International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2019.129.136

Research Article
Ethacrynic Acid vs. Furosemide in Patients with Fluid Overload Associated with Cardiac Intensive Care

Jinfeng Han, Nan Li and Yushan Wang

Department of Intensive Care Unit, The First Hospital of Jilin University, Changchun, 130021 Jilin, China

Abstract

Background and Objective: Adequate fluid removal may decrease the mechanical ventilation time in intensive care. Ethacrynic acid as diuretic required comparatively in fewer dose than furosemide. The objective of the study was to compare the efficacy and safety of ethacrynic acid with furosemide in fluid overload patients associated with cardiac intensive care. **Materials and Methods:** A total of 248 patients with signs of volume overload in the cardiac intensive care unit were subjected to randomize. Patients were received 0.8 mg kg^{-1} h^{-1} of furosemide (FR group, n = 124) or 0.5 mg kg^{-1} h^{-1} ethacrynic acid (EA group, n = 124) at 1 mL h^{-1}, for maximum 3 days. Serum creatinine, urine output, body weight loss, cost of interventions and treatment-emergent adverse effects were evaluated. The Chi-square for independence or one-way ANOVA was performed at 95% of confidence level. **Results:** Furosemide and ethacrynic acid, both decreased serum creatinine and increased urine output. Patients of FR group had high weight loss than EA group at the time of discharge ($p<0.0001$). Hypocalcemia and hypomagnesemia had been reported in FR group and tinnitus and hearing loss had been reported in EA group during the follow-up period. Ethacrynic acid treatment was highly expensive treatment than frusemide ($p<0.0001$). **Conclusion:** Ethacrynic acid is safe and effective but costly alternative of frusemide.

Key words: Cardiac intensive care unit, ethacrynic acid, frusemide, fluid overload, hearing loss, serum creatinine, urine output

Received: September 13, 2018 Accepted: October 12, 2018 Published: December 15, 2018

Citation: Jinfeng Han, Nan Li and Yushan Wang, 2019. Ethacrynic acid vs. furosemide in patients with fluid overload associated with cardiac intensive care. Int. J. Pharmacol., 15: 129-136.

Corresponding Author: Yushan Wang, Department of Intensive Care Unit, The First Hospital of Jilin University, Changchun, 130021 Jilin, China
Tel/Fax: 0086-0431-88782222

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The fluid overload is the major issue in adults and children associated with the cardiac intensive care unit[1] because adequate fluid removal may decrease the mechanical ventilation time of patients[2]. Thiazides diuretics e.g., metolazone, chlorothiazide and hydrochlorothiazide are less effective than loop diuretics[3]. Therefore, loop diuretics are recommended for management of the fluid overload associated with any conditions for every age of patients[4]. Generally used diuretics in adult and children are furosemide, ethacrynic acid, bumetanide, torsemide and mannitol[1,4]. For the fluid overload in patients associated with the cardiac intensive care unit, loop diuretics are helpful in ventricular failure to manage fluid accumulation[5].

Intensivists using furosemide for management of the fluid overload associated with the cardiac intensive care unit[1,4]. Continuous infusion of furosemide leads to a significantly superior and gradual increase in urine output than bolus administration[6]. However, furosemide therapy has to toxicity[2] and worsening of renal functions[4,6]. Mannitol is also used for the fluid overload associated with the cardiac intensive care unit but the results of the study are not satisfactory[7]. Ethacrynic acid is approved as a diuretic in 1967 by USFDA. It has no sulfonamide in the structure[8]. Ethacrynic acid has caused a high metabolic alkalosis than furosemide but the comparatively fewer dose is required to increase urine output[1]. Torsemide and bumetanide as first-line treatment have limited evidence for superiority than furosemide in fluid overload[9,10]. A sulfa moiety containing loop diuretics (torsemide, bumetanide and furosemide) have chances of sulfonamide allergies, in such conditions, ethacrynic acid is used to maintain fluid overload[11,12]. Therefore, use of diuretics treatment in young and adult with the fluid overload associated with the cardiac intensive care unit is required to justify.

The primary goal of the trial was to increase urine output in young and adult patients with the fluid overload associated with the cardiac intensive care unit. The secondary endpoint was to compare the efficacy and safety of ethacrynic acid with furosemide.

