ORIGINAL ARTICLE

Comparing the sodium excreting efficacy of furosemide and indapamide combination against furosemide and metolazone combination in congestive heart failure patients: A randomized control trial

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Abstract

Objective: To compare efficacy and safety of indapamide-furosemide combination against metolazone-furosemide combination in refractory heart failure patients.

Method: The randomised controlled trial was conducted at Rehman Medical Institute, Peshawar, Pakistan, from January 1 to June 30, 2018, and comprised refractory heart failure patients who were randomised into two groups using lottery method Group 1 received intravenous furosemide 40mg Q12hr with metolazone 5mg Q24hr, while group 2 received intravenous furosemide 40mg Q12hr with indapamide 2.5mg Q24hr. Both groups were assessed for urinary sodium excretion, total urine output and decrease in weight on day one, day three and day five of admission. SPSS 22 was used for data analysis.

Result: Of the 150 patients, there were 75(50%) in each of the two groups. Mean age in group 1 was 64.8±11.2 years, while it was 66.3±12.9 years in group 2. Both groups showed increased urinary sodium excretion and total urine output ($p>0.05$). Hypokalaemia was the most common adverse event 66%. Mean hospital stay was not significantly different between the groups ($p>0.05$).

Conclusion: There was no significant differences between adverse events and efficacy between patients receiving either indapamide-furosemide combination or metolazone-furosemide combination.

Keywords: Heart failure, Refractory, Loop diuretics, Thiazides, Metolazone, Indapamide. Urinary sodium. (JPMA 69: 1794; 2019) DOI:10.5455/JPMA.3401

Introduction

Heart failure (HF) is the leading cause of hospital admission among the elderly patients accounting for more than 1 million patient admissions annually in the United States.[1] Due to backflow congestion,[2] HF patients require frequent readmissions.[3] In patients admitted with acute HF, loop diuretics are the cornerstone of treatment.[4] Higher doses of loop diuretics increase the risk of adverse cardiac events (ACEs) and renal failure.[5] Diuretic Optimisation Strategies Evaluation (DOSE) trial[6] established the safety of high doses loop diuretics, but many patients become refractory to it, requiring multiple readmissions and prolonged hospital stays.[7] Thiazide diuretics, which increase sodium excretion, and diuresis in refractory HF patients are recommended as add-on therapy.[8] The use of low-dose metolazone as top-up to loop diuretics as a part of an effective and relatively safe treatment strategy in refractory HF has been supported by an observational study.[9] Combination treatment with indapamide and furosemide is effective in patients with massive oedema, but has not been studied in refractory HF patients resistant to loop diuretics.[10] When searched, literature showed no data currently available comparing the diuretic efficacy of combination therapy of indapamide, metalozone with furosemide in congestive heart failure (CHF) patients. Metolazone is expensive and not readily available in the open market. Therefore, unavailability of data about other thiazide diuretics leaves refractory HF patients with limited treatment options.

The current study was planned to compare the efficacy of indapamide with metolazone in combination with furosemide in patients admitted with refractory HF who were resistant to loop diuretics.

Patients and Methods

The randomised controlled trial (RTC), registered with Sri Lanka Clinical Trials Registry (SLCTR) on December 20, 2017, was conducted at the cardiology department of Rehman Medical Institute, Peshawar, Pakistan, from January 1 to June 30, 2018. After taking approval from the institutional review board, patients were recruited using universal sampling technique. Those included were patients admitted with diagnosis of refractory HF having New York Heart Association (NYHA) class III, IV[11] and who did not respond to intravenous (IV) furosemide dose of

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120mg (40mg Q8hr). The subjects were enrolled regardless of gender, socioeconomic status (SES), ethnic background and geographical locations.

Those excluded were individuals with chronic liver disease having ultrasonographic evidence of liver fibrosis, chronic obstructive pulmonary disease (COPD) with evidence of restrictive lung disease on spirometry, and those malnourished with serum albumin concentration <3gm/dl.

The subjects were randomised into two groups using lottery method. It was a blinded study and patients were given medications without showing them labels of medicines, and access to medication file was denied during the study period.

