ORIGINAL ARTICLE

Role of Spot Urine Sodium in Furosemide Stress Test in Volume-overloaded Critically Ill Patients with Acute Kidney Injury

Suhas P[1], Rahul K Anand[2], Dalim K Baidya[3], Maya Dehran[4]

Received on: 07 September 2024; *Accepted on*: 07 November 2024; *Published on*: 30 November 2024

Abstract

Introduction and aims: Urine output (UO) in response to furosemide stress test (FST) can predict the progression of acute kidney injury (AKI). This study aimed to assess if changes in UO, urine spot sodium (USS), urine spot sodium creatinine ratio (USSCR) and changes in these parameters over 6 hours could differentiate between progressive and non-progressive AKI.

Materials and methods: Fifty critically ill adults with AKI in acute kidney injury network (AKIN) stages I and II with volume overload were included in this prospective study. The FST was performed with 1 mg/kg intravenous bolus. Hourly UO, USS, USSCR, maximum USS difference (USSDMAX), and maximum USSCR difference (USSCRDMAX) were documented. Any progression of AKI was noted till day 3.

Results: A total of 50 patients were recruited and $n = 10$ had progressive AKI (PAKI) and $n = 40$ had non-progressive AKI (NPAKI). Urine output at 1 and 2 h were significantly less in PAKI group. USS0, USS2, USS6, and USSDMAX were comparable between the groups. USSCR0 and USSCR6 were comparable between the groups whereas USSCR2 and USSCRDMAX were significantly less in PAKI group. USSDMAX did not correlate with UO1 (correlation coefficient 0.2, $p = 0.16$). However, USSCRDMAX showed a poor but significant correlation with UO1 (correlation coefficient 0.3, $p = 0.03$).

Conclusion: To conclude, hourly UO in the first two hours and maximum change in USSCR within 6 hours following the FST may have an important role in early differentiation of progressive AKI in critically ill patients.

Keywords: Acute kidney injury, AKI progression, Furosemide stress test, Urine spot sodium, Urine spot sodium creatinine ratio.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24862

Highlights

Hourly urine output (UO) in the first 2 hours and maximum change in urine spot sodium creatinine ratio (USSCR) within 6 hours following the furosemide stress test (FST) may have important role in early differentiation of progressive acute kidney injury (AKI) in critically ill patients.

Introduction

The current concept of fluid therapy in critically ill patients has four phases: resuscitation (rapid fluid administration); optimization (fluid administration is done after assessing risks and benefits); stabilization (fluid is given only if the patient is fluid responsive) and evacuation (excess fluid is eliminated).[1] Deresuscitation or fluid evacuation is very important as fluid overload may be associated with difficulty in weaning from mechanical ventilation, gastrointestinal complications, delirium, dyselectrolytemia, and kidney dysfunction in critically ill patients.[2]

Acute kidney injury may be commonly associated with adverse outcomes like death, prolonged intensive care unit (ICU) and hospital stay, and increased cost of treatment in critically ill patients.[3] Many biomarkers were used for early detection of AKI but they lack specificity.[4] Furosemide stress test is a relatively new tool to measure renal functional reserve, which may have good prognostic performance in predicting AKI)[5] Low spot urinary sodium and chloride may be associated with subsequent development of AKI in critically ill patients.[6] Previous studies have shown a good correlation between urinary spot sodium creatinine ratio and 24-hour urinary sodium excretion.[7] Urine spot sodium (USS) accurately predicted poor natriuretic response to loop diuretics in acute decompensated heart failure patients.[8] However, the exact role of USS, USSCR, and their change in response to FST in critically ill volume-overloaded patients is not clear. Therefore, this preliminary study was conducted to examine USS, USSCR, and their dynamics in response to FST in ICU patients with volume overload

[1]Department of Critical Care Medicine, PK Das Institute of Medical Sciences, Ottapalam, Kerala, India

[2,4]Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences (AIIMS), New Delhi, India

[3]Department of Anaesthesiology, Critical Care and Pain Medicine, All India Institute of Medical Sciences (AIIMS), Guwahati, Assam, India

Corresponding Author: Rahul K Anand, Department of Anesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences (AIIMS), New Delhi, India, Phone: +91 9013082271, e-mail: drrahulkanand@gmail.com

How to cite this article: Suhas P, Anand RK, Baidya DK, Dehran M. Role of Spot Urine Sodium in Furosemide Stress Test in Volume-overloaded Critically Ill Patients with Acute Kidney Injury. Indian J Crit Care Med 2024;28(12):1107–1111.

