Stressful life events and acute kidney injury in intensive and semi-intensive care unities

Eventos vitais estressores e lesão renal aguda em centros de terapia semi-intensiva e intensiva

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ABSTRACT

Introduction: Several studies point out that pathophysiological changes related to stress may influence renal function and are associated with disease onset and evolution. However, we have not found any studies about the influence of stress on renal function and acute kidney injury. **Objective:** To evaluate the association between stressful life events and acute kidney injury diagnosis, specifying the most stressful classes of events for these patients in the past 12 months. **Methods:** Case-control study. The study was carried out at *Hospital São Paulo*, in *Universidade Federal de São Paulo* and at *Hospital dos Servidores do Estado de São Paulo*, in Brazil. Patients with acute kidney injury and no chronic disease, admitted to the intensive or semi-intensive care units were included. Controls included patients in the same intensive care units with other acute diseases, except for the acute kidney injury, and also with no chronic disease. Out of the 579 patients initially identified, 475 answered to the Social Readjustment Rating Scale (SRRS) questionnaire and 398 were paired by age and gender (199 cases and 199 controls). **Results:** The rate of stressful life events was statistically similar between cases and controls. The logistic regression analysis to detect associated effects of the independent variables to the stressful events showed that: increasing age and economic classes A and B in one of the hospitals (*Hospital São Paulo* – UNIFESP) increased the chance of a stressful life event (SLE). **Conclusions:** This study did not show association between the Acute Kidney Injury Group with a

RESUMO

Introdução: Diversos estudos evidenciam que as alterações fisiopatológicas, quando associadas ao estresse, podem influenciar a fisiologia renal e estão associadas ao aparecimento de doenças. Entretanto, não foi encontrado nenhum estudo que tivesse realizado investigação associando estresse e lesão renal aguda. **Objetivo:** Avaliar a associação entre os eventos vitais estressores e o diagnóstico de lesão renal aguda, especificando as classes de eventos mais estressores para esses pacientes, nos últimos 12 meses. **Métodos:** Estudo caso-controle. Foi realizado no Hospital São Paulo da Universidade Federal de São Paulo e no Hospital dos Servidores do Estado de São Paulo. Foram incluídos pacientes com lesão renal aguda, sem doenças crônicas, assistidos em Centros de Terapia Intensiva ou semi-intensivas. Os Controles incluíram pacientes assistidos nos mesmos Centros de Terapia Intensiva, com outras doenças agudas, exceto lesão renal aguda e, também, sem doenças crônicas. Dos 579 pacientes inicialmente identificados, 475 responderam ao instrumento *Social Readjustment Rating Scale* (SRRS) e 398 pacientes foram pareados por idade e sexo (199 casos/199 controles). **Resultados:** Constatou-se que a frequência dos eventos vitais estressores nos casos apresentava equivalência estatística aos controles. A regressão logística para examinar os efeitos combinados das variáveis independentes associados aos eventos estressantes evidenciou que: o aumento da idade e as classes econômicas AB intensificam a chance da presença do evento estressante em cerca de duas vezes; as classes socioeconômicas AB do Hospital São Paulo elevam a chance de evento estressante. **Conclusões:** O presente estudo não evidenciou que o grupo com

higher frequency of stressful life events, but that old age, higher income, and type of clinical center were associated.
Keywords: Acute kidney injury. Intensive Care Units. Stress, psychological. Social class.

lesão renal aguda estivesse associado à maior frequência de eventos estressores, mas idade e renda elevadas e, ainda, o tipo de centro clínico estão associados.
Palavras-chave: Lesão renal aguda. Unidades de Terapia Intensiva. Estresse psicológico. Classe social.

Introduction

The acute kidney injury (AKI) is a serious disease associated with high morbidity and mortality rates. Its prevalence depends mostly on the medical environment where the study is conducted. Studies related to the incidence and mortality rates of AKI in an intensive care unit (ICU) show very high rates.[1-3] Many conditions are associated with AKI, such as cardiocirculatory surgeries, polytraumatism, septicemia, use of contrast, bleeding, among others.[3-6] The high mortality rate of these pathologies, especially in ICU, brings out the need for attention for this disease.[1-7]

Studies on chronic kidney diseases have shown the importance of ethnical,[8] environmental,[9,10] socioeconomical,[11-15] and psychic factors, modulating the disease, its complications and progonosis.[16] Many investigations have demonstrated that chronic stress conditions are associated with allostatic overload,[17,18] that is, the attempt of the body to find stability through stressful change, thus leading to changes in cortisol and insulin levels, in the hypothalamo-hypophyseal axis (HPA), kinins, and other proinflammatory elements, among other homeostatic changes. These changes have physiological implications, including alterations in renal physiology.[19-21] However, the ratio of some subjects as to the adaptation to stressful events is still unknown, even though some of them seem compensated.