Group 1 received IV furosemide in concentration of 40mg Q12hr with metolazone 5mg Q24hr, while group 2 received IV furosemide 40mg Q12hr with indapamide 2.5mg Q24hr. Urinary sodium analysis was done from spot urine specimen by collecting 10ml mid-stream urine in a sterilised bottle, using an ion-selective electrode method (Modular DPE chemistry; Roche Diagnostics, Mannheim, Germany). Total urinary output was calculated following catheterisation and collection of 24-hour urinary specimen in a calibrated urinary bag. Weight was assessed using Minebea Intec (Germany) machine at baseline, on day 3 and day 5 of admission.

The primary efficacy endpoint was defined as the increase in natriuretic effect determined by urinary sodium level in spot urinary sample after combined diuretic therapy in both groups on day 1, 3 and 5 after the initiation of therapy. Secondary efficacy endpoints included an increase in total urine output at day 1, 3 and 5 with loss of body weight in kilograms.

The safety endpoints included impairment in renal function determined by increase in serum creatinine level of >0.6mg/dl from the baseline value on the day of the initiation of the combined diuretic therapy, hypotension determined as a systolic blood pressure SBP <90mmHg or a 20% decrease in SBP from baseline, cardiac arythmias determined as development of any abnormal ectopy recorded on rhythm strip of bedside monitor or 12-lead electrocardiogram (ECG), and metabolic derangements which included hypokalaemia, defined as serum potassium <3.5mEq/L, hypomagnesemia, defined as serum magnesium <1.6mg/dl, hyponatraemia, defined as serum sodium <135mEq/L, hyperuricaemia, defined as serum uric acid $\geq$7.3mg/dL in males and $\geq$6.2mg/dL in females, and hyperglycaemia, defined as increase in serum random blood glucose >200mg/dl.

Data was analysed using SPSS 22. Shapiro-Wilk test was applied to check the distribution of data. Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and categorical variables were expressed as frequencies and percentages. Median and interquartile ranges (IQRs) were expressed for right skewed data. Group differences were assessed by chi square test for categorical variables, while Fisher exact test was used where sample size was smaller. T test was used for the comparison of mean between the groups. P<0.05 was considered significant.

Results

Of the 173 subjects assessed, 153(88.4%) were included. Group 1had 77(50.3%) patients, while group 2 had 76(49.7%). Subsequently, 2(2.6%) patients from group 1

Table-1: Baseline Characteristics of the study population (N=150).

Variable	Group I n = 75 (Furosemide & Metolazone)	Group II n = 75 (Furosemide & Indapamide)	P value
Age (Years)	64.8 ± 11.2	66.3 ± 12.9	0.91
Gender Males	48(64%)	47(62%)	0.86
Females	27(36%)	28(38%)	0.88
LVEF (% IQR)	32%(IQR 23-45)	30%(IQR 20-40)	0.71
Bundle Branch Block	11(14.6%)	8(10.6%)	0.64
Cardiac Assist Devices	6(8%)	2(2.6%)	0.81
Vulvular Heart Disease	8(10.6%)	9(12%)	0.56
Serum Creatinine(mg/dl)	1.6(IQR 1.4-2.6)	1.8(1.3-2.8)	0.69
eGFR			
15-30	45(60%)	48(64%)	0.76
31- 45	18(24%)	17(22.6%)	0.88
>45	12(16%)	10(13.3%)	0.72
Body Mass Index(kg/m^2)	23.76 ± 5.83	25.8 ± 6.33	0.91
Diabetes	27(36%)	25(33.3%)	0.77
Coronary Artery Disease	21(28%)	28(37.3%)	0.88
Hypertension	30(40.5%)	28(37.3%)	0.91
Hyperlipidaemia	39(52%)	23(30.7%)	0.57
Atrial fibrillation	35(29.3%)	24(32%)	0.72
Smoking	44(58.6%)	46(61.3%)	0.03
Systolic BP(mmHg)	140.6 ± 16.9	138.9 ± 18.3	0.04
Diastolic BP(mmHg)	82.3 ± 7.6	84.6 ± 8.1	0.88
NYHA Class	2.4 ± 1.3	2.6 ± 0.9	0.77
In hospital Treatment			
Vasodilators	32(42.6%)	30(40%)	0.84
Antiplatelets	58(77.3%)	61(81.3%)	0.75
Digoxin	8(10.6%)	12(16%)	0.91
Beta Blockers	69(92%)	67(89.3%)	0.88
ACEI/ARBs Aldosterone Antagonist	39(52%)	44(58.6%)	0.71
NPPV	16(21.3%)	13(17.3%)	0.64
IABP	6(8%)	7(9.3%)	0.69
	2(2.6%)	1(1.3%)	0.73

LVEF: Left ventricular ejection fraction. IQR: Interquartile range.
BP: Blood pressure. NYHA: New York Heart Association.
NPPV: Non-invasive positive-pressure ventilation. IABP: Intra-aortic balloon pump.