MATERIALS AND METHODS

Drugs and reagents: Ethacrynic acid (Edecrin®) was purchased from Aton Pharma, Inc., USA. Furosemide (Lasix®) was purchased from Sanofi-Aventis Pharma Beijing Co., Ltd., China. Normal saline was purchased from Baxter, USA.

Ethical consideration and consent to participate: The study had been registered in the Research registry (www.researchregistry.com), UID No. research registry 4401 dated 12 February, 2017. The protocol (FJU/CL/25/02 dated 1 February, 2017) had been approved by the First Hospital of Jilin University review board. The study had adhered to the law of China, 2013 Declarations of Helsinki and consolidated standards of reporting trials (CONSORT) guidelines. A written informed consent had been signed by the patient or their relative(s) (legally authorized person) before study regarding interventions, pathology and publication of trial in all formats (hard and/or electronics) irrespective of time and language.

Inclusion criteria: Patients age 15 years and above and below 65 years[13,14], hospitalized in the First Hospital of Jilin University, Changchun, Jilin, China and the referring hospitals from 15 February, 2017 to 31 December, 2017 for cardiac intensive care unit having signs of volume overload were included in the trial. Patients signed an informed consent form were only included in the study. The estimated fluid overload was the same in both populations (7.12±0.15% vs. 7.18±0.31%, $p = 0.054$; fluid overload was calculated[2] as per Eq. 1) at the time of the enrollment and the other demographic characteristics of the enrolled patients were reported in Table 1.

$$\text{Fluid overload} = (\text{Total fluid in-Total fluid out}) \times 100 \quad (1)$$

A total of 338 patients with fluid overload associated with cardiac intensive care were assessed for eligibility.

Exclusion criteria: Patients age below 15 years and above 65 years[13,14], patients with cardiac issues (systolic blood pressure <80 mm Hg) and renal instability (serum creatinine >3.99 mg dL^{-1}), who had not signed informed consent form were excluded from the trial. Female patients with pregnancy and lactation period were excluded from the study. Patients who needed dialysis or ultrafiltration at the time of enrollment were excluded from the trial.

Design of experiment: A total of 248 patients were subjected to simple randomization in a 1:1 ratio. The blinding was carried out by prefilled envelopes. The sample size was found by Open-Epi-English 3.01 (Epidemiologic Statistics for Public Health, USA) and found to be 124 for both groups. Two sided-confidence intervals were 95%, ($\alpha = 0.05$), the outcome in both groups was 95%, risk ratio detected was 1 and the normal approximation was 1.073%. CONSORT flow diagram of the study was presented in Fig. 1.

Table 1: Demographic characteristics of the enrolled patients

	Characteristics		
	Groups (n = 124)		
Interventions	Furosemide (FR)	Ethacrynic acid (EA)	Comparisons between groups (p-value)
Age (year)			
Minimum	18	19	0.054
Maximum	64	63	
Mean±SD	45.12±5.14	43.93±4.51	
Gender			
Male	45(36)	42(34)	0.083
Female	79(64)	82(66)	
Body weight (kg)	55±5.47	54.42±3.89	0.337
Systolic arterial pressure (mm Hg)	82.15±1.14	82.45±2.12	0.166
Hemoglobin (%)	12.15±1.45	12.45±1.35	0.093
Heart rate (beats/min)	71±6	73±10	0.057
Estimated fluid overload	7.12±0.15%	7.18±0.31%	0.054
Heart disease			
Ischemia	18(15)	16(13)	0.775
Idiopathic cardiomyopathy	23(19)	21(17)	
Coronary artery disease	51(41)	48(39)	
Valvular disease	28(22)	31(25)	
Hypertrophic cardiomyopathy	4(3)	8(6)	
Diabetes			
Present	12(90)	8(6)	0.484
Absent	112(10)	116(94)	
Serum creatinine (mg dL^{-1})	1.32±0.08	1.29±0.15	0.051
Urine output (mL day^{-1})	1812±75	1832±90	0.059

Data were represented as Mean±SD (continuous data) and number (percentage for categorical data), The Chi-square for independence (for constant data) and one-way ANOVA (for continuous data) were used for statistical analysis, A $p<0.05$ was considered significant, all patients have Chine PR origin

Interventions: Patients in the ER group were received 0.5 mg kg^{-1} h^{-1} ethacrynic acid[14]. Patients of the FR group were received 0.8 mg kg^{-1} h^{-1} of furosemide[15]. Both interventions were made diluted with normal saline and administered at 1 mL h^{-1}. All interventions were run for a maximum of 3 days. Except for researchers, patients, nursing staff and all evaluators were kept blind for interventions.

