54.7%, respectively). There was a reduction in the time of RRT and shorter time of use of mechanical ventilation. However, the onset of early RRT may be a detrimental exposure, since the return of renal function may occur spontaneously in some patients.²¹

The right time to initiate RRT, in patients with AKI, is very controversial within nephrology. There is no consensus on how to define early or late hemodialysis. In life-threatening situations corrected by RRT, such as hyperkalemia, severe metabolic acidosis and respiratory failure due to fluid accumulation, the immediate onset of RRT is evident.²²

There is an increase in the incidence of AKI, with increased resource utilization and mortality. Treatment is largely supportive and the prognosis of patients requiring dialysis remains poor. The dialysis method of choice and the ideal time to start the RRT are dependent on the general state of the patient.⁴

LRA occurs in up to 65% of patients with septic shock and is independently, associated with increased risk of death, in patients with sepsis. Sepsis is the cause of AKI in approximately 33% of patients in the Intensive Care Unit.⁵ However, it is important to note that causes rarely occur in isolation, multiple

renal insults (hemodynamic, septic and nephrotoxic, frequently associated with pre-existent kidney insufficiency). Although they are common, their mechanisms for the AKI still remain unclear.²³

Acute septic kidney injury is generally considered to be a global or regional consequence of hypoperfusion caused by tissue damage by ischemia-reperfusion. Prevention strategies include hemodynamic optimization, fluid management of patients with septic shock, avoidance or appropriate use of nephrotoxic drugs such as antibiotics and contrast medications.²³

The etiology of AKI in this study corroborates with the literature studied, with sepsis being the main cause. However, higher indices were presented (65.9%) in this study, in relation to those found in other studies. In a multicenter study, the etiology of AKI was also a consequence of sepsis in 40.7%, followed by hypovolemia (34.1%), drug-related (14.4%), cardiogenic shock (13.2%), hepatorenal (3.2%) and renal obstruction (1.4%).

In Germany, in a prospective randomized study, that analyzed the effects of continuous versus intermittent hemodialysis on mortality, severe sepsis and septic shock were responsible for 65% of the AKI etiology. About 80% of the patients analyzed required mechanical ventilation and vasoactive drugs on the first day of RRT²⁴. In this study, more than 90% of patients required mechanical ventilation and 68% of noradrenaline. In Finland, 61.8% required mechanical ventilation and 63.9%, of vasoactive drugs.¹⁸

The main focus of infection was pulmonary infection, with almost half the population, 41.1%, a fact that matches the results obtained in Japan (30%).¹⁹

Most of the patients in these studies are under mechanical ventilation, a fact that evidences the relation between infection and ventilatory support. According to ANVISA, in Brazil, the incidence of respiratory infection revolves around 16.25 cases per thousand days of MV use in an adult ICU, reaching 21.06 cases per 1000 days in ventilator use in the ICU. High numbers compared to the United States, which represent a total of 2.4 and 1.2 cases in clinic-surgical and coronary hospitals, respectively.²⁵

CONCLUSION

Sepsis is a serious recurring problem in hospital environments, especially, in the highly complex sectors, such as Intensive Care Units. Thus, it can be inferred that the results

allowed us to know the prevalence of sepsis as a disease and its direct correlation with the elevation of the mortality rate of patients with acute kidney injury on renal replacement renal replacement therapy.

The guidelines of international campaigns, to better manage the patient with sepsis, should have a greater coverage and adherence of health professionals, since the morbidity and mortality still remain high. Preventing the onset of infection, should be prevented from progressing to more serious forms, such as sepsis and multiple organ failure and consequent renal involvement. Improvements in basic care to prevent infection, such as training of the health team, use of appropriate and quality materials, should be strengthened.

Just as the AKI should be prevented and diagnosed early, avoiding the most severe (dialytic), form aimed at reducing in-hospital mortality and also its chronicity, which leads to an increase in financial expenses. Prevention actions and awareness of the population in the basic health area are fundamental for reducing factors that cause kidney damage. To individualize the care of the critical patient in the RRT, adjusting their clinical conditions for dose, time, type of dialyzer and dialysis mode to better meet their needs.

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