Stress, anxiety and depression can be associated to the onset of diseases,[22-25] tissue and cell injuries.[26,27] According to some authors, these conditions may lead to renal repercussions, such as the maintenance of high pressure levels[22] and the association with the presence of calculi in the urinary system,[1,28], among other manifestations.

It is important to say that, although this is a relatively new field of study, many authors have focused on the association of social and environmental factors, stress, anxiety and depression with chronic kidney diseases. A review of national and international literature shows there have been no investigations to correlate stress and acute kidney conditions up until now. Since pathophysiological changes associated with stress have components that may influence renal physiology, the objective of this study was to analyze if stressful events might be associated with AKI among patients who were in an ICU. Besides, the second objective was to check which events have been more frequent in this population.

Material and methods

It is a case-control study carried out at *Hospital São Paulo* (HSP), connected to *Universidade Federal de São Paulo* (UNIFESP) and at *Hospital do Servidor Público Estadual de São Paulo* (HSPE). Both services have different characteristics concerning their population.

HSP is known for being a university hospital that cares for patients in the Brazilian National Health System (*Sistema Único de Saúde – SUS)*, with a varied range of patients from different social classes. *Hospital dos Servidores* cares for employees of the State of São Paulo, which consists of a relatively homogeneous and specific population. The addition was related to the number of ICUs and beds. UNIFESP has 11 ICUs, among which are: emergency rooms I and II (eight beds in each); Cardiac Intensive Care Unit (ICU) (eight beds); Cardiac Surgery ICU (six beds); Cardiac Surgery (semi with six beds); General ICU (eight beds); Neurosurgery ICU (eight beds); ICU health insurance (eight beds); Nephrology ICU (four beds); Cardiology ICU (eight beds); Pediatric and Semipediatric ICU (not used in this study). HSPE has three ICUs: Adult (20 beds), Coronary Unit (6 beds) and Neurosurgery (8 beds).

As to the number of assistant doctors in each unit at HSP, in UNIFESP, there are: emergency room ICU I and II – one resident in each unit; General, Neurosurgery and Cardiac Surgery – three residents in each unit; Health Insurance ICU – two residents; Nephrology, Cardiology ICU, and Cardiac Surgery Semi ICU, with one resident. AS to the number of assistant doctors in HSPE, data are: the Adult ICU has the assistance of an intensive care doctor and three residents; the Coronary Unit has two residents and Neurosurgery has one resident.

In this study, 199 patients were included. They all had AKI confirmed by medical records of nephrologists or intensive care doctors who were responsible for the units and complementary examinations, mostly in need of renal replacement therapy in the ICUs. The diagnostic criteria are clearer for patients with AKI who underwent dialysis; among many factors, the prevalence was the clinical and laboratory reference of data sum. However, for patients with AKI who were not submitted to dialysis, diagnosis was not unanimous due to the difficulties of finding consensus not only between services, but also between professionals of the field. Thus, the choice was to accept the diagnosis of these patients respecting the experience of the doctors, since they work in well established units and are very experienced in this field. The expectation is that a single national and international consensus can be accepted and adopted in order to avoid difficulties to compare studies, or even to ensure a similar clinical condition to the included patients and to improve future analyses.

Patients with speech or visual disabilities that could jeopardize the test were excluded from the study, as well as those with psychological disorders, psychosis, intellectual disability, people on alcohol abuse or dependency, those using drugs and pregnant women.

Control group was comprised of patients with any acute medical disease, except for 'renal issues', hospitalized in semi-intensive or intensive care units in the same hospitals during the same period. Diagnoses were confirmed by medical records and examinations. Controls were paired by cases, gender and age, with maximum interval of three years. Besides, they should be lucid and about to be discharged from treatment units. Patients excluded from the study were: those with cancer or HIV and other chronic diseases, such as diabetes mellitus or chronic lung, heart and gastroenterologic diseases; patients who were diagnosed with AKI and/or needed to be treated for AKI in any stage of life; those who had hearing, speech or visual disabilities that could stop the interview; patients with psychological disorders, such as psychosis, those with intellectual disability people, people on alcohol abuse or dependency, those using drugs and pregnant women.