Laboratory tests: All patients were subjected to complete blood analysis including hemoglobin value, serum creatinine, Blood Urea Nitrogen (BUN), plasma B-type natriuretic peptide (BNP), serum sodium and serum potassium levels at the time of admission, each day and after 3 days of completion of interventions. Plasma BNP evaluated by immunofluorescence assay. About <99.99 pg mL^{-1} was considered normal and the analytical sensitivity was <4.99 pg mL^{-1} for procedural assay[6].

In-hospital outcomes: All patients were subjected to average fluid overload, the estimated glomerular filtration rate (eGFR), urine output/day and body weight loss at the time of admission and after 3 days of completion of interventions[6].

Information regarding treatment-emergent adverse effects and cost of interventions were collected from the Digital Imaging and Communications in Medicine (DICOM) files of patients and pharmacy records.

Statistical analysis: The chi-square for independence (for constant data)[1] and one-way analysis of variance (ANOVA, for continuous data)[16] was used for statistical analysis at 95% of confidence level. Tukey test (considering critical value [q] >3.328 as significant) was used for *post-hoc* analysis. SPSS 22 Software (BM Analytics, Chicago, IL, USA) was used for analysis. Intention-to-treat method of analysis was preferred.

RESULTS

Furosemide (1.32±0.08 mg dL^{-1} vs.1.11±0.15 mg dL^{-1}, $p<0.0001$, $q = 17.87$) and ethacrynic acid (1.29±0.15 mg dL^{-1} vs. 1.12±0.16 mg dL^{-1}, $p<0.0001$, $q = 12.34$) both decreased serum creatinine after 3 days of interventions. Both had same intensity to decrease serum creatinine level ($p = 0.84$, Fig. 2). Furosemide was decreased BUN, BNP, serum sodium and serum potassium levels. However, ethacrynic acid was failed in maintaining laboratory data. The event of decreased serum potassium levels and BNP were the same in both groups ($p = 0.63$, Table 2).