Source of support: Nil

Conflict of interest: None

and early stage of AKI. Our hypothesis was that change in USS and USSCR in response to FST will correlate with a change in UO and can identify the progression of AKI.

Materials and Methods

Design and Setting

Patient recruitment for this prospective study was undertaken between July 2018 and June 2019 in the ICU of a tertiary care institute in northern India, after institutional ethics committee approval (Reference number: IECPG- 676/ 31.01.2018, RT18/28.02.2018 dated 06.03.2018) and registration in Clinical Trials Registry of India (www.ctri.nic.in; CTRI/2018/12/016723). Fifty critically ill patients aged 18–80 years with hypervolemia and acute kidney injury (AKIN stages I and II) with systolic BP ≥100 mm Hg; on norepinephrine infusion ≤ 10 µg/minute were included from a mixed medical-surgical ICU within 7 days of ICU admission. Exclusion criteria were significant hemodynamic instability (norepinephrine ≥10 µg/minute or equivalent), electrolyte imbalance, pre-existing chronic kidney disease (CKD), AKI-AKIN stage III, chronic liver disease, and heart diseases including heart failure.

Volume overload in a patient was defined by one of the following criteria: (i) positive fluid balance >1 liter/day after 48 hours of ICU admission, (ii) cumulative fluid balance >8 liter/week, (iii) percentage of cumulative fluid balance adjusted for body weight >10% [Percentage of fluid overload = (total fluid intake – total fluid output)/body weight at admission × 100].[9]

Study Protocol

Intravenous furosemide 1 mg/kg was injected over 10 minutes and response to diuretic therapy was monitored in terms of UO, USS, and USSCR. Hourly UO and daily serum creatinine were followed up to 72 hours to see the progression of the AKIN stage. Urine spot sodium was measured with the direct ion-selective electrode (SE) method. Serum creatinine was measured daily, using modified Jaffe's method. Baseline creatinine for comparison was taken as the lowest serum creatinine for the past 6 months. In the absence of previous baseline values, the lowest serum creatinine since current admission was taken for comparison.[10] During the study, any adverse hemodynamic events or major electrolyte disturbances were appropriately managed as per institute protocol.

Data collection

The following data were collected:

- Baseline demographics, diagnosis, and critical illness severity scores including Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA).
- Average hourly UO for 6 hours before FST and 8 hours following FST.
- Urine spot sodium (USS) just before (0), at 2 and 6 hours after FST.
- USSCR just before (0), and at 2 and 6 hours after FST.
- Maximum urine spot sodium difference (USSD MAX): calculated by maximum value after FST minus pre-FST value.
- Maximum urine spot sodium creatinine ratio difference (USSCRD MAX): calculated by maximum value after FST minus pre-FST value.
- AKI-AKIN stage, renal replacement therapy, adverse hemodynamic events, and major electrolyte disturbance such as hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia up to 72 hours.

Sample Size Calculation and Statistical Analysis

In a previous study on critically ill patients, Zazzeron L et al. found that USS at 2 h was 116 (97–129) after FST. Assuming at least 10% decrease in USS in AKI patients compared with non-selected critically ill patients estimated sample size was $n = 50$ with alpha error of 0.05 and power of 90%.[11] Data analysis was performed in Stata 16.0. Quantitative variables were reported as means ± standard deviation (SD). Clinical outcome was expressed as frequency and percentage. The distribution of data on age, biochemical parameters, APACHE-II score, and SOFA score were reported as mean ± SD or median with range. Chi-square test was used to compare categorical data, and a Student's *t*-test for numerical data. Pearson and Spearman's rank correlation was performed to measure the degree of association. To study the association between USSD MAX, USSCRD MAX, and first-hour UO following FST, and progressive AKI, Mann–Whitney *U* Test was used. Independent *t*-test was used to see the association between UO of the second hour following FST and progressive AKI. Repeated measures ANOVA was used to see the changes in USS and USSCR in response to FST. Spearman's rank correlation was used to see the association between changes in USS represented as USSD MAX and UO of the first hour following FST. Statistical significance was fixed at p-value < 0.05.