Table-2: Comparison of primary and secondary outcomes.

Variable	Group I (Furosemide & Metolazone)	Group II (Furosemide & Indapamide)	P value
Weight (Kg)			
Baseline	65.8±10.9	67.4±11.2	0.99
At Day 3	62.4±10.3	63.9±10.7	0.9
At Day 5	58.9±11.4	60.5±10.9	0.88
Urinary Sodium Excretion (mEq/L)			
Baseline	48.9±43.6	45.8±46.3	0.9
At Day 3	141.8±35.8	138.3±41.1	0.71
At Day 5	156.9±33.2	152.8±35.7	0.88
Urine Output (ml)			
Baseline	890±178	917±212	0.66
At Day 3	1580±230	1595±255	0.88
At Day 5	1835±276	1812±313	0.9

were discharged earlier than day 5, while 1(1.3%) patient in group 2 died during hospital stay before day 5 due to renal cell carcinoma with metastasis. The final study sample stood at 150, with 75(50%) subjects in each of the two groups. Mean age in group 1 was 64.8±11.2 years, while it was 66.3±12.9 years in group 2. Overall, there were 95(63%) males and 55(37%) females. There was no difference in comorbidities between the two groups. Median left ventricular ejection fraction (LVEF) was 31% (IQR: 20-45%). Bundle branch block was present in 19(12.6%) subjects, while 8(5.3%) were treated with cardiac assist devices, like cardiac resynchronisation therapy, pacemakers, defibrillators. All the baseline characteristics are mentioned in Table-1.

There was no statistically significant difference in the primary and secondary efficacy endpoints between the groups (p>0.05). Baseline sodium excretion with furosemide alone was 48.9±43.6 in group 1 and 45.8±46.3 in group 2. Sodium excretion increased to 141.8±35.8 on day 3 and 156.9±33.2 on day 5, respectively, with the addition of metolazone to furosemide in group 1, whereas sodium excretion increased to 138.3±41.1 and 152.8±35.7 on day 3 and day 5, respectively, with the addition of indapamide to furosemide in group 2.

Baseline urine output was 890±178ml in group 1 and 917±212ml in group 2. Baseline urine output increased to 1580±230ml and 1835±276ml on day 3 and day 5, respectively, with the addition of metolazone to furosemide in group 1 and 1595±255 ml on day 3 and 1812±313 ml on day 5 with addition of indapamide to furosemide in group 2.

In group 1, a decrease in net weight was observed as 62.4±10.3kg and 58.9±11.4kg on day 3 and on day 5, respectively, with the addition of metolazone to furosemide from baseline value of 65.8±10.9kg. In group 2, with the addition of indapamide, net weight decreased from baseline value of 67.4±11.1kg to 63.9±10.7kg and 60.5±10.9 on day 3 and day 5, respectively. Primary and secondary endpoints of both groups are mentioned in Table-2.

