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"Positive Cumulative Fluid Balance as a Risk Factor for the Development or Progression of Acute Kidney Injury in Patients Admitted to the Intensive Care Unit of the General Hospital "Dr. Manuel Gea Gonzalez".

TESIS:
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CONTENIDO

"Positive Cumulative Fluid Balance as a Risk Factor for the Development or Progression of Acute Kidney Injury in Patients Admitted to the Intensive Care Unit of the General Hospital "Dr. Manuel Gea Gonzalez".

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Abstract

Introduction: During the last years, the importance of fluid overload as a risk factor for mortality and worse outcomes has been consistently documented in critically ill patients with acute kidney injury (AKI) in the intensive care unit (ICU). However, the evidence of the relationship between positive fluid balance and risk for development and/or progression of AKI has not been clearly described. We hypothesized that positive cumulative fluid balance (CFB) is a risk factor for development or progression of AKI in critically ill patients of a general ICU in a single center in Mexico City.

Methods: Records of all the patients admitted to ICU of the General Hospital "Dr. Manuel Gea Gonzalez" from May 2013 through April 2014 were retrospectively evaluated. After applying exclusion criteria, 138 records remained for complete analyses. We calculated the CFB by the sum of the daily intakes and outputs recorded during the whole stay of the patient in ICU, insensible losses were taken into account. Daily records of serum creatinine were evaluated and development of AKI was defined by the RIFLE criteria. Progression of AKI was defined as the change to a worse grade of the RIFLE criteria at any time during the ICU stay. CFB was evaluated at the day of discharge and was defined as positive when it exceeded 5,000cc. Balances between 0cc and 4,999cc were considered "neutral" and balances below 0cc were considered "negative". Baseline characteristics and outcomes were compared using t-test, Mann-Whitney and X^2 tests. To test the association of positive CFB with AKI development or progression, we performed a logistic regression analysis, adjusting for age, sepsis, shock, nefrotoxic drugs and APACHE score as confounders.

Results: Of the 138 evaluated patients, 90 (65.2%) developed AKI during the ICU stay. Positive CFB was identified in 28 patients, 26 (92.9%) of these patients developed AKI. 110 patients had neutral or negative CFB, 64 (58.2%) of these patients developed AKI. 92.9% of patients with positive CFB developed AKI compared to 58.2% of patients with neutral or negative CFB ($p<0.001$). None of the 90 patients with AKI suffered progression of AKI. The unadjusted odds ratio for developing AKI with positive CFB of $\geq$5,000cc was 9.3 (95% CI 2.1-41.4). Death occurred in 32 (23.2%) of the 138 patients. The median CFB of the survivors was -1,824cc (IQR -9,790 to 630), compared to a median of 5,920cc (IQR 1,574-12,720) in the non survivors ($p<0.001$). After adjusting for confounders, positive CFB remained a significant risk factor for developing AKI (OR 18.9, 95% CI 2.03-176.29)

Conclusion: In a cohort of critically ill patients admitted to ICU, positive cumulative fluid balance of 5,000cc or more was a risk factor for the development of AKI and was associated with increased mortality, however positive CFB does not seem to increase the risk of progression of AKI during the ICU stay. Further, larger studies are needed to confirm whether the reduction in fluid accumulation could have a significant impact on development of AKI and mortality.

1. Introduction

Acute kidney injury (AKI) is a complex syndrome that includes diverse etiologies and clinical scenarios [1]. The reported prevalence in critically ill patients from intensive care units (ICUs) is high; typically between 40% and 67% and AKI-associated mortality ranges between 46.5% and 74.4% [2–4]. Within the multifactorial etiology of AKI, the role

and pathophysiology of fluid overload is not well understood. This situation obeys several reasons, for example, limitations in assessing the real intravascular volume, the difficulty for establishing an adequate "dose" of fluids for each patient, etc. The amount of administered fluids is determinant for patient outcomes; insufficient fluid resuscitation would generate hypo-perfusion of vital organs while excess in administration can contribute to the development of organ edema and other complications[5]. The objective of an intense fluid resuscitation is to prevent or revert renal ischemia and dilute nefrotoxins. This treatment approach has been used for more than 50 years, nevertheless the evidence for its beneficial effects is scarce [6]. During the last years, the importance of fluid overload as a risk factor for mortality and worse outcomes has been consistently documented in critically ill patients with AKI in the ICU[6]. Each day more and more studies show this association and it is suggested that positive fluid balance above 5% to 10% of total body weight (TBW) is associated with worsening of organ function in critically ill patients, and is not associated with improvement in renal function [7]. Nevertheless, the evidence of the relationship between positive fluid balance and risk for development and/or progression of AKI has not been clearly described. Therefore, we hypothesized that positive cumulative fluid balance (CFB) is a risk factor for development or progression of AKI in critically ill patients of a general ICU in a single center in Mexico City.

