Early initiation of dialysis: mortality and renal function recovery in acute kidney injury patients

Início precoce da diálise: mortalidade e recuperação da função renal em pacientes com lesão renal aguda

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ABSTRACT

Introduction: The decision of when to start dialysis in Acute Kidney Injury (AKI) patients with overt uremia is strongly established, however, when blood urea nitrogen (BUN) levels is < 100 mg/dL the timing of initiation of dialysis remains uncertain. Purpose: The aim of this study was to assess mortality and renal function recovery AKI patients started on dialysis at different BUN levels. **Methods:** This was a retrospective study performed at Medical School Hospital, São Paulo, Brazil, enrolling 86 patients underwent to dialysis. **Results:** Dialysis was started when BUN ≤ 75 mg/dl in 23 patients (Group I) and BUN > 75 mg/dl in 63 patients (Group II). Hypervolemia and mortality were higher in Group I than in Group II (65.2% *vs*. 14.3% - $p < 0.05$, 39.1% *vs*. 68.9%- $p < 0.05$, respectively). Among survivors, the rate of renal function recovery was higher in Group I (71.4% and 36.8%, respectively - $p < 0.05$). Multivariate analysis showed that sepsis, age > 60 years, peritoneal dialysis and BUN > 75 mg/dl at dialysis initiation were independently related with mortality. **Conclusions:** Lower mortality and higher renal function recovery rates were associated with early dialysis initiated at lower BUN leves in AKI patients.

Keywords: acute kidney injury, dialysis, mortality, renal insufficiency.

RESUMO

Introdução: A decisão de quando iniciar a diálise em pacientes com lesão renal aguda (LRA) que apresentam síndrome urêmica está bem estabelecida, entretanto, com ureia < 200 mg/dl o melhor momento para iniciar a diálise torna-se incerto. **Objetivo:** Este estudo teve como objetivo avaliar a mortalidade e a recuperação da função renal em pacientes com LRA, cujo início da diálise ocorreu em diferentes níveis de ureia. **Métodos:** Estudo retrospectivo desenvolvido em hospital escola, no estado de São Paulo, Brasil, envolvendo 86 pacientes submetidos à diálise. **Resultados:** A diálise foi iniciada com uréia ≥ 150 mg/dl em 23 pacientes (grupo I) e uréia > 150 mg/dl em 63 pacientes (grupo II). Hipervolemia e mortalidade foram mais frequentes no grupo I que no grupo II (65,2 x 14,2% - $p < 0,05$; 39,1 x 68,9% - $p < 0,05$, respectivamente). Entre os sobreviventes, a recuperação renal foi maior no grupo I (71,4 e 36,8%, respectivamente, $p < 0,05$). A análise multivariada mostrou risco independente de mortalidade relacionado à sepse, idade > 60 anos, diálise peritoneal e uréia > 150 mg/dl no início da diálise. **Conclusão:** Menor mortalidade e maior recuperação renal estão associadas com o diálise iniciada precocemente, conforme baixos níveis de ureia, em pacientes com LRA.

Palavras-chave: diálise, insuficiência renal, lesão renal aguda, mortalidade.

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INTRODUCTION

Despite technological and conceptual improvements in dialysis the treatment of acute kidney injury (AKI) have resulted in a slow decline in mortality and it remains associated with high mortality rate and need for dialysis reaching up to 80% in patients in Intensive Care Units (ICU).[1-4] These data show that dialysis offer only partial and limited replacement of the multiple kidney functions, being insufficient to treat AKI as a component of multiple organ system failure.[2,5,6] In clinical

condition, AKI rarely presents in isolation but is usually a complication of several diseases.[1,4,7]

The decision of when to start dialysis in AKI patients with overt uremia is strongly established and historically blood urea nitrogen (BUN) levels higher than 100mg/dL is associated with higher mortality. In these situations, the beginning of dialysis should not be delayed.[8,9] However, when BUN levels is < 100 mg/dL the timing of initiation of dialysis vary widely and this clinical practice remains uncertain.[8] Palevsky *et al.*,[7] in a review, emphasize that the optimal management of renal replacement therapy is still unclear, and conclude that further studies are necessary to evaluate the timing of therapy initiation in AKI patients.

The timing of dialysis initiation in AKI has been discussed since its introduction over 50 years ago. Early studies reported lower mortality rates when dialysis was initiated prior to the onset of uremic symptoms giving rise to the concept of "early dialysis".[10-12] According to this concept, dialysis should be started in asymptomatic patients when BUN reaches 100 mg/dl. Some years later, Gettings *et al.*[13] showed that survival rate was significantly increased among post-traumatic AKI patients who were started on dialysis when BUN < 60 mg/dl compared to those who starting dialysis when BUN > 60 mg/dl (39% *vs.* 20.3%; $p = 0.041$). In a meta-analysis, Seabra *et al.*[14] suggested that early dialysis may be associated with improvement in survival among AKI patients, whereas Bagshaw *et al.*[15] demonstrated that late dialysis initiation might be associated with longer length of stay and higher risk of dialysis dependence on discharge.