Results

Fifty patients with AKIN stage I and II AKI were enrolled in the study and by 72 hours $n = 10$ patients had progression of AKI by at least one stage and were named as progressive AKI (PAKI). In the remaining $n = 40$ patients AKIN stage was either static or resolved and were named as non-progressive AKI group (NPAKI). Demographic and clinical parameters of PAKI and NPAKI patients at baseline are provided in Table 1. PAKI patients had increased weight; higher positive fluid balance and SOFA score at baseline. Among the 10 patients in PAKI group, seven patients had progression from AKIN stages 2–3 and three patients had progression from AKIN stages I–3.

Urine output, urine electrolyte, and creatinine data are provided in Table 2 and Figure 1. Urine output at 1 and 2 hour and USSCRD MAX were significantly less in PAKI group. However, USSD MAX was comparable between the groups. USS0, USS2, USS6, USSCR0, and USSCR6 were comparable between the groups whereas USSCR2 was significantly less in PAKI group.

USSCRD MAX was lower in PAKI group compared with NPAKI and was associated with the progression of AKI ($p = 0.01$; Table 2). Maximum urine spot sodium difference was higher in PAKI than in NPAKI but there was no association with the progression of AKI ($p = 0.68$; Table 2). UO1 and UO2 had a significant association with AKI progression ($p < 0.001$; Table 2).

Maximum urine spot sodium difference did not correlate with UO1 (correlation coefficient 0.2, $p = 0.16$; Fig. 2). However, USSCRD MAX showed a poor but significant correlation with UO1 (correlation coefficient 0.3, $p = 0.03$; Figs 3 and 4).

Discussion

We found that the maximum change in USSCR within 6 hours of FST may be a good predictor for AKI progression over three days. We also found that compared with USS, USSCR is a better measure of natriuretic response to FST. This study confirms the utility of the first 2 hour UO after FST for predicting AKI progression within 3 days following the FST. Urine spot sodium, and USSCR of all recruited patients increased from the baseline for the first 2 hours

Table 1: Baseline and clinical data in both the groups

Parameters	*Total (n = 50)*	*PAKI (n = 10)*	*NPAKI (n = 40)*	*Significance (p-value)*
Age (years) (Mean ± SD)	51.68 ± 18.91	47.8 ± 21.15	52.65 ± 18.46	0.5
Female *n* (%)	27 (54%)	4 (40%)	23 (57.5%)	0.5
Weight (kg) (Mean ± SD)	71.52 ± 12.21	81.7 ± 8.54	68.98 ± 11.71	0.002
Positive fluid balance (mL/day) at recruitment [Median (max–min)]	1485 (470–6789)	2362 (470–6700)	1363.5 (859–6789)	0.05
APACHE II (Mean ± SD)	20.74 ± 4.92	20.7 ± 4.62	20.75 ± 5.05	0.98
SOFA A (Mean ± SD)	11.32 ± 2.70	11.5 ± 2.64	11.28 ± 2.75	0.81
SOFA 0 (Mean ± SD)	11.98 ± 3.53	13.5 ± 1.72	11.6 ± 3.77	0.02
Baseline Creatinine (Mean ± SD)	0.862± 0.172	0.910 ± 0.119	0.85± 0.182	0.221
Comorbidities				
Diabetes mellitus	15	4	11	0.440
Hypertension	15	3	12	0.98
Respiratory (chronic obstructive pulmonary disease, bronchial asthma and tuberculosis)	10	3	7	0.377
Cardiac (coronary artery disease and rheumatic heart disease)	7	2	5	0.541
Cerebrovascular accident	3	1	2	0.552
Hypothyroidism	8	2	6	0.700
Diagnosis				
Sepsis/septic shock	43	8	35	0.541
Respiratory disease	21	4	17	0.886
Cardiac disease	4	1	3	0.794
Central nervous system disease	1	0	1	0.800
Liver disease	5	2	3	0.258
Endocrine disorder	3	1	2	0.496
Post surgical	9	2	7	0.854
Others (tropical fever, urinary tract infection, skin and soft tissue infections etc.)	10	2	8	0.970