Table 1. RIFLE GFR criteria for Acute Kidney Injury [8]

(R) Risk	Increased creatinine x 1.5 or GFR decrease > 25%
(I) Injury	Increased creatinine x 2 or GFR decreased > 50%
(F) Failure	Increased creatinine x 3 or GFR decreased >75% or creatinine ≥ 4mg/dl
(L) Loss	Persistent AKI = complete loss of renal function > 4 weeks
(E) ESRD	End Stage Renal Disease

2. Material and Methods

We made a retrospective analyses of all the records of patients admitted to a 7 bed, polyvalent ICU of a general hospital in Mexico City from May 2013 to April 2014. A total of 209 records were evaluated. We included the records of patients older than 18 years who stayed for at least 48 hrs in the ICU, with any diagnosis and that had measurements of sCr at admission and at least one measurement every day. Records of patients with chronic kidney disease (CKD) stage 5 and those with incomplete data were excluded. After applying these criteria, 138 records remained for complete analyses. Sex , age, presence of comorbidities, presence of sepsis, vasopressor use, use of nephrotoxic drugs, APACHE score at admission, SOFA score at admission, sCr measurement at admission and at each day of the stay and daily fluid balance were assessed from each record. We calculated the CFB by the sum of the daily intakes and outputs recorded during the whole stay of the patient in ICU, insensible losses were taken into account. CFB was evaluated at the day of discharge and was defined as positive when it exceeded 5,000cc, balances between 0cc and 4,999cc were considered "neutral" and balances below 0cc were considered "negative". Daily records of sCr were evaluated and development of AKI was defined by the RIFLE glomerular filtration rate criteria (GFR) [8](table 1). We took admission sCr as "baseline creatinine". Progression of AKI was defined as the change to a worse grade of the RIFLE criteria at any time during the ICU stay. Each record was evaluated from the day of admission until the day of discharge. Mortality during ICU stay and days of ICU stay were evaluated as secondary outcomes.

2.1 Statystical Analyses

Baseline characteristics and outcomes were compared using t-test, Mann-Whitney and X^2 tests. To test the association of positive CFB with AKI development or progression, we performed a

logistic regression analysis, adjusting for age, sepsis, shock, nefrotoxic drugs and APACHE score as confounders.

3. Results

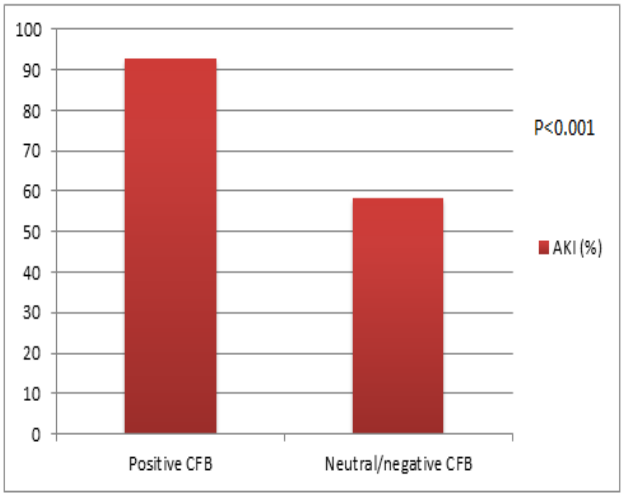
During the period from May 2013 to April 2014, a total of 209 patients were admitted to the ICU of a general hospital in Mexico City. We evaluated all the records and 138 completed the criteria for analyses. 71 records were not included mainly because incomplete data. The mean age of the patients was 47 years old (18y-90y), 68 (49.3%) were male. The mean APACHE score at admission was 20.3 (4-45) and mean SOFA score at admission was 9 (0-19). Fluid balance at admission had a median of 422cc (IQR -487.5-1457.3). At discharge 28 patients (20.3%) had positive fluid balance with a median of 11,380cc (IQR 6,998-14,564) and 110 (79.7%) had neutral/negative fluid balance with a median of -1,686cc (IQR -9062-452)(table 2). From the total cohort of 138 patients, 90(65.2%) presented AKI at admission or during the ICU stay, 15 (10.7%) were classified as Risk (R), 6 (4.3%) were classified as Injury (I) and 48 (34.3%) were classified as Failure (F). Any of the patients presented progression of AKI during the ICU stay. 26 (92.9%) of the patients with positive CFB developed AKI compared to 64 (58.2%) of patients with neutral or negative CFB ($p < 0.001$) (figure 1).