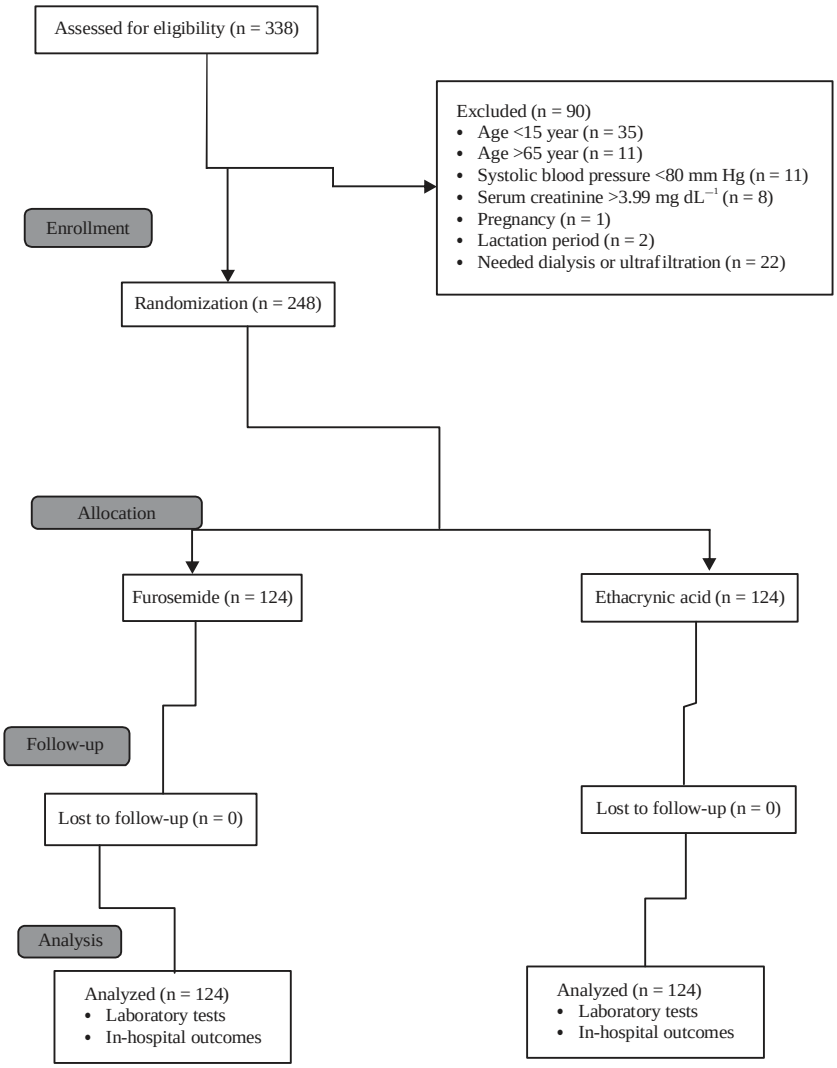

Fig. 1: CONSORT flow-chart of the study
Two sided-confidence intervals were 95%, (α = 0.05)

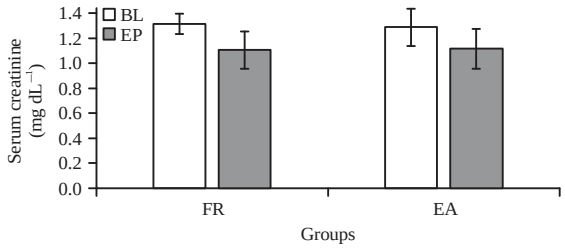

Fig. 2: Effects of interventions after 3 days on serum creatinine
One-way ANOVA was used for statistical analysis, Tukey test was used for *post-hoc* analysis. A p<0.05 and q>3.328 were considered significant, BL: Baseline, EL: After 3 days of intervention

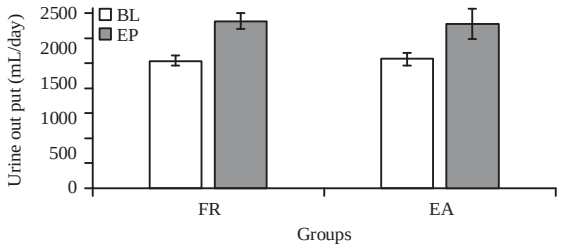

Fig. 3: Effects of interventions on urine output after 3 days
One-way ANOVA was used for statistical analysis, Tukey test was used for post-hoc analysis. A p<0.05 and q>3.328 were considered significant, BL: Baseline, EL: After 3 days of intervention

Furosemide (1812±75 mL/day vs. 2375±115 mL/day, p< 0.0001, q = 60.63) and ethacrynic acid (1832±90 mL/day vs. 2335±215 mL/day, p<0.0001, q = 37.33) both were increased urine output. However, the intensity of improvement in urine output was the same for both (p = 0.069, Fig. 3).

Table 2: Results of laboratory tests at the end of 3 days of intervention

	Characteristics											
	Groups (n = 124)								Comparisons between groups			
									BL		EP	
Interventions	Furosemide (FR)				Ethacrynic acid (EA)							
Level	BL	EP	p-value	q-value	BL	EP	p-value	q-value	p-value	q-value	p-value	q-value
BUN (mg dL^{-1})	101±8	95±7	<0.0001	9.092	103±9	102±5	0.281	N/A	0.066	N/A	<0.0001	12.174
BNP (pg mL^{-1})	781±77	741±65	<0.0001	6.083	756±120	725±132	0.054	N/A	0.052	N/A	0.227	N/A
Na (mEq L^{-1})	131±7	125±9	<0.0001	8.65	132±11	129±15	0.074	N/A	0.394	N/A	<0.0001	4.095
K (mEq L^{-1})	4.12±0.51	3.99±0.41	0.028	3.34	4.15±0.52	4.02±0.55	0.057	N/A	0.65	N/A	0.63	N/A
Urine pH	7.31±0.12	7.41±0.03	<0.0001	35.3	7.29±0.05	7.39±0.03	<0.0001	29.41	0.08	N/A	<0.0001	9.1