All patients were examined from 2007 to 2009 and agreed to participate by signing the informed consent form, which is required by the Ethics Committees. The study was approved by the Ethics Committees in both hospitals: HSP, at UNIFESP, on June 1st, 2007; protocol n. 0720/07; and HSPE, on March 25, 2008, Protocol n. 007/08.

Procedures

The examined patients agreed to participate and were personally and individually examined by trained researchers who were not involved with the treatment. Those who refused to participate continued with routine treatment in the services. A standard questionnaire was used to obtain sociodemographic and clinical data. Questionnaires were given by four interviewers who were graduated psychologists with post-graduation in Hospital Psychology. One of them was the main responsible for the study, and provided theory and practical hours for the questionnaires before the field research. Then the responsible psychologists accompanied the field research daily.

The interviewers received a training program that was divided into two parts:

- Theory module: consisted of presentations on general and specific objectives of the research; methodology; themes to be studied; clinical characteristics of cases and controls and, also, of clinical centers that would be the field of study. This theory module was comprised of eight meetings of three hours each, thus accounting for 24 hours.
- Training module to give the questionnaires: consisted of seven meetings that accounted for 14 hours. During this module, interviewers know and understood each question, from screening to inclusion or exclusion in Case and Control Groups, as well as questions from the sociodemographic clinical questionnaire and from the Social Readjustment Rating Scale (SRRS). These interviewers went through training that included the standardization of procedures.

The cases, that is, patients with AKI, were selected by order of arrival to the centers, as well as controls. The latter were selected after the application of a questionnaire with questions concerning inclusion and exclusion criteria that had been approved by the Ethics Committees of UNIFESP and HSPE. Interviews were programmed to start on the second day after ICU discharge.

Evaluation of life events

Stressful life events (SLE) were analyzed by the SRRS questionnaire, which was developed in 1967 by Holmes and Rahe[29] and translated and adapted to Brazil in 1984, by Lipp.[30]

SRRS is a widely used tool for field work, and it implies that the required effort for a person to adjust to society after going through stressful events

can trigger the onset of several diseases, in case the search for homeostasis surpasses the maximum limits of resistance.

This scale analyzes only major events in people's lives, and not daily events. Researchers have organized a list of meaningful events, such as: divorce, death in the family, changing jobs, birth of a child in the family etc. The list is given to the subjects who will be examined, thus questioning if they have been exposed to any of these events in the period of one year prior to the event that is being studied (that is, AKI diagnosis and ICU admission).

SLE scores are evaluated by the anticipated impact of each of the possible events. Expectations as to impact have been formatted for the American population. Afterwards, this questionnaire was translated and validated in our society, thus respecting similarities in the population. Total scores were divided into four impact categories: < 119, as low; 119-999 = moderate; 200-200 = average; > 300 = high.

The instrument is simple, validated (Appendix 1), and used as an indicator for greater events, pointing out minor problems. In this study, a positive condition of SRRS was considered as participants with scores ≥ 200 (average to high impact).

Variable analysis

Clinical assessed variables were: time of ICU or semi-intensive care stay (registered in days) of cases and controls; time of disease/diagnosis (registered in days); time of treatment and, for cases, time of dialysis.

Clinical Centers were separately examined: HSP/UNIFESP and HSPE.

The analyzed sociodemographic variables were: gender, age, marital status (married, previously married, or single); income (AB, CDE, according to the Brazilian Association of Population Studies – ABEP);[31] religion, ethinicity (white, brown, yellow, black); and place of birth (São Paulo, another city in the State, another State, another country).

Statistical analysis

Sociodemographic and clinical characteristics were described for AKI in terms of descriptive statistics, with mean, standard deviation, median, minimum and maximum for quantitative variables; frequencies were used for qualitative variables. The multiple linear regression analysis was used to check for the relation of the following parameters: group, gender, marital status, ethnicity and social class, together with the clinical parameters: time of hospital stay, ICU and dialysis as independent variables with the SRRS. The Stepwise method was used to select the variables that best explain the SRRS. All statistic tests considered the 5% significance level.