Based on the values established in the literature, the primary goal of this study was to evaluate mortality among patients with AKI who were started on dialysis at different BUN levels.

Methods

This retrospective study was performed at Botucatu Medical School Hospital, São Paulo, Brazil, over a 5-year period. Inclusion criteria were patients older than 18 years, with AKI[16] caused by presumed Acute Tubular Necrosis (ATN), no symptoms of uremia, and underwent dialysis for longer than 48 hours. In all cases, dialysis had been indicated due to progressively increasing BUN levels associated or not with metabolic acidosis (pH < 7.2), hypervolemia and hyperkalemia (K > 6.5 mEq/L). Exclusion criteria were AKI of other etiologies, patients who started dialysis with BUN > 150 mg/dL for any reason, renal transplantation, pregnancy, ATN-ISS[17] ≥ 0.9, and continuous renal replacement therapy (CRRT).

According to BUN levels at the time of initiation of dialysis, patients were allocated into Group I (G 1): BUN ≤ 75 mg/dl or Group II (G 2): BUN > 75 mg/dl.

The prognostic scores used were APACHE II[18] and ATN-ISS[19] obtained at the time of ICU admission and at the first nephrology evaluation, respectively. Based on ATN-ISS, patients were classified as low (< 0.3), intermediate (0.3 - 0.7) or high risk (> 0.7).

Patients were followed up until they died, or recovered renal function, or received dialysis for over 30 days.

ATN etiology was classified as ischemic (due to low cardiac output or hypovolemia), nephrotoxic (associated with drugs or heme pigments)[19] or septic[20] (sepsis or septic shock). ATN was excluded in patients with pre-renal, post-renal or known or suspected diagnosis of vasculitis, glomerulonephritis or acute intersticial nephritis (on the basis of clinical history, physical examination, urinalysis and hematologic tests and renal ultrasonograph).[19]

Hypervolemia was considered in patients with positive fluid balance 3 days before nephrology consultation, presented one of the following criteria: clinical sign (edema), bilateral lung infiltrates on the chest radiograph or need to increase the fraction of inspired oxygen in patients on mechanical ventilation.

Renal function recovery (partial or complete) was defined as no need for dialysis after up to 30 days of follow up.

This study was reviewed and approved by the local Committee of Research Ethics.

Statistical analysis

Statistical analysis was performed using Stata version 8.2 (Stata Corp,College Station, Tex).

Data were expressed as mean ± SD or median, according to the normality of their distribution. Categorical data were expressed as frequency (%). Differences in clinical and laboratory parameters between groups were evaluated by Student's t-test or the Mann-Whitney test. Chi-square test or Fisher's exact test were used to compare as proportions. The outcome event was death. Univariate analysis was performed and the variables with significant associations were candidates for multivariable analysis. Multivariable logistic regression was performed using backward variable selection, with $p < 0.25$.[21] Significance level was set at $p < 0.05$ for all analyses.

Results

Of the 700 patients assessed, 333 required dialysis. Of these, 247 (74.2%) were excluded according to the study criteria. The remaining 86 patients were assigned to GI (23) or G II (63).

Main clinical and laboratory characteristics of the patients were similar, as shown in Table 1. Clinical signs of hypervolemia were more frequent in G I (65.2% and 14.3%; $p < 0.05$).

There was no difference among the dialytic methods between groups. Peritoneal dialysis was perfomed in 52.8% in GI and 68.2% in GII. Hemodialysis was performed in 43.5% in GI and 20.7% in GII.Both methods were performed in 4,3% in GI e 11.1% in GII. Regardless of the dialytic method used, 44.8% of the dialysis sessions were quantified by Kt/V urea,[22] and no difference per session (GI = 0.6 ± 0.2 and GII = 0.5 ± 0.1) or per week (GI = 4.1 ± 1.0 and GII = 3.5 ± 0.4) was observed. Follow-up length and dialysis duration were similar in both groups (18 ± 12 and 17 ± 14 days; 12 ± 9 and 11 ± 8 days)

By the end of the follow-up, overall mortality rate was 61.6%. In GI, mortality was lower than in GII (39.1% and 68.9%, respectively - $p < 0.05$). Among survivors, the rate of renal function recovery was higher in GI (71.4%) compared with GII (36.8%, $p < 0.05$).