Data expressed as Mean ± SD, Median (max–min)] or n (%). APACHE, acute physiology and chronic health evaluation; NPAKI, non-progressive AKI; PAKI, progressive AKI; SOFA, sequential organ failure

Table 2: Urine output, Urine electrolyte and creatinine data before and after FST

Parameters	*Total patients (n = 50)*	*PAKI (n = 10)*	*NPAKI (n = 40)*	*Significance (p-value)*
UO1 (Mean ± SD) (mL)	241.4 ± 174.30	53.7 ± 18.42	288.33 ± 163.71	<0.001
UO2 Mean ± SD) (mL)	199.82 ± 127.60	44.7 ± 24.78	238.6 ± 112.26	<0.001
USS0 (Mean ± SD) (mmol/L)	54.4 ± 25.27	47.1 ± 29.65	56.23 ± 24.13	0.312
USS2 (Mean ± SD) (mmol/L)	105.1 ± 30.13	100.9 ± 28.63	106.15 ± 30.76	0.627
USS6 (Mean ± SD) (mmol/L)	68.34 ± 26.08	76.2 ± 28.65	66.36 ± 25.41	0.291
USSCR0 (Mean ± SD)	1.03 ± 0.65	0.68 ± 0.57	1.11 ± 0.65	0.054
USSCR2 (Mean ± SD)	7.77 ± 6.04	4.47 ± 3.80	8.6 ± 6.24	0.014
USSCR6 (Mean ± SD)	2.43 ± 2.95	1.96 ± 1.32	2.54 ± 3.24	0.38
USSD MAX (Mean ± SD) (mmol/L)	52 ± 24.85	54.3 ± 10.15	51.43 ± 27.39	0.68
USSCRD MAX (Mean ± SD) (mmol/L)	27.28 ± 143.96	3.81 ± 3.32	33.15 ± 160.81	0.01

Data expressed as Mean ± SD. NPAKI, non-progressive AKI; PAKI, progressive AKI; UO, urine output; USS, urine spot sodium; USSCR, urine spot sodium creatinine ratio; USSCRD MAX, maximum change in urine spot sodium creatinine ratio; USSD MAX, maximum change in urine spot sodium

and then decreased in the next 4 hours after FST which correlates with available literature.[11]

We observed UO in the first 2 hours in response to FST was significantly less in PAKI patients. Similar findings were observed by Chawla LS et al.[12] They found that a cut-off urine volume of less than 100 mL per hour in the first 2 hours following FST was highly predictive for the progression of AKI (sensitivity 87% and specificity 84%).[12] In the current cohort UO were 53 mL and 44 mL at 1 h and

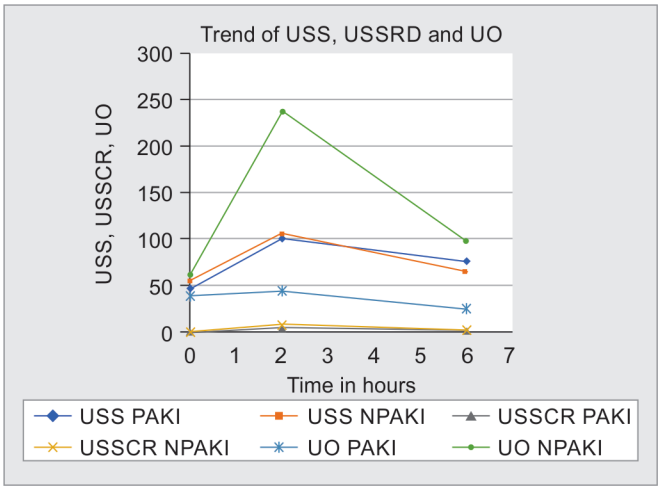

Fig. 1: Graph showing the urine spot sodium (mmol/L) (USS), mean urine spot sodium creatinine ratio (USSCR) of the patients just before furosemide stress test (FST) 2 hours after FST and 6 hours after FST. It shows the trend of hourly urine output in mL (UO) 6-hour average before FST, at 2 hours after FST and 4–8-hour average post-FST. PAKI, Progressive AKI and NPAKI, Non-progressive AKI