Data were represented as Mean±SD, One-way ANOVA was used for statistical analysis, Tukey test was used for *post-hoc* analysis, A p< 0.05 was considered significant, A q>3.328 was considered significant, BUN: Blood urea nitrogen, BNP: Plasma B-type natriuretic peptide, Na: Serum sodium level, K: Serum potassium level, BL: Baseline, EP: After 3 days of intervention, N/A: Not applicable, <2.6 mEq L^{-1} serum potassium level was considered as hypokalemia, pH>7.5 was considered as metabolic alkalosis

Table 3: Results of in-hospital outcomes at the end of 3 days of intervention

	Characteristics											
									Comparisons between groups			
	Groups (n = 124)								BL		EP	
Interventions	Furosemide (FR)				Ethacrynic acid (EA)				p-value	q-value	p-value	q-value
Total time of the continuous infusion (h)	65.12±3.15				66.32±6.45				N/A	N/A	0.064	N/A
Level	BL	EP	p-value	q-value	BL	EP	p-value	q-value				
eGFR												
¥Mild kidney dysfunction	64(52)	89(72)	<0.0001	5.76	61(49)	76(61)	<0.0001	3.41	0.08	N/A	0.0002	3.37
*Moderate kidney dysfunction	60(48)	35(28)			63(51)	48(39)						
¶Urine output (mL kg^{-1} h^{-1})	2±0.5	3.2±0.6	<0.0001	23.5	2.1±0.6	3.15±0.6	<0.0001	19.49	0.155	N/A	0.512	N/A

Data were represented as Mean±SD (continuous data) and number (percentage for categorical data), The Chi-square for independence (for constant data) and one-way ANOVA (for continuous data) were used for statistical analysis, Tukey test was used for *post-hoc* analysis, A p<0.05 was considered significant, A q>3.328 was considered significant, eGFR: The estimated glomerular filtration rate, ¥<60 mL min^{-1}/1.73 m^2, *15-29 mL min^{-1}/1.73 m^2, BL: Baseline, EP: After 3 days of intervention, N/A: Not applicable, ¶Goal of urine output 3 mL kg^{-1} h^{-1}

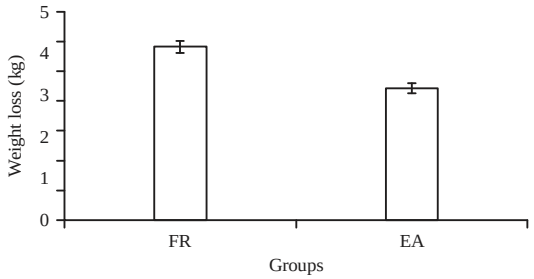

Fig. 4: Weight loss of patients at the time of discharge

One-way ANOVA was used for statistical analysis. A p<0.05 was considered significant

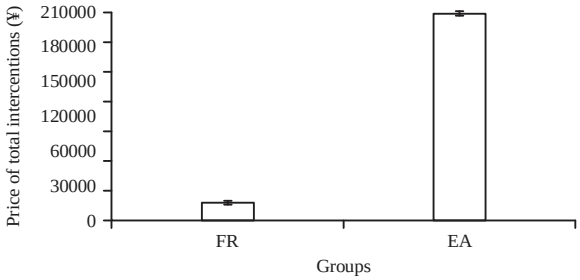

Fig. 5: Price of total interventions

One-way ANOVA was used for statistical analysis. A p<0.05 was considered significant, price included for fluid over-load treatment only, price reported per patient in ¥, 6 ¥ is equal to 1 $

Patients in the FR group had higher weight loss than EA group at the time of discharge (4.15±0.15 kg vs. 3.16±0.12 kg, p<0.0001, Fig. 4).

There was no significant difference for a total time of the continuous infusion between groups (p = 0.064). Furosemide and ethacrynic acid both had improved eGFR but furosemide had the greater intensity to improve eGFR than ethacrynic acid (p = 0.0002, q = 3.37, Table 3).

