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Furosemide stress test predicts acute kidney injury progression in intensive care unit

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ABSTRACT

Introduction: Clinical tools to predict acute kidney injury (AKI) in intensive care unit (ICU) are lacking.
Objectives: This prospective study was conducted to assess the utility of furosemide stress test (FST) to predict AKI and its progression to severe stages and requirement of hemodialysis (HD).
Patients and methods: Patients in AKI stage I or II were given a standardized dose of frusemide as per protocol. The study cohort included 62 patients. Response to FST was assessed by urine output (UOP) at 2 hours. Study patients were subsequently divided into two groups, those with UOP >200 mL (group A) and those with UOP <200 mL (group B).
Results: Group A constituted 71% (n = 44) of cases. Of them, 2 (4.54%) patients progressed to AKI Network (AKIN) stage III. Group B constituted 29% of cases (n = 18). Of them, 12 (66%) cases progressed to AKIN stage III. In group A, 4.5% (n = 2) of cases required HD. In comparison, 55% (n = 10) of group B patients required HD during the hospital stay. Mortality rate was 6.8% (n = 3) in group A and 33.3% (n = 6) in group B. The duration of stay was more in the patients with UOP <200 mL group compared to UOP >200 mL group.
Conclusion: FST may be a reliable predictor of AKI progression to severe stages and requirement of dialysis in ICUs.

Implication for health policy/practice/research/medical education:
Frusemide stress test can be used as a clinical tool to predict progression of acute kidney injury and dialysis requirement in intensive care settings.
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Introduction

Acute kidney injury (AKI) is associated with significant morbidity and mortality in ICU settings. Oliguria and azotemia often occur late in the course of AKI (1). Biomarkers are promising tools since their levels change over time and according to the severity of injury; however, none of them have robust evidence to incorporate into clinically practice. Studies on AKI diagnosis based on biomarkers have yielded inconsistent results (2). There is an urgent need for more simple and sensitive indicators for diagnosis of AKI.

In many clinical conditions, intrinsic AKI is due to acute tubular injury. Hence, functional assessment of renal tubular function is an 'ideal' option to detect AKI. Furosemide, a loop diuretic has pharmacokinetic properties that help in the functional assessment of the renal tubules. After it is actively secreted into the proximal convoluted tubule, furosemide inhibits luminal Na-K-2Cl co-transporters throughout the thick ascending limb of loop of Henle. Furosemide induced increase in urine output (UOP) helps in assessing integrity of renal tubular function in a patient developing AKI in its early phase. Therefore, response to furosemide challenge could be conducted for clinical assessment of tubular function. Some investigators have suggested that furosemide may decrease tubular oxygen consumption and thereby, its early administration in AKI could be protective (3).

Objectives

This prospective study was carried out to assess the

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utility of furosemide stress test (FST) to predict AKI and its progression to severe stages and requirement of hemodialysis (HD).

Patients and Methods

Study design

This prospective study was conducted at SRM medical college hospital from March 2017 to March 2018. The study cohort consisted 62 patients. Critically ill patients more than 18 years age admitted to the ICU and who developed AKI were included in the study. AKI was classified based on Acute Kidney Injury Network (AKIN) criteria (4). Patients with systolic blood pressure of <100 mm Hg were excluded since they could develop hypotension with diuretic administration. Patients with pre-existing renal dysfunction, transplant recipients, pregnant individuals were also excluded from the study.

Patients who satisfied the study criteria were given a standardized dose of furosemide at 1 mg/kg, as described by Chawla et al (5). Patients who had received loop diuretics within the previous seven days were likely to have a blunted response and hence received an intravenous dose of 1.5 mg/kg. Demographic and clinical data and UOP at the end of two hours were collected. Clinical outcomes measured were AKI progression, requirement of HD, duration of hospital stay and death.

Statistical methods

Statistical analysis was done by SPSS software 19.0. Descriptive statistics such as frequency, percentage, mean± standard error are employed to describe the data. Inferential statistics such as the chi-square test and Fishers' exact probability test were used to analyse the data. *P* value less than 0.05 was considered significant.

Results

The study cohort included 62 AKI patients in ICU, who fit in to eligibility criteria. Four (6.5%) patients were in the age group of 30 to 45 years, 24 (38.7%) patients belonged to 46 to 60 years age group, 25 (40.3%) patients were in 61-75 years age group and 9 (14.5%) patients were >75 years. The study cohort included 38 (61.3%) males and 24 (38.7%) females. Baseline characteristics of the study population are described. Sepsis was the commonest etiology of AKI and diabetes mellitus was the commonest comorbid condition in the study cohort (Table 1).

UOP at the end of two hours was measured in patients after they received furosemide dose as per protocol. None of the patients developed hypotension with furosemide bolus dose. For convenience, patients with UOP > 200 mL were included in 'group A' and those with <200 mL in 'group B'. 'Group A' constituted 71% (n=44) of cases and 'group B' constituted 29% (n=18) of cases. The mean UOP was 373.5 ± 151.16 mL and 111 ± 68.73 mL in 'group A' and 'group B' respectively (*P*<0.0001).