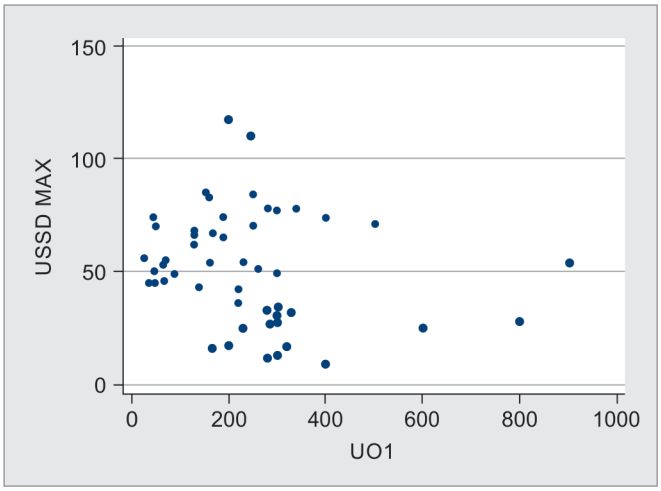

Fig. 2: Scatter plot representing correlation between maximum changes in urine spot sodium (USSD MAX in mmol/L) and urine output at first hour (UO1 in mL) in response to furosemide stress test (FST)

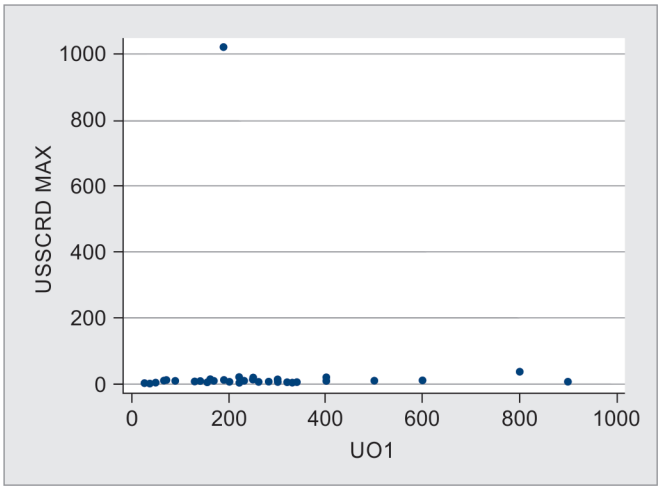

Fig. 3: Scatter plot representing correlation between maximum changes in urine spot sodium creatinine ratio (USSCRD MAX) and urine output at first hour (UO1) in response to furosemide stress test (FST)

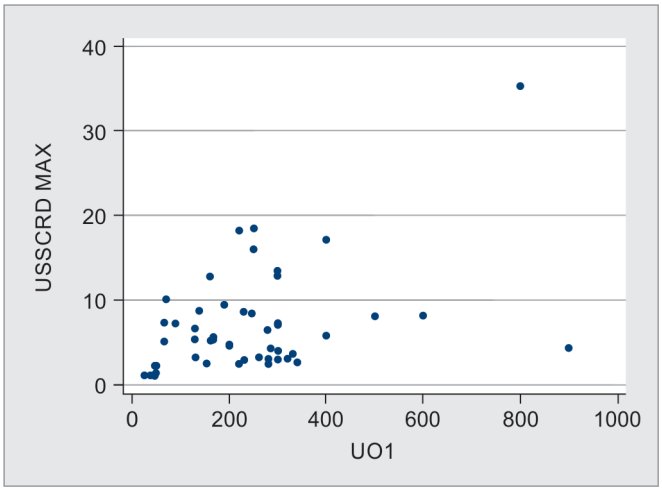

Fig. 4: Scatter plot representing correlation between maximum urine spot sodium creatinine ratio (USSCRD MAX) and urine output (mL) of first hour (UO1) in response to furosemide stress test (FST), excluding values above 1,000

2 h, respectively in PAKI patients. Two-hour UO following FST outperformed various biomarkers in the prediction of progression to AKI in a previous study.[10]

Musso et al. observed that daily monitoring of urinary spot sodium and fractional excretion of sodium showed significant changes, 24 hours before the development of AKI in ICU patients.[13] Current study evaluated changes in USS and USSCR following FST in 6 hours. In contrast to the above study, the current study found stress dose diuretic-induced changes in urinary spot sodium are not a good predictor of AKI progression but stress dose diuretic-induced changes in USSCR were found to be a predictor of AKI progression.

