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SEQUENTIAL NEPHRON BLOCKADE IN ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS

Nephrology

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ABSTRACT

Background: Diuretic use in acute kidney injury (AKI) is debatable. Contrasting outcomes have been reported in AKI. Sequential nephron blockade (SNB) has never been studied in ICU population admitted with AKI. **Methods:** Consecutive medical-ICU patients admitted with oliguric AKI over 1-year period were recruited. SNB as a diuretic strategy was administered. Responders (R) and non-responders (NR) were compared. Demographic data, clinical profile, treatment and outcomes were compared between the groups using t-test and Chi-square test. Predictors of mortality were explored using bivariate and multivariate logistic regression analysis and expressed as Odds ratio (OR) with 95% confidence-interval (CI). **Results:** Of 331 ICU patients admitted with AKI, 312 patients received SNB. The mean (SD) age was 64.14±14.79 years with male preponderance (196:116). Admission SOFA score was significantly (p<0001) higher (9.6±3.8) in non-responders than responders (63±3.6). Overall, 80.13% patients were responders and 19.6% patients received Renal replacement therapy (RRT). Significant difference (p<0001) for diuretic response and dialysis were seen with pre-existing diabetes, higher KDIGO stage and SOFA score (>9) at ICU admission, sepsis, shock, mechanical ventilation, positive fluid balance, lengthy ICU stay and mortality. On multivariate logistic regression analysis, SOFA score >9 (OR 4.50; 95%CI 2.30-8.80), negative diuretic response (OR 0.45; 95%CI 0.34-0.59), RRT need (OR 1.78; 95%CI 1.25-2.19) and a higher positive fluid balance (OR 2.82; 95%CI 1.76-3.89) were independently associated with death. **Conclusions:** SNB in oliguric AKI patients resulted in lesser need for dialysis and better outcomes. A negative response, need for dialysis and a higher positive fluid balance were independently associated with mortality.

KEYWORDS

Acute kidney injury (AKI), Dialysis, Diuresis, Mortality, Non-responder

INTRODUCTION

Acute kidney injury (AKI) is common in Intensive Care Units (ICU) with an incidence ranging from 20% to 50%, depending on baseline characteristics of patients and criteria used to define it [1]. Among RIFLE (Risk, Injury, and Failure; and Loss; and End-stage kidney disease), AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes), the latter two detected more patients with AKI [2, 3]. AKI is associated with high morbidity, and poor long term outcomes and is an independent risk factor for mortality in ICU patients [1, 4-7]. Treatment of AKI includes volume resuscitation, vasoactive drugs and diuretics which can influence outcomes. Oliguric AKI has a worse prognosis than non-oliguric AKI [8, 9]. Loop diuretics (LD) can convert oliguric AKI into non-oliguric AKI preventing dialysis in some patients [10]. Despite contradictions, LD are widely used in clinical practice to increase urine output (UO) and reduce fluid overload, which is associated with adverse outcomes [11-16]. The KDIGO Clinical Practice Guidelines for AKI recommends against the use of routine LD for the prevention and/or treatment of AKI and recommends it only in managing fluid overload [17]. Three different meta-analysis [18-20], and other studies [21, 22] found no difference in mortality between diuretics and a placebo in AKI. However, a subgroup of patients receiving furosemide as a preventive measure had better survival [18]. Another study reported that furosemide administration was associated with improved short-term survival and recovery of renal function in critically ill patients with AKI. It was especially effective in patients with AKI UO stage 2-3 [23, 24]. Diuretic resistance is a major cause of recurrent hospitalizations in patients with AKI and predicts death in such patients [25]. Previous studies have not explored a specific diuretic strategy, like sequential nephron blockade which could possibly overcome this problem. Sequential nephron blockade (SNB) has increased UO and improved clinical symptoms in patients with Cardio-renal syndrome [25-31]. This study evaluated the effect of a time limited trial of SNB with furosemide and metolazone as a diuretic strategy in critically ill patients with AKI on clinical outcomes.