Table 2. Main characteristics of the whole population according to fluid balance

Variable	All		Positive global fluid balance		Neutral/negative fluid balance		p-value
	N		N		N		
	138	(100%)	28	20.3%	110	79.7%	
Age , mean ±SD	47.1	±19.4	58.4	±14	44.2	±19.6	0.001
Sex							
Male, n(%)	68	49.3	16	57.1	52	47.3	0.401
APACHE, mean ±SD	20.3	±9.3	24.4	±7.6	19.3	±9.4	0.012
SOFA, mean ±SD	9	±3.7	11.5	±3.2	9	±3.6	0.001
Vasopressor use n(%)	79	57.2	23	82.1	56	50.9	0.003
Type n(%)							
Surgical	75	54.3	20	71.4	55	50.0	0.056
Medical	63	45.6	8	28.6	55	50.0	
Sepsis, n(%)	76	55.1	27	96.4	49	44.5	0.001
Cardiogenic shock, n(%)	9	6.5	1	3.6	8	7.3	0.686
Comorbidities, n(%)	72	52.2	11	39.3	61	55.5	0.668
Serum creatinine, median (IQR)	1.1	0.78-2.1	1.47	0.90-1.69	1	0.70-2.21	0.542
Fluid balance at admission, median (IQR)	422	(-487.5 to 1457.3)	1316	497-3549	124	(-715-1028)	<0.001
Global fluid balance, median (IQR)	-646	(-5354 to 3266)	11380	6998-14563	-1686	(-9062-452)	<0.001

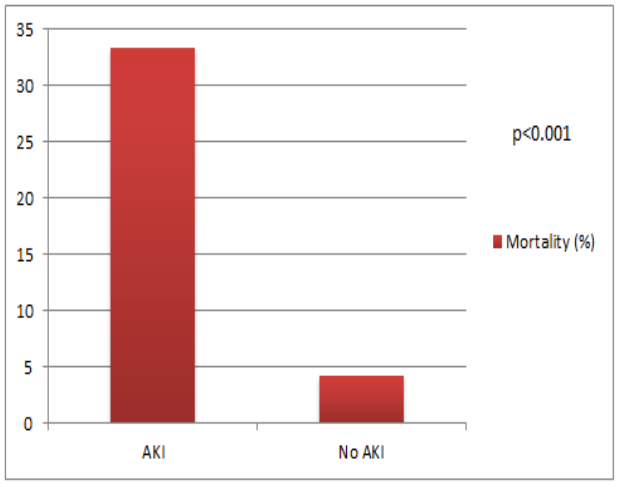
In the univariate analyses, positive fluid balance was found to be a risk factor for the development of AKI with an OR of 9.3 (95% CI 2.1-41.4). After adjusting for confounders, positive CFB remained a

Figure 1. Development of AKI according to cumulative fluid balance



significant risk factor for developing AKI (OR 18.9, 95% CI 2.03-176.29). 32 patients (23.2%) died during the ICU stay. The mortality among those who presented with or developed AKI was 33.3% compared with 4.2% of patients without AKI (p<0.001)(figure2). The median CFB among survivors was -1,824cc (IQR -9,790 to 630), compared to a median of 5,920cc (IQR 1,574-12,720) in the non survivors (p<0.001)(figure 3). Patients with AKI had a median ICU stay of 7 days (IQR 3-14.5) compared with a median of 4.5 days