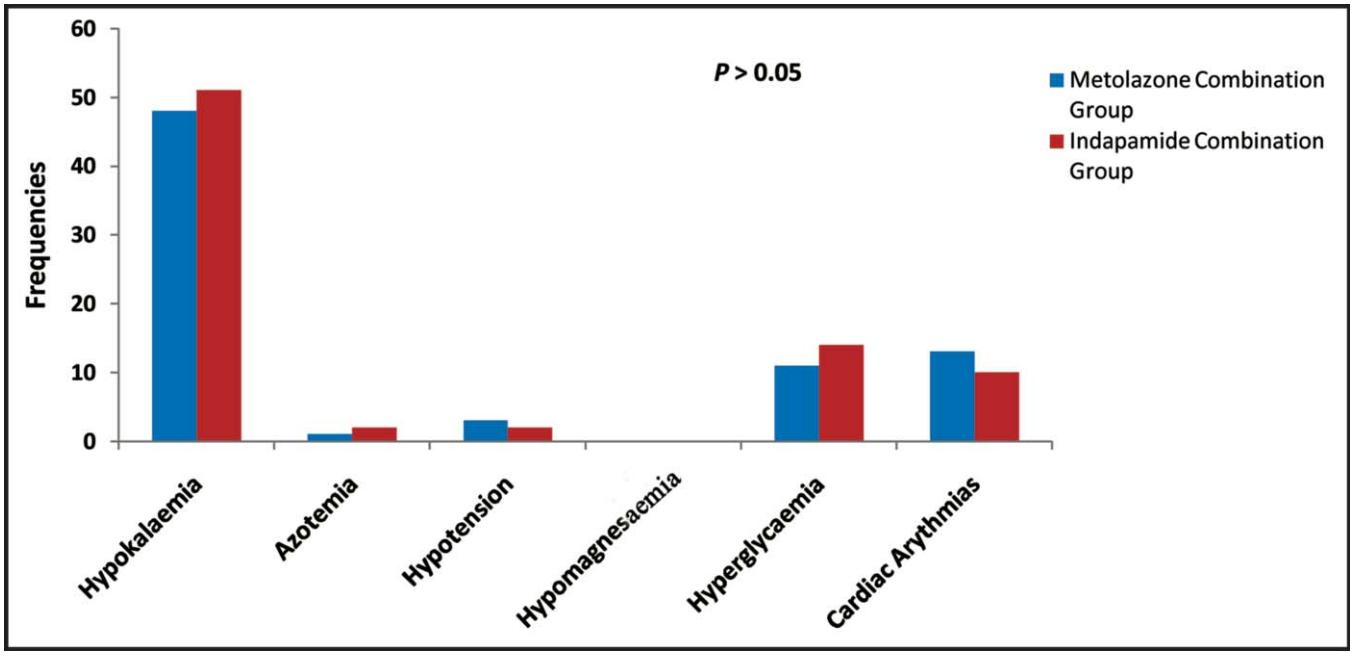

Figure: Adverse events in metolazone and indapamide combination groups.

No significant difference was observed between both the groups in terms of the defined safety endpoints (p>0.05). Hypokalaemia, which occurred in 99(66%) patients, including 72(72.7%) women and 27(27.3%) men, was the most common ACE. Azotemia and worsening of renal profile was observed in 6(4%) subjects while 4(2.7%) developed ectopic cardiac rhythm. The serum uric acid level increased by 18%, while the blood glucose level rose by 8%. However, there were no reported cases of the development of acute gout or new onset diabetes mellitus (DM). Also, 12(8%) subjects required ionotropic support due to hypotension, but there were no reported cases of subjects developing hypomagnesaemia as shown in Figure-1.

In subjects with severely impaired renal function (Creatinine Clearance [CrCL]: 15-30 mL/min), there was no significant difference in net sodium excretion at day 3 and 5, whereas in subjects with moderately impaired renal function (CrCL: 31-45mL/min) there was increased urine output in group 1 compared to group 2. The use of ionotropic support and median hospital stay was similar in both the groups (p=0.88).

Discussion

Epidemiological gender-based studies have reported HF as a more common entity among male patients compared to females.[12] In both our cohorts there was preponderance of male patients. Most HF patients develop diuretic resistance and its treatment with traditional loop diuretics does not alleviate its symptomatology.[7] The treatment of such patients with acute decompensated heart failure (ADHF) having diuretic resistance becomes very tricky and is supported by the addition of thiazide-type diuretics to loop diuretics.[9] According to American College of Cardiology / American Heart Association (ACC/AHA) guidelines, it is class II-A recommendation in inadequate diuresis to either intensify the treatment with higher doses of IV diuretics or to add a second diuretic.[13] Since higher doses of furosemide has toxic effects,[5] the addition of metolazone to furosemide is widely studied and accepted.[9] But there is very limited data about the efficacy and safety of indapamide. Additionally, whether indapamide is equally effective and safe as metolazone had not been studied. According to literature review, the current study is the first to compare the efficacy of metolazone with indapamide head to head as add-on diuretic added to loop diuretics in refractory HF in patients.