Figure 1 shows the distribution of GI and GII patients according to ATN-ISS. Among the patients with intermediate severity scores, mortality rate was lower in GI (22.2%) than in GII (76%; $p < 0.05$). This did not occur in patients classified as low or high severity. Delivered Kt/V urea per session (0.54 and 0.49, respectively) and per week (3.9 and 3.4) was similar in two groups.

Table 2 shows the univariate analysis of the clinical and lab variables associated with death. Age > 60 years, peritoneal dialysis, ATN-ISS > 0.3, and BUN > 75 mg/dl at dialysis indication, were associated with death. Sepsis was associated with higher mortality, although no statistically significant difference was observed.

Multivariate analysis showed that sepsis, age > 60 years, peritoneal dialysis and BUN > 75 mg/dl at dialysis initiation were independently associated with mortality (Table 3).

Prognostic scores were not included in these analyses.

Discussion

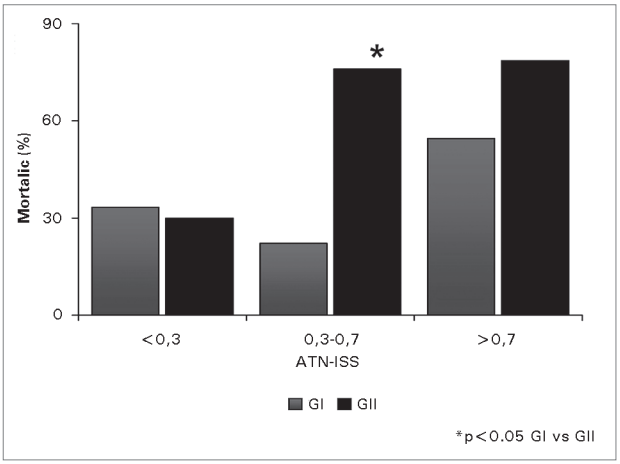
The majority of studies on the timing of initiation of renal replacement therapy have used BUN levels to indicate dialysis, although its use is flawed because it may reflect other situations not related to kidney

Table 1 Clinical and laboratory characteristics of the patients submitted to dialysis

	Group I (n = 23)	Group II (n = 63)	*p*-value
Male gender (%)	47.8	69.8	> 0.05
Age (years)	61 (43.7-70.2)	63 (51-71.7)	> 0.05
Age > 60 years	52.2	50.8	> 0.05
ATN-ISS	0.61 (0.4-0.8)	0.67 (0.5-0.8)	> 0.05
APACHE II	21 (17-24)	28 (18-31)	> 0.05
Mechanical ventilation (%)	65.2	68.2	> 0.05
Vasoactive drug (%)	56.5	52.4	> 0.05
Baseline creatinine (mg/dl)	1.2 (0.9-1.5)	1.3 (1-2.4)	> 0.05
Baselinecreatinine > 1.5 mg/dl (%)	21.7	46	> 0.05
Oliguria (%)	47.8	33.4	> 0.05
BUN at dialysis indication (mg/dl)	56 ± 13	118 ± 26	< 0.001
Presence of sepsis (%)	30.4	30.1	> 0.05
Hypervolemia (%)	65.2	14.3	< 0.05
AKIN	-	-	-
1	7/23 (30,43%)	17/60 (28.33%)	> 0.05
2	6/23 (26,08%)	9/60 (15%)	-
3	10/23 (40,47%)	34/60 (56,66%)	-

Oliguria: urine output 24 hs < 400ml. Data expressed as median or mean ± SD.

Figure 1. Distribution of the patients submitted to dialysis according to different ATN-ISS values.



function such as gastrointestinal hemorrhages, inadequate supply of nutritional substrates and hypercatabolic states.[8] Gettings *et al.*[13] demonstrated that patients with post-traumatic AKI who were submitted to dialysis with BUN < 60 mg/dl had higher survival when compared with patients that initiated dialysis with BUN > 60 mg/dl (39% *vs.* 20.3%, $p < 0.05$). The authors also stratified patients according to BUN levels and showed that the difference in survival remained in patients with BUN levels above and below 70 mg/dL (37% *vs.* 18.4%; $p = 0.035$)

In 2006, the Program to Improve Care in Acute Renal Disease (PICARD), a multicenter observational study, analyzed the timing of intermittent hemodialysis and CRRT

Table 2 Univariate analysis of death-related variables in patients submitted to dialysis