Two (4.54%) patients in 'group A' and 12 (66%) cases in 'group B' progressed to AKIN stage III. All cases (n=2) who progressed to AKIN stage III in 'group A' ultimately required HD, whereas 10 cases in 'group B' required HD during the hospital stay. The mean duration of hospital stay after FST was 7.0 ± 2.41 days and 12.27 ± 6.46 days in 'group A' and 'group B', respectively. Three patients (6.8%) in 'group A' died during the hospital stay. Mortality rate was 33.3% (n=6) in 'group B'. The in-hospital mortality was significantly high in 'group B' (*P* = 0.014) (Table 2).

Table 1. Baseline characteristics of the study population (n = 62)

	Group A (UOP >200 mL) (n =44)	Group B (UOP <200 mL) (n =18)	*P* value
Age (y)	62.93± 13.00	62.38 ± 12.39	0.8787
Male: Female	1.4:1	1.57:1	
Admission serum creatinine (mg/dL)	1.35 ± 0.5	1.44 ± 0.54	0.5319
Peak serum creatinine (mg/dL)	2.12 ± 0.68	2.8 ± 0.86	0.0016
Comorbidities (n)	Diabetes 27 Hypertension 12 CAD 6 CVD 3 COPD 2	Diabetes 15 Hypertension 3 CAD 2	
Primary diagnosis (n)	Sepsis 19 Cardiorenal syndrome 11 Trauma 2 Burns 2 Acute hepatitis 2 Carcinoma rectum 1 Bowel perforation 1 Drug induced 1 Scrub typhus 1 Multifactorial 4	Sepsis 13 Cardiorenal syndrome 3 Trauma 1 Multifactorial 1	
Urine output (mL)	373.5 ±151.16	111±68.73	<0.0001
Mean duration of hospital stay after FST (days)	7.0 ±2.41	12.27±6.46	<0.0001

Table 2. Dialysis requirement and mortality

	Group A (UOP >200 mL) (n =44)	Group B (UOP <200 mL) (n =18)	*P* value
HD requirement	2 (4.5%)	10 (55.5%)	0.0001
No dialysis requirement	42 (95.5%)	8 (44.5%)	
In-hospital mortality (Fisher exact probability 7.237)			
Alive	41 (93.2%)	12 (66.7%)	0.014
Death	3 (6.8%)	6 (33.3%)	

Discussion

AKI is a common complication in ICU patients as a part of multiorgan failure and is significantly associated with high mortality rates (1). The early detection of AKI and the prediction of its progression have significant prognostic and therapeutic implications. An accurate prediction model for AKI progression and severity might help to mitigate risks associated with late renal replacement therapy (RRT) initiation. Investigators have tested oliguria, sodium creatinine ratio, potassium creatinine ratio and FST for predicting AKI in ICU settings (6-8). Burns et al demonstrated that urine potassium excretion correlated to creatinine clearance predicted AKI (8). Chawla et al showed that FST is a dependable test to predict progression of AKI in their seminal study (5). They included 77 study participants which comprised retrospective and prospective cohorts. The test comprised diuretic challenge with one-time dose of 1.0–1.5 mg/kg intravenous furosemide in critically ill patients with stage I or II AKI. The primary outcome was progression to stage III AKI within 14 days of the diuretic challenge. They concluded that a urine volume of less than 200mL at two hours following FST was an ideal cut-off for predicting AKI progression with a sensitivity of 87.1% and specificity 84.1%. Lumlertgul et al, in their FST trial used the same criteria of UOP of < 200 mL at 2 hours for early vs late initiation of RRT (9). Elsaegh et al demonstrated the superiority of the same criteria of FST over serum cystatin C in predicting progression of AKI. FST had a sensitivity of 89.29% and specificity of 93.75% when compared to 82.14% sensitivity and 31.25% specificity with cystatin C (10).

Koyner et al subsequently demonstrated the superiority of FST over several biomarkers in predicting AKI progression, dialysis requirement and mortality in the same study cohort of Chawla et al (5,6,11). The biomarkers used for comparison with FST were fractional excretion of sodium (FeNa), urine and plasma neutrophil gelatinase associated lipocalin (NGAL), urine albumin creatinine ratio, urinary IL-18, kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases (TIMP2), IGF-binding protein-7 (IGFBP-7) and uromodulin. In their cohort of 77 patients, HD requirement was 14.2% (n =11). In the study by Elsaegh et al conducted in settings of sepsis and AKI, 20% of patients required HD (10), while in our study cohort, 16% of patients required HD. FST also predicted the in-hospital mortality. In the study by Koyner et al, 20.7% patients of the entire cohort died in the hospital (11). In our study, 14.5% of entire cohort died.

Predicting AKI in ICU using FST has several advantages. It could be easily done and incurs absolutely no cost for the test. The only requirement is that a urinary catheter has to be placed to quantify urine volume. Unlike biomarkers, FST does not require a sophisticated lab. Those patients with low-UOP with FST could be planned for early renal replacement therapy. In particular, FST would be helpful to triage patients in secondary care centres for timely intervention or referral.

Conclusion

To conclude, FST serves as a useful clinical tool to predict progression of AKI, dialysis requirement and mortality in ICU patients with AKI.

Limitations of this study

This is a single centre study and the sample size is relatively small. Correlation of study findings with urinary and serum biomarkers would have added value to the study.

Authors' contribution

SJM and LV collected data and prepared the draft. VJ and RP edited the draft. SS approved the final version of the manuscript. All the authors were involved in managing the case. All authors read and signed the final version of the paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethical clearance was obtained from the institutional ethics committee prior to the study (Ref#1129/IEC/2017). Informed consent was obtained from study participants or their surrogates. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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