The variables associated with impact of stress ≥ 200 were examined by three models. The first one included the group with and without kidney injury and sociodemographic variables. The second added clinical parameters, time of hospital stay and time in the ICU; the third model added parameters that were different from the previous models.

Results

Out of the 579 patients that were initially identified, 475 answered to SRRS; out of these, 398 patients were paired by age and gender, being 199 cases with AKI and 199 in the control group. The social, demographic and clinical characteristics of the participants are described in Table 1.

Table 2 presents the results of the logistic regression to analyze the combined effects of the independent variables associated with stressful events. After adjustment, it was clear that increased age and social class AB leads the odds ratio to twice as many chances of a stressful event. In the complete model (model 3) it was observed that the social class AB and the HSP of UNIFESP increase the chances of a stressful event. Patients with AKI were not associated with the presence of stressful events in any model.

Table 3 shows the classes of events that appeared more in the samples.

Discussion

About one third of the participants with AKI reported stressful events in the 12 months prior to the interview. Data showed that high social status in one of the hospitals (HSP/UNIFESP) is associated with higher levels of SLE. However, no significant statistical association was proved between SLE and patients with AKI.

The stress, which is a result of the subject's perception and effort to adapt facing stressful events,[17] should be understood as a process, and not as a simple mechanism. A set of physiological or pathophysiological events may cause allostatic imbalance, thus leading to acute or chronic changes that can facilitate the onset of diseases, as pointed out by many studies in literature.[10,17,23] The influence of the environment, stress and anxiety on the renal diseases is better documented for the chronic condition.[28] Since AKI is associated with many acute medical conditions, such as polytraumatisms, use of

Table 1 Sociodemographic characteristics of the studied sample (n = 398)

Variables/Group	AKI		No AKI	
	Total	%	Total	%
Sociodemographic variables				
Gender				
Female	79	39.7	79	39.7
Male	120	60.3	120	60.3
Age				
18 to 59 years	69	34.7	72	36.2
Older than 60 years	130	65.3	127	63.8
Income				
AB	41	20.6	49	24.6
CDE	158	79.4	150	75.4
Ethnicity				
White	141	70.9	134	67.3
Brown	33	16.6	37	18.6
Yellow	4	2.0	5	2.5
Black	17	8.5	19	9.5
Marital status				
Married/ Living together	131	65.8	124	62.3
Separated/ Divorced/ Widow(er)	52	26.1	54	27.1
Single	16	8.0	21	10.6
SRRS (200)				
< 200	145	72.9	152	76.4
≥ 200	54	27.1	47	23.6
Semi-intensive or intensive care unit				
HSPE	85	42.7	85	42.7
HSP/ Unifesp	114	57.3	114	57.3
Clinical variables				
Mean age – years (SD)	63.8 (14.9)		63.6 (14.6)	
Time of disease (days) (SD)	615 (1618)		1102 (2655)	
Time of hospital stay (days) (SD)	24.3 (26.1)		18.6 (18.7)	

SD: standard deviation; AKI: acute kidney injury.

Table 2 Logistic regression for the study of variables associated with stressful events

Factor	Coefficient	EP	p-value	OR	95% CI
Model 1					
Age (years)	0.69	0.24	0.005	1.99	[1.23 – 3.22]
Social class (AB)	0.98	0.26	< 0.001	2.65	[1.58 – 4.45]
Model 2					
Age	0.68	0.27	0.013	1.98	[1.16 – 3.39]
Social class (AB)	0.72	0.30	0.018	2.05	[1.13 – 3.7]
Model 3					
Social Class (AB)	0.71	0.30	0.018	2.04	[1.13 – 3.69]
Hospital at UNIFESP	0.84	0.29	0.004	2.31	[1.3 – 4.09]

Model 1: Groups with and without AKI; gender, age, income, ethnicity, marital status; Model 2: Model 1 + time of hospital stay, time of disease, ICU, dialysis; Model 3: Model 2 + clinical center; AKI: acute kidney injury.