The current study is one of the first studies to assess stress dose diuretic-induced changes in USS and USSCR and its relation with the progression of AKI. However, the study had a few limitations as well. This is just a preliminary study to see how diuretic and natriuretic responses to FST will differentiate AKI progression in ICU patients. Moreover, the current study measured urine spot samples at fixed intervals which may be different from the absolute amount of electrolyte excretion. More frequent or continuous electrolyte excretion monitoring may be more informative and may provide better results.[11] Measurement of hourly UO is easy to conduct in ICUs and urine spot electrolyte monitoring is a cheaper and easier test to perform. We did not measure other urinary electrolytes like potassium and chloride. Our study had a small sample size and we did not perform the regression analysis to predict the progression of AKI due to the small event rate. Moreover, the study follow-up period was only 3 days.

To conclude, hourly UO in the first two hours and maximum change in USSCR within 6 hours following the FST may have an

important role in the early differentiation of progressive AKI in critically ill patients.

Orcid

Suhas P https://orcid.org/0009-0000-2617-8411
Rahul K Anand https://orcid.org/0000-0002-7852-1231
Dalim K Baidya https://orcid.org/0000-0001-7811-7039
Maya Dehran https://orcid.org/0000-0002-0258-739X

References

1. Zampieri FG, Bagshaw SM, Semler MW. Fluid therapy for critically ill adults with sepsis: A review. JAMA 2023;329(22):1967–1980. DOI: 10.1001/jama.2023.7560.
2. Besen BAMP, Gobatto ALN, Melro LMG, Maciel AT, Park M, et al. Fluid and electrolyte overload in critically ill patients: An overview. World J Crit Care Med 2015;4(2):116–129. DOI: 10.5492/wjccm.v4.i2.116.
3. Kulkarni AP, Bhosale SJ. Epidemiology and pathogenesis of acute kidney injury in the critically ill patients. Indian J Crit Care Med 2020;24(Suppl 3):S84–S89. DOI: 10.5005/jp-journals-10071-23394.
4. Bhosale SJ, Kulkarni AP. Biomarkers in acute kidney injury. Indian J Crit Care Med 2020;24(Suppl 3):S90–S93. DOI: 10.5005/jp-journals-10071-23398.
5. Chawla LS, Ronco C. Renal stress testing in the assessment of kidney disease. Kidney Int Rep 2016;1(1):57–63. DOI: 10.1016/j.ekir.2016.04.005.
6. Maciel AT, Park M, Macedo E. Urinary electrolyte monitoring in critically ill patients: A preliminary observational study. Rev Bras Ter Intensiva 2012;24(3):236–245. PMID: 23917824.
7. Doenyas-Barak K, Beberashvili I, Bar-Chaim A, Averbukh Z, Vogel O, Efrati S, et al. Daily sodium and potassium excretion can be estimated by scheduled spot urine collections. Nephron 2015;130(1):35–40. DOI: 10.1159/000430105.
8. Testani JM, Hanberg JS, Cheng S, Rao V, Onyebeke C, Laur O, et al. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. Circ Heart Fail 2016;9(1):e002370. DOI: 10.1161/CIRCHEARTFAILURE.115.002370.
9. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: Evaluation and management. BMC Nephrol 2016;17(1):109. DOI: 10.1186/s12882-016-0323-6.
10. Koyner JL, Davison DL, Brasha-Mitchell E, Chalikonda DM, Arthur JM, Shaw AD, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol 2015;26(8):2023–2031. DOI: 10.1681/ASN.2014060535.
11. Zazzeron L, Ottolina D, Scotti E, Ferrari M, Bruzzone P, Sibilla S, et al. Real-time urinary electrolyte monitoring after furosemide administration in surgical ICU patients with normal renal function. Ann Intensive Care 2016;6(1):72. DOI: 10.1186/s13613-016-0168-y.
12. Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care 2013;17(5):R207. DOI: 10.1186/cc13015.
13. Musso CG, Silva D, Propato F, Molina Y, Velez-Verbel M de los Á, Lopez N, et al. Daily urinary sodium excretion monitoring in critical care setting: A simple method for an early detection of acute kidney injury. Indian J Nephrol 2021;31(3):266–270. DOI: 10.4103/ijn.IJN_53_20.