Variables	Survivors (n = 33)	Non-survivors (n = 53)	*p*
Gender (%)			
Male	37.9	62.1	0.95
Female	38.6	61.4	-
Age group (%)			
≤ 60 years	50.0	50.0	0.04
> 60 years	29.2	70.8	-
Type of admission (%)			
Non-surgical	28.8	71.2	0.02
Surgical	52.9	47.1	-
Presence of sepsis (%)	24.0	76.0	0.08
Baseline creatinine > 1.5 mg/dl (%)	32.4	67.6	0.32
Dialysis method (%)			
Hemodialysis	58.1	41.9	0.005
Peritoneal dialysis	27.3	72.7	-
Dialysis indication (%)			
Hypervolemia	40.0	60.0	0.86
Others	37.8	62.2	-
ATN-ISS (%)			
< 0.3	69.2	30.8	0.03
0.3-0.7	38.2	61.3	-
> 0.7	28.2	71.8	-
BUN at dialysis indication (%)			
≤ 75 mg/dl	60.9	39.1	0.01
> 75 mg/dl	30.2	69.8	-

initiation. Patients in the early dialysis group had BUN ≤ 76 mg/dL and patients in late group had BUN > 76 mg/dL. Although there was no statistical difference between the two groups in mortality rate after 14 days (80% and 75%, respectively) and 28 days (65% and 59%), patients from the late group had approximately double the risk of mortality than those in the early group.[23]

Some relevant studies were designed to assess dialysis doses and survival in AKI patients with BUN < 70 mg/dl at dialysis start.[24-26] According to Seabra

Table 3 Multivariate analysis of death-related variables in patients submitted to dialysis

Variables	OR	CI 95%	*p*
Sepsis	3.32	1.00 - 11.04	0.05
Age > 60 years	2.92	1.05 - 8.12	0.04
Peritoneal dialysis	2.96	1.08 - 8.07	0.03
BUN > 75 mg/dl	3.70	1.24 - 11.04	0.02

et al.,[14] the early initiation of dialysis might improve survival in hospitalized AKI patients, but not on renal function recovery.

Schiffl *et al.*[27] reported complete renal recovery in 57% of survival patients who were treated with dialysis, but they did not evaluate BUN levels prior to dialysis. Gettings *et al.*[13] found no difference in the rate of renal function recovery between early (100% of survivors) and late dialysis (91.6% of survivors). Bagshaw *et al.*,[15] in an observational prospective study using several criteria for the definition of early dialysis, showed that late dialysis (timing relative to hospital and ICU admission) was associated with longer duration of renal replacement therapy, longer hospital stay and higher risk of dialysis dependence, although when late dialysis was stratified by serum urea there was no difference in hospital mortality. Other investigators, such as Mehta *et al.*,[28] Augustine *et al.*[29] and Palevsky *et al.*[30] did not mention the use of initiation timing to minimize the impact of dialytic therapy on renal recovery in AKI.

This present study showed lower mortality rate and higher renal function recovery among patients undergoing early dialysis despite the possible start of dialysis for volume overload problems in this group, since hypervolemia can be associated with organs dysfunction, mortality and non-recovery of kidney function in critically ill AKI patients.[31-34]

In this study, delivered dialysis doses were not measured in all cases. Nonetheless, the two groups were similar in delivered dialysis dose, regardless of the method employed and it was very close to those reported in the literature,[27,29] suggesting that the difference in survival between the two groups was not associated with the delivered dialysis dose, but with the benefits of early dialysis initiation.

In this study, mortality was assessed according to ATN-ISS severity. Among patients with a moderate severity score (ATN-ISS between 0.3 and 0.7), mortality rate was lower when dialysis was initiated early, but this did not occur when severity was higher or lower (ATN-ISS < 0.3 or > 0.7). This finding suggests that early dialysis may be more beneficial to patients with moderate levels of severity because patients with lower severity levels can achieve spontaneous clinical recovery and those with higher severity show high risk of death regardless of the timing of dialysis initiation. Paganini *et al.*[35] found similar results when analyzing prognostic scores and delivered dialysis doses.

Multivariate analysis showed that mortality was associated with advanced age, sepsis, peritoneal dialysis and BUN > 75 mg/dl at dialysis initiation. The results concerning peritoneal dialysis should be interpreted carefully because data from literature are conflicting.[36,37]

However, it should be considered, that all types of dialytic treatment may intensify the insult or delay renal function recovery. Moreover, further studies should investigate other indicators for dialysis in AKI patients, as biochemical and clinical evolution (trends),[9] because BUN levels can be influenced by many factors.

This study had some limitations such as its retrospective design, reduced number of patients and performed in a single center. Furthermore, other aspects as patient nutritional status and correction of the acid-base balance were not assessed. Nonetheless, the lower mortality and improved renal function recovery observed in patients treated with dialysis started at lower BUN levels (despite the possible start for volume overload problems) suggest that such a clinical practice may be taken in selected groups of patients.

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