Figure 2. Mortality according to the development of AKI



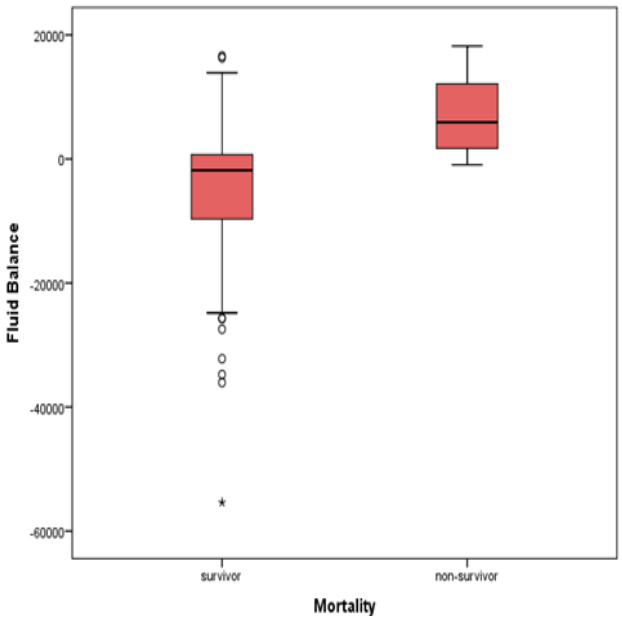
(IQR 3-8.75) in patients without AKI (p=0.113).

4. Discussion

As we stated before, AKI is a complex renal syndrome that includes diverse clinical scenarios and etiologies; and certainly the hypoperfusion/hypoxia phenomena is involved in the pathogenesis of many of the new cases [1]. Because of this, fluid management is still considered the mainstay for the treatment of these patients [9]. This treatment approach may be strongly correlated with the development and/or worsening of AKI, increased in-hospital mortality and worse outcomes, especially in critically-ill patients [9–16]. In recent years, several studies have been conducted in order to try to demonstrate this association. One of the most important of these studies took place in Australia and New Zealand, where the "RENAL" group investigators analyzed the data of patients from 35 ICUs and concluded that daily negative cumulative fluid balances were associated with better clinical outcomes [7]. The "RENAL" study reports a mortality of 57.2% among patients with positive CFB versus 32.3% with patients with negative CFB with a statistical significant "*p*" value of <0.001 [7]. Our study was aimed to increase the existing evidence that state the correlation between positive CFB and development of AKI as well as its association with increased mortality and worse outcomes. In our critical-ill patients cohort we found a prevalence of AKI of 65.2% which consistent with that reported by other authors [13]. We also found a similar prevalence of patients with fluid overload (20.2%) with that reported in previous studies [16]. Our main hypothesis was confirmed and we found a positive correlation between positive cumulative fluid balance and development of AKI (figure 1) with a statistical significant "*p*" value of <0.001 and an odds ratio of 18.9 after adjusting for confounders. We also hypothesized that fluid overload would worsen AKI

stage, and patients diagnosed with AKI would present progression in the severity of the initial diagnosis, nevertheless none of our patients presented with this situation. Mortality and days of ICU stay were evaluated as secondary outcomes. Many previous studies reported increased mortality among critically-ill patients with positive CFB [15–19] and we found similar data with an important increase in mortality among those critically-ill with positive CFB. Nevertheless, patients with positive CFB were older, were more critically-ill with higher APACHE II and SOFA scores and had prevalence of sepsis and AKI. We also made a comparison of the median CFB between survivors and non-survivors and we found that non-survivors presented with a much more positive CFB than survivors with a statistical significant "*p*" value of <0.001 (figure 3). This was also demonstrated by other authors in the past [20]. ICU stay was found to be higher between those patients with positive CFB, nevertheless this was not statistically significant in our study.

Figure 3. CFB among survivors and non-survivors



Our study has several weaknesses, first of all it is a single-center study and it was conducted retrospectively. Also the ICU stay among the cohort is very heterogenic and we evaluated the final CFB; this means that we may have overlooked some patients that presented with positive CFB during the first days of stay but had neutral or negative CFB at the end of their ICU stay. It has also some strengths, mainly the fact that we took into account the insensible losses for calculating the daily CFB, this is rarely done by other studies.

5. Conclusion

A positive cumulative fluid balance of more than 5,000cc is a risk factor for the development but not for progression of acute kidney injury among critically-ill patients. Positive CFB is also associated with an increase in mortality among these patients. More prospective controlled trials are needed to increase the available evidence to confirm these associations.

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