MATERIAL AND METHODS

This prospective, observational study was conducted in the medical ICU of a tertiary care hospital over one year. All patients aged more than 18 years admitted between 1st January 2020 and 31st December 2020 with AKI according to KDIGO- urine output criteria were given a time limited trial of diuretics with SNB [32]. KDIGO-criteria has shown good effectiveness in predicting in-hospital mortality [33]. Oliguria-based criteria improve patients' risk estimation and clinicians' ability to evaluate AKI [34]. Serum creatinine was not used in diagnosing AKI due to possibility of a delay in its raise when compared to urine output, which could delay the required intervention. Patients with age less than 18 years, chronic kidney disease, defined as a previously documented high serum creatinine value or dialysis dependent and those with unstable hemodynamics defined as vasoactive ionotropic score more than 25 [35] were excluded.

Sample size determination

The incidence of AKI in our ICU patients during 2019-2020 was 26.4%. The required sample size was determined by using the following formula:

$N = (Z)^2 \times p(1-p) \div d^2$

N = the desirable sample size, Z = 1.96 (critical value at 95% level of significance), p = 0.312 (proportion of patients with AKI in ICU during previous year), d = 0.05 (acceptable marginal error) and 1 − p = proportion of patients that do not possess the character of interest. Replacing with values results in:

$N = (1.96)2\ (0.264)\ (0.736) / (0.05)2 = 299$

By adding 10% drop out, the final minimum sample size required was 329.

Definitions

AKI:

It was defined according to KDIGO-urine output criteria. Stage 1 was defined as urine output of <0.5 ml/kg/hour for 6 to 12 hours; stage 2 as urine output of <0.5 ml/kg/hour for 12 to 24 hours, and stage 3 as urine output of <0.3 ml/kg/hour for >24 hours or anuria for >12 hours [36].

Body Weight:

Preadmission documented body weight was considered. If unavailable, predicted body weights were calculated and used.

UO Assessment:

All patients were catheterized and urine output was measured hourly. Patients with urine output of <0.5 ml/kg/hour for 6 consecutive hours despite adequate fluid resuscitation and maintaining a mean arterial pressure of > 65mm/Hg, were administered diuretics. Clinical and laboratory parameters were used to ensure adequate fluid resuscitation. All patients had a documented increased serum creatinine value before

treatment [36].

Treatment:
Injection furosemide 1mg/kg up to a maximum of 60 mg intravenous(IV) bolus was given followed by infusion at 10mg/hour up to a maximum of 20 mg/hour. Urine output was monitored for 6 hours for a response. Tablet Metolazone 10 mg was administered to patients not responding to furosemide. Nonresponders(NR) were initiated on dialysis if needed according to standard indications [37]

Response:
It was defined as an increase in urine output to more than >0.5 ml/kg/hour or a cumulative urine output of 300 ml over 6 hours after diuretic administration.

Non-response:
It was defined as urine output of <0.5 ml/kg/hour hour or a cumulative urine output of <300 ml over 6 hours after diuretic administration.

Sepsis and shock were defined according to Sepsis 3 guidelines [38].

Data collection and outcomes:
Demographic data, clinical profile, treatment and outcomes were retrieved from the hospital electronic database. Outcomes studied were diuretic response, hospital mortality, length of stay, ventilator-free days, and need for RRT. Ethics and scientific approval were obtained from the Institutional Review Board (IRB). The study was performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from the patient/relative.

Statistical analysis:
Clinical features and outcome were compared between diuretic responders and non-responders using t test and Chi-square test as appropriate. Predictors of mortality were explored using bivariate and multivariate logistic regression analysis. The continuous data were summarized using mean (SD). The odds ratio [95% Confidence Interval (CI)] was provided as estimate of effect size as the risk of non-responders over responders. All statistical analysis was performed using SPSS Statistics 21.0. A p-value of <0.05 was considered significant.