Tinnitus and hearing loss had been reported in both groups during the follow-up period (Table 4).

Table 4: Treatment-emergent adverse effects during the follow-up period

	Effects			
	Groups (n = 124)		Comparisons between groups	
Interventions	Furosemide (FR)	Ethacrynic acid (EA)	p-value	q-value
*¥Hypocalcemia	8(6)	0(0)	0.0043	5.05
*$Hypomagnesemia	9(7)	0(0)	0.0024	5.37
*¶Tinnitus and hearing loss	15(12)	23(19)	0.214	N/A
Oral and gastric irritation	4(3)	1(1)	0.083	N/A
Cramping	3(2)	1(1)	0.158	N/A
Constipation	4(3)	1(1)	0.083	N/A
*¶Blurred vision	5(4)	2(2)	0.06	N/A
*¶Thrombophlebitis	15(12)	16(13)	0.319	N/A
*¶θHypotension	7(6)	13(10)	0.014	2.423

¥<4.5 mg dL^{-1}, $<1.8 mg dL^{-1}, θ<90/60 mm Hg, Data were represented a number (percentage), One-way ANOVA was used for statistical analysis, Tukey test was used for *post-hoc* analysis, A p<0.05 was considered significant, A q>3.328 was considered significant, *Furosemide-emergent toxic effect, ¶Ethacrynic acid-emergent toxic effect, for statistical analysis, the treatment-emergent effect was considered as 'one' and absent of effect as considered as 'zero', N/A: Not applicable

Ethacrynic acid was highly expensive treatment than frusemide (215, 156±1985 ¥/patient vs. 19,455±1035 ¥/patient, p< 0.0001, Fig. 5).

DISCUSSION

In the present study, the patients had received furosemide or ethacrynic acid as 1 mL h^{-1} maximum for 3 days as a continuous infusion. Infusion had superiority to boluses because urinary outputs were easily maintained[17]. The oral low dose is not sufficient to decrease fluid overload and oral high dose (above ceiling dose; 80 mg/day for frusemide and 150 mg/day for ethacrynic acid)[18] had worsened outcomes[19] because have more adverse effects[18]. Continuous loop diuretic infusion is more effective with acceptable adverse effects[20]. Furosemide has significant improvement in urinary outcomes than torsemide and bumetanide in fluid over-load conditions[9]. Ethacrynic acid also has significant improvement in urinary outcomes like furosemide with fewer toxic effects[12]. Available studies have also used frusemide[1,6,15,19] and ethacrynic acid[1,12] in fluid overload associated with cardiac surgeries. However, trials had used frusemide[1,21] and ethacrynic acid[1,8] in neonates and pediatric patients (age group 104-181 days) but frusemide[13] and ethacrynic acid[14,22] were not recommended below 15 years and above 65 years of age. There may chance of adverse effects. With respect to objectives and selection of research subjects of the study, authors justified continuous loop diuretics in patients with fluid overload.

Frusemide was given satisfactory laboratory tests and in-hospital outcomes. While ethacrynic acid only provided an improvement in serum creatinine level and urine output. The results were in line with an available research study[1] and meta-analysis[23]. The half-life of frusemide is 2.8 h and that of ethacrynic acid was 2 h in renal dysfunction, time to peak effect is 15-30 min for ethacrynic acid and for frusemide 30 min[11,24]. The response of ethacrynic acid was less effective and fewer manageable than that of furosemide.

The intensity of improvement in urine output was the same for ethacrynic acid and frusemide (p = 0.069). The low dose of ethacrynic acid can be given good urine output than frusemide. These results were in line with published studies[1,8]. With respect to results of urine output, ethacrynic acid could be a safe option in fluid overload.

Ethacrynic acid and frusemide both were increased potassium and sodium excretion through urine. Metabolic acidosis is the common adverse effect of any loop diuretic[8,25]. Hypokalemia is easily overcome using oral intake of potassium[2]. With respect to laboratory test results, loop diuretics used in the study had acceptable treatment-emergent adverse effects.