Table 3 Ten common events pointed by the participants according to SRRS (AKI, n = 199; with no AKI, n = 199)*

Events/positive answers	AKI		No AKI	
	n	%	n	%
Christmas	120	60.3	114	57.6
Change in eating habits	92	46.2	81	40.9
Change in sleeping habits	78	39.2	74	37.4
Personal injury or disease	73	36.7	59	29.6
Death of a family member	57	28.6	54	27.1
Change in personal habits	54	27.1	43	21.7
Birth of a child in the family	44	22.1	40	20.2
Illness of a family member	42	21.1	42	21.1
Change in recreation	37	18.6	42	21.1
Death of a close friend	31	15.6	30	15.2
Others	628		579	
Total	1.020		1.018	

* Participants can give multiple answers to the listed events; AKI: acute kidney injury; SSRS: *Social Readjustment Rating Scale*.

contrast, among others, the role of the vital event can be less relevant in these situations. However, As the Control Group also had participants with other acute conditions, the possible differences as to the exposure to stressful events must have been eased, since literature shows the association between stressful events and other diseases.[22-25] Participants with high income are more susceptible to stressful events. It is possible to consider that the low income population may not give as much importance to stressful events analyzed in this study, since it is more used to the restrictions imposed by daily life. When resilience is not developed, that is, the subject's ability to adapt, there may be another explanation to understand this result. It goes against the findings in studies performed with patients who had nephrolithiasis, including one in this research group, in which low-income participants were more exposed to stressful events.[1,28]

Participants assisted at HSP, of UNIFESP, presented twice as many chances of going through a stressful event than the ones in the other studied clinical center (HSPE). HPS cares both for patients at SUS and the population who pay for health insurance, unlike HSPE, which is addressed to the state employee. It is convenient to consider if the exposure to psychosocial, environmental and cultural stimuli can be different among population groups.

The present data showed that both the participants with AKI and the controls reported a list of similar stressful events. The ten most cited items were practically in the same order. The participants in this study were patients with acute conditions who were hospitalized in ICUs. There is the possibility that the reported events can be related both to the AKI group and the Control Group, thus easing the differences. This hypothesis is reinforced by the events reported in both groups, since they are very similar.

To sum up, this study did not show that the group with AKI was mostly associated with stressful events, but that the increased age and high income, as well as the type of clinical center, are influential factors. New studies can be performed with Control Groups, such as healthy subjects, in order to increase the difference, if possible, of the impact of stressful events in subjects with AKI.

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Appendix 1. Social readjustment rating scale

SOCIAL READJUSTMENT RATING SCALE

(Holmes and Rahe, 1976)

1.	Death of spouse	Yes	No
2.	Divorce	Yes	No
3.	Marital separation	Yes	No
4.	Jail term	Yes	No
5.	Death of close family member	Yes	No
6.	Personal injury or illness	Yes	No
7.	Marriage	Yes	No
8.	Fired at work	Yes	No
9.	Marital reconciliation	Yes	No
10.	Retirement	Yes	No
11.	Change in health of family member	Yes	No
12.	Pregnancy	Yes	No
13.	Sex difficulties	Yes	No
14.	Gain of new family member	Yes	No
15.	Business readjustment	Yes	No
16.	Change in financial state	Yes	No
17.	Death of close friend	Yes	No
18.	Change to a different line of work	Yes	No
19.	Change in number of arguments with spouse	Yes	No
20.	Home mortgage over $ 100,000	Yes	No
21.	Forclosure of mortgage or loan	Yes	No
22.	Change in responsibilities at work	Yes	No
23.	Son or daughter leaving home	Yes	No
24.	Trouble with police	Yes	No
25.	Outstanding personal achievement	Yes	No
26.	Spouse begins or stops work	Yes	No
27.	Begin or end school	Yes	No
28.	Change in living conditions	Yes	No
29.	Revision of personal habits	Yes	No
30.	Trouble with boss	Yes	No
31.	Change in work hours or conditions	Yes	No
32.	Change in residence	Yes	No
33.	Change in schools	Yes	No
34.	Change in recreation	Yes	No
35.	Change in church activities	Yes	No
36.	Change in social activities	Yes	No
37.	Mortgage or loan of less than $ 100,000	Yes	No
38.	Change in sleeping habits	Yes	No
39.	Change in number of family get-togethers	Yes	No
40.	Change in eating habits	Yes	No
41.	Vacation	Yes	No
42.	Christmas (reunion, gathering)	Yes	No
43.	Fines for minor infractions	Yes	No
44.	Other problems: _____	Yes	No

Check the events that happened to you in the year prior to this hospital admission