RESULTS

During the study period, 1382 ICU patients were screened; 331 patients had oliguric AKI; 19 patients were excluded. 312 patients received SNB. Among them, 250 patients responded to SNB, while 62 patients did not respond. Dialysis requirement was more in SNB non-responders than responders (Figure 1).

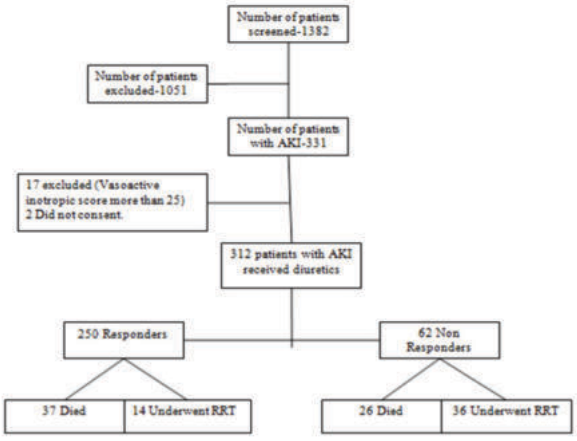

Figure 1: Strobe diagram

Baseline demographic data: The mean (SD) age of the entire cohort was 64.1 (14.7) years with a male predominance (1.7:1). The SNB non-responder arm had a significantly higher SOFA score [mean (SD): 5.4 (3.1) vs. 9.6 (3.8); p < 0.001], and patients with diabetes [n (%): 38 (61.2%) vs. 108 (43.2%); p = 0.011], sepsis [n (%): 43 (69.3) vs. 76 (30.4); p < 0.001] and shock [n (%): 48 (77.4) vs. 54 (21.6); p < 0.001] when compared with SNB responders. Other clinical features and co-morbidities at admission were similar (Table 1). The mean (SD) serum creatinine (mg/dl) was significantly higher among non-responders as compared to responders [4.21 (0.97) vs. 2.6 (1.2); p < 0.001].

Table 1: Demographic data

Variable	Overall (n=312)	Responders (n=250)	Non responders (n=62)	P value
Age (SD)	64.14(14.79)	64.94(14.98)	60.78(13.89)	0.21
Male: Female (n)	196:116	153:93	39:23	0.98
SOFA Score (SD)	7.78(4.8)	6.14 (3.8)	9.7 (4.1)	<0.001
Predicted mortality %(SD)	33.3(20)	21.5(20.2)	50 (20.2)	<0.001
Co-morbid illnesses				
Diabetes, n (%)	146 (46.8)	108 (43.2)	38 (61.2)	0.011
Hypertension, n (%)	137 (43.9)	105 (42.0)	32 (51.6)	0.214
CAD, n (%)	77 (24.7)	56 (22.4)	21 (33.8)	0.061
CHF, n (%)	25 (8)	17 (6.8)	8 (12.9)	0.113
Malignancy, n (%)	25 (8)	21 (8.4)	4 (6.4)	0.613
KDIGO Stage, n (%)				
1	109(34.9)	108(43.2)	1(1.6)	<0.001*
2	112(35.9)	100(40)	12(19.3)	
3	91(29.1)	42(16.8)	49(79.1)	
Sepsis, n (%)	119(38.1)	76(30.4)	43(69.3)	<0.001
Shock, n (%)	102(32.7)	54(21.6)	48(77.4)	<0.001

Values expressed are number of patients (n) and percentages (%) unless specified; SD – Standard Deviation; SOFA - Sequential organ failure assessment; CAD- Coronary artery disease; CHF- Congestive heart failure; AKIN – Acute kidney injury network; * Fischer Exact p value.

Outcomes
SNB non-responders had a significantly higher mortality as compared to responders [41.9% vs. 14.8%, p <0.001]. Non-responders also had a significantly higher positive fluid balance [4.2 L vs.1.7 L, p < 0.001], need for RRT [41.9% vs.14.8%, p < 0.001] and mechanical ventilation [62.9% vs. 41.6%, p = 0.003] as compared to responders. Duration of ICU and hospital stay, and ventilation free days were similar in both arms (Table 2).