Ethacrynic acid treatment had the only toxicity as treatment-emergent adverse effects but has a high cost of therapy than frusemide. Metabolism of ethacrynic acid has done by liver[11,26] while that of frusemide has done by proximal tubules of kidney[11,27] and no generic brand is available for ethacrynic acid in China PR[11,12]. With consideration of toxic effects reported in the study and the cost of interventions, ethacrynic acid is a safe but expensive alternative over to frusemide.

There were several limitations of the trial, for examples, rehospitalization and death during the follow-up period was not considered in the analysis. The possible justification was that the trial had the objective of decrease fluid overload only. As the level of confidence at the time of the enrollment was considered as 95%, that seems that the enrolled patients had also put on the other medications due to cardiac critical care. Present medications, history of the patients, the demographical parameters, diet (soft/hard) also have effects

on the results of the treatment. The study was not evaluated such parameters for synergistic or inhibitory effects of interventions. The study had performed with 1 mL h^{-1} infusion of interventions. The researchers have no references for the same. The dosing regimen (1 mL h^{-1}) was selected from the clinical experiences of the authors.

CONCLUSION

A randomized, double-blind, clinical trial concluded that frusemide is cheap and has satisfactory laboratory and in-hospital results with somewhat manageable treatment-emergent adverse effects. However, ethacrynic acid is safe and effective but costly alternative of frusemide in young and adult patients with fluid overload associated with the cardiac intensive care unit.

SIGNIFICANCE SENTENCE

A randomized, double-blind, clinical trial for fluid overload associated with the cardiac intensive care unit demonstrated that ethacrynic acid is safe and effective alternative of frusemide but costly. The finding will help the Intensivists to uncover the critical areas of the loop diuretics that many physicians are not able to explore.

ACKNOWLEDGMENT

Authors are thankful for all the medical and non-medical staff of the First Hospital of Jilin University, Changchun, Jilin, China.

REFERENCES

1. Ricci, Z., R. Haiberger, C. Pezzella, C. Garisto, I. Favia and P. Cogo, 2015. Furosemide versus ethacrynic acid in pediatric patients undergoing cardiac surgery: A randomized controlled trial. Crit. Care, Vol. 19. 10.1186/s13054-014-0724-5.
2. Claure-Del Granado, R. and R.L. Mehta, 2016. Fluid overload in the ICU: Evaluation and management. BMC Nephrol., Vol. 17. 10.1186/s12882-016-0323-6
3. Price, J.F., 2017. Diuretics and Invasive Fluid Management Strategies, in Heart Failure in the Child and Young Adult. Elsevier, Houston, pp: 495-510.
4. Kellum, J.A. and N. Lameire, 2013. Diagnosis, evaluation and management of acute kidney injury: A KDIGO summary (Part 1). Crit. Care, Vol. 17. 10.1186/cc11454.
5. Felker, G.M., K.L. Lee, D.A. Bull, M.M. Redfield and L.W. Stevenson *et al*., 2011. Diuretic strategies in patients with acute decompensated heart failure. N. Engl. J. Med., 364: 797-805.
6. Palazzuoli, A., M. Pellegrini, G. Ruocco, G. Martini and B. Franci *et al*., 2014. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: A prospective randomized trial. Crit. Care, Vol. 18. 10.1186/cc13952.
7. Nomani, A.Z., Z. Nabi, H. Rashid, J. Janjua and H. Nomani *et al*., 2014. Osmotic nephrosis with mannitol. Renal Failure, 36: 1169-1176.
8. Miller, J.L., J. Schaefer, M. Tam, D.L. Harrison and P.N. Johnson, 2014. Ethacrynic acid continuous infusions in critically ill pediatric patients. J. Pediat. Pharmacol. Ther., 19: 49-55.
9. Wargo, K.A. and W.M. Banta, 2009. A comprehensive review of the loop diuretics: Should furosemide be first line? Ann. Pharmacother., 43: 1836-1847.
10. Buggey, J., R.J. Mentz, B. Pitt, E.L. Eisenstein, K.J. Anstrom, E.J. Velazquez and C.M. O'connor, 2015. A reappraisal of loop diuretic choice in heart failure patients. Am. Heart J., 169: 323-333.
11. Abel, E.E., S.L. Folse, P.K. Burcham, S. Spevetz and K. Pickworth, 2012. Drug shortages alert loop diuretics (furosemide, bumetanide, torsemide). Society of Critical Care Medicines, USA. http://www.learnicu.org/Lists/Web%20Contents/Attachments/9640/DrugShortageAlert,%2011.15.12.pdf
12. Nguyen, B.D., M.C. Roarke, J.R. Young, M. Yang and H.H. Osborn, 2015. Diuretic renal scintigraphy in patients with sulfonamide allergies: Possible alternative use of ethacrynic acid. J. Nucl. Med. Technol., 43: 239-241.
13. Anonymous, 2007. Package leaflet: Information for the user furosemide 10 mg/ml solution for injection or infusion furosemide. http://www.hpra.ie/img/uploaded/swedocuments/Furosemide%20PIL%20-2167203-20072016102047-636046068612445000.pdf
14. Anonymous, 1994. Edecrin (ethacrynic acid) dosing, indications, interactions, adverse effects. Aton Pharma, Inc., USA. https://reference.medscape.com/drug/edecrin-ethacrynic-acid-342422
15. Allen, L.A., A.T. Turer, T. DeWald, W.G. Stough, G. Cotter and C.M. O'Connor, 2010. Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. Am. J. Cardiol., 105: 1794-1797.
16. Llorens, P., O. Miro, P. Herrero, F.J. Martin-Sanchez and J. Jacob *et al*., 2014. Clinical effects and safety of different strategies for administering intravenous diuretics in acutely decompensated heart failure: A randomised clinical trial. Emerg. Med. J., 31: 706-713.