Table 2: Treatment data and outcomes

Variable	Overall (n=312)	Responders (n=250)	Non responders (n=62)	P value
Treatment data				
Invasive ventilation, n (%)	143(46.79)	104)41.6)	39(62.9)	0.003
Fluid balance*	2.1 (0.23)	1.7(0.11)	4.2(0.33)	<0.001
Dialysis, n (%)	61(19.55)	36(14.4)	25(40.3)	<0.001
Outcome data				
Mortality, n (%)	63(20.19)	37 (14.8)	26 (41.93)	<0.001
ICU LOS †	5.68(4.8)	5.16 (3.9)	6.81 (3.97)	<0.001
Hospital LOS †	8.9(5.9)	8.2 (4.8)	9.6 (7.2)	0.07
Ventilation free days†	4.9(9.2)	5.5 (9.9)	4.1 (8.7)	0.304

Values expressed are number of patients (n) and percentages (%) unless specified; ICU – Intensive care unit; LOS-Length of stay; † expressed as mean (SD).

Factors associated with mortality
On bivariate logistic regression analysis, SOFA score, serum creatinine levels, KDIGO stage 3, diabetes mellitus, coronary artery disease (CAD), sepsis and shock, need for invasive mechanical ventilation and RRT, diuretic response, fluid balance at 48 hours of AKI diagnosis, and ventilator free days were associated with mortality (Table 3). On multivariate logistic regression analysis, SOFA score > 9 (OR 4.50; 95% CI 2.30, 8.80), negative diuretic response (OR 0.45;

95% CI 0.34, 0.59), need for RRT (OR 1.78; 95% CI 1.25, 2.19) and a higher positive fluid balance (OR 2.82; 95% CI 1.76, 3.89) were independently associated with mortality. Ventilator free days were not included in the multivariate analysis since it incorporated outcome (mortality) in its estimation and the increased mortality in the non-responder arm could skew the data [39].

Table 3: Factors associated with mortality**.**

Factor	Bivariate analysis			Logistic regression analysis		
	OR	95% CI	P value	OR	95%CI	P value
Age	1.01	0.96 – 1.07	0.59	0.927	0.85-1.01	0.62
SOFA Score	3.45	2.12-4.18	<0.001	4.5	2.3-8.8	<0.001
KDIGO stage 3	1.3	1.01-2.48	<0.001	1.92	0.85-3.29	0.39
Diabetes	2.78	1.55-4.98	<0.001	0.34	0.07-1.73	0.257
CAD	2.07	1.14-3.76	0.015	1.1	0.44-2.71	0.844
Sepsis	3.07	1.74-5.4	<0.001	1.3	0.20-8.45	0.782
Shock	5.24	2.91-9.44	<0.001	2.76	0.29-5.64	0.371
Invasive ventilation	6.94	3.24-10.87	<0.001	0.88	0.36-2.17	0.782
Diuretic response	0.24	0.13-0.44	<0.001	0.45	0.34-0.59	0.017
Dialysis	4.29	2.32-7.95	<0.001	1.78	1.25-2.19	0.003
Fluid balance	3.47	1.84-5.6	<0.001	2.82	1.76-3.89	0.002
ICU LOS	1.21	0.92-1.37	0.324			
Hospital LOS	1.13	0.97-1.22	0.288			
VFD	0.84	0.78-0.89	<0.001			

OR –Odds ratio; CI – Confidence Interval; SOFA – Sequential organ failure assessment; AKIN - Acute kidney injury network; CAD-Coronary artery disease; ICU- Intensive care unit; LOS-Length of stay; VFD-Ventilation free days Variables were incorporated in the multivariate analysis if $p<0.05$ on bivariate logistic regression analysis; VFD was not incorporated in the multivariate logistic model as non-responder group had increased mortality which can skew the data and it incorporates outcome (death) in its analysis.

DISCUSSION

This study explored if a time limited trial of SNB in oliguric AKI could improve clinical outcomes. Mortality in non-responders was nearly thrice (41.9% vs. 14.8%) as that of responders. The high mortality among non-responders in our study is consistent with other reports [23, 34]. In our study, SOFA score > 9, negative diuretic response, need for RRT and a higher positive fluid balance were independently associated with mortality. A recent study reported that severity of AKI, hyperkalemia, duration of AKI, and short length of hospital stay to be associated with mortality [40]. Another study found that oliguric AKI was associated with a higher risk of requiring acute and long-term dialysis > 90 days, and higher hospital mortality than non-oliguric AKI [41]. The predicted mortality according to a SOFA score of 9 and more was similar to that of our study (22.5% vs. 20.5%) [42]. A negative diuretic response leads to higher positive fluid balance in oliguric AKI patients. Both of them were independently associated with mortality in our study, similar to previous reports [24, 43, 44]. Fluid overload leads to complications like pulmonary edema, cardiac failure, delayed wound healing, tissue breakdown, and impaired bowel function. All these significantly contribute to mortality. Finally, need for dialysis in AKI was associated with higher mortality similar to other reports [45].

In our study, majority (80%) of oliguric AKI patients responded to SNB and became non-oliguric. Also, the mean (SD) serum creatinine was 2.94 (1.18) with majority (70%) of our study patients in KDIGO stage 1 or 2 before intervention. This could be due to earlier detection of AKI due to continuous urine output monitoring in the ICU. Also, the mean sofa score in patients with KDIGO stages 1 and 2, was lesser compared to those in stage 3, implying a relatively less sick cohort. It was observed that a higher KDIGO stage was associated with non-response, higher requirement of dialysis and increased mortality, similar to previous reports [46]. Dialysis requirement was also lesser among responders when compared to non-responders (14.4% vs. 40.3%). The predominant indications for dialysis among responders were refractory hyperkalemia and metabolic acidosis. It is interesting to note that in KDIGO stage 3, almost half (46%) of patients responded to SNB and mortality rate was 65%. A study evaluating furosemide stress test with similar patient characteristics reported 26% response to furosemide and a mortality rate of 100% among patients with stage 3 AKI [47]. This could possibly be due to diuretic resistance, which was overcome with SNB. It is interesting to note that there was an incremental response to SNB on urine output response among KDIGO stage 1 and 2, but not in stage 3. This could be due to the established tubular necrosis in stage 3. Diabetes and coronary artery disease in oliguric AKI patients are reported to influence outcomes, but our study found no significant influence [48, 49]. Sepsis was the most common association with AKI (38%) followed by shock (30%), similar to previous reports [50–53]. Nearly two-thirds of oliguric AKI patients with sepsis responded to SNB. Hence, early diagnosis of sepsis with optimal treatment could convert oliguric AKI to non-oliguric AKI in such patients, potentially improving outcomes [54]. But, presence of multi-organ dysfunction in sepsis and shock indicated by a higher SOFA score of > 9, resulted in SNB failure, increased need of dialysis and a higher mortality.

Limitations

Our study has certain limitations. Being a single center observational study, presence of confounders is possible and its external validity could be questioned. However, the patient characteristics and incidence of AKI were similar to previous reports. The overwhelming response to SNB in our patients could be due to a relatively less sick cohort. This could be due to early diagnosis of AKI with hourly urine output monitoring. This was because the cornerstone in our study was administration of diuretics according to urine output, and monitoring the response to it.

CONCLUSIONS

This study has demonstrated that a majority of oliguric AKI patients respond to a time limited trial of sequential nephron blockade, resulting in lesser need for dialysis and better outcomes. Strategies to overcome diuretic resistance require exploration in randomised control studies.

Declarations

Consent for publication- Informed consent for the publication of the study details were taken from the patient/patient's relative.

Availability of data and materials- The data collected and analyzed during the current study are available from the corresponding author on request.

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Conflict of interest and Financial support – None

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