17. Bellomo, R., J.R. Prowle and J.E. Echeverri, 2010. Diuretic therapy in fluid-overloaded and heart failure patients. Contrib. Nephrol., 164: 153-163.
18. Oh, S.W. and S.Y. Han, 2015. Loop diuretics in clinical practice. Electrolytes Blood Pressure, 13: 17-21.
19. Shah, R.V., S. McNulty, C.M. O'connor, G.M. Felker, E. Braunwald and M.M. Givertz, 2012. Effect of admission oral diuretic dose on response to continuous versus bolus intravenous diuretics in acute heart failure: An analysis from diuretic optimization strategies in acute heart failure. Am. Heart J., 164: 862-868.
20. Salvador, D.R.K., F.E. Punzalan, N.R. Rey, M.R. Bernado and M.D. Nablo, 2005. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst. Rev., Vol. 3. 10.1002/14651858.CD003178.
21. Van der Vorst, M.M., J. Den Hartigh, E. Wildschut, D. Tibboel and J. Burggraaf, 2011. An exploratory study with an adaptive continuous intravenous furosemide regimen in neonates treated with extracorporeal membrane oxygenation. Crit. Care, Vol. 11. 10.1186/cc6146.
22. Anonymous, 2005. Tablets Edecrin® (Ethacrynic acid) and intravenous sodium Edecrin® (Ethacrynate sodium), NDA 16-092/S-042. https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/16092s042,16093s044lbl.pdf
23. Chiong, J.R. and R.J. Cheung, 2010. Loop diuretic therapy in heart failure: The need for solid evidence on a fluid issue. Clin. Cardiol., 33: 345-352.
24. Molnar, J. and J.C. Somberg, 2009. The clinical pharmacology of ethacrynic acid. Am. J. Ther., 16: 86-92.
25. Maehle, K., B. Haug, H. Flaatten and E.W. Nielsen, 2014. Metabolic alkalosis is the most common acid-base disorder in ICU patients. Critical Care, Vol. 18. 10.1186/cc13802.
26. Lin, C.W., P. Gonzalez and F. Yuan, 2011. Cellular pharmacokinetic and pharmacodynamic analyses of ethacrynic acid: Implications in topical drug delivery in the eye. Mol. Vision, 17: 2507-2515.
27. DuBois, B.N., J. Pearson, T. Mahmood, D. Nguyen, K. Thornburg and G. Cherala, 2014. Perinatal growth restriction decreases diuretic action of furosemide in adult rats. Eur. J. Pharmacol., 728: 39-47.