Furosemide blocks the sodium-potassium-chloride (Na-K-2Cl) symporter at the level of ascending loop of Henle and is, hence, called loop diuretics.[10] Inhibitors of the Na-Cl symporter at distally convoluted tubules are called thiazides because they are derivative of benzothiazides.[10] Similarly, drugs which act on Na-Cl symporter at distal convoluted tubule but are not thiazides are called thiazide-like derivative. Metolazone is a thiazide-like diuretic which has slow absorption and very large volume of distribution. It has a high renal clearance and has effective diuretic profile when used in combination therapy with furosemide to manage patients with refractory oedema.[14] According to a study,[15] metolazone increased urine output to 4828ml after 72 hours, while in the current study the daily urine output was 1580±230ml at day 3 and 1835±276ml at day 5 which was comparable. Indapamide is another alternative diuretic used in combination therapy with loop diuretics. It exerts a vasodilating effect by liberating prostacyclins, which has free radical scavenging effect.[16] The current study showed no significant difference in urine output of patients treated with metolazone and indapamide combination regimens with furosemide.

Both furosemide and thiazide achieve their diuretic effects by mainly blocking the sodium reabsorption, implying that sodium excretion in urine is the most suitable marker to assess the diuretic efficacy of combination therapy of furosemide with thiazides.[10] Spot urine estimation of sodium level has been validated as accurate[17] and we used the same method for urinary sodium excretion analysis. Metolazone blocks the Na+-Cl- symport in ascending loop of Henle and distal convoluted tubules it increases natriuresis.[18] The result of our current study showed that natriuresis increased from 48.9±43.6 to 141.8±35.8 and 156.9±33.2 on day 3 and day 5, respectively, when metolazone was added to furosemide. Similar trend was observed with the addition of indapamide to furosemide, showing comparable efficacy with no statistical difference.

The cardiac safety profile of indapamide was established by the Perindopril pR Otectiona Gainst RE current Stroke Study (PROGRESS) trial.[19] It demonstrated that the combination of angiotensin-converting-enzyme inhibitor (ACEI) and indapamide resulted in a greater reduction in blood pressure and a reduction in cardiovascular major adverse events compared to ACEI therapy alone in subjects with stroke or previous transient ischaemic attacks.[20] The cardiovascular safety profile makes it excellent choice for diuresis in HF patients.

Thiazides alone or in combination with loop diuretics effectively treat hypertension even in chronic renal disease with very low glomerular filtration rate (GFR; <30), but they are less effective in natriuresis and diuresis of

chronic kidney disease (CKD) patients.[21] Similar trend was observed in the current study where no statistical difference was observed between indapamide combination and metolazone combination when natriuresis and renal impairment was compared in CKD patients between the cohorts. The main reason was decrease in GFR leading to decrease in drug delivery to tubular fluid causing decrease diuretic efficacy of both the drugs, hence showing no significant difference on comparison. Same reason is quoted by other studies for furosemide decrease potency in stage-5 CKD patients caused by increased sodium reabsorption in downstream segment and delivery of only 15-20% drug to tubular fluid distally.[21]

Furosemide alone induces various electrolyte abnormalities which include hypokalaemia, hypomagnesaemia, hypocalcaemia, hyponatraemia and hyeruricaemia.[22] Indapamide, on the other hand, also lowers serum potassium levels.[23] Our results showed that hypokalaemia was the most common adverse event which occurred more frequently in women. It was quite obvious and added nothing extra to the fear factor because furosemide alone also induces severe hypokalaemia by increasing distal excretion of potassium ions and secondarily causing mineralocorticoid excess.[24] Increased prevalence in women was reasonable because in our study women were generally more elderly compared to male HF patients. Another reason that explains this discrepancy is that men generally consume more potassium in their diet then women.[25] Both decreased dietary intake and old age were the biggest contributors to hypokalaemia which explains preponderance of elderly women in terms of experiencing more hypokalaemia with diuretic combination treatment compared to men. Our results are supported by another study.[26]

Other than these adverse events, which are both reversible and preventable, indapamide was very well tolerated and showed equally comparative efficacy and potency to metolazone when used in combination treatment with furosemide in patients with ADHF refractory to loop diuretics.

The current study had its limitations. It was a single-centre study and our results can't truly depict the trend in the general population even though it will provide a platform to conduct large, randomised multicentre head-to-head trials. Readmission of patients was not taken into consideration which would have established long-term efficacy. No restriction was made on including patients with preserved ejection failure, but majority of the patients had a very low ejection fraction, and, as such, it can't be truly reflective of patients with preserved LVEF.

Conclusion

In patients hospitalized with acute HF requiring combination diuretic therapy, there was no statistically significant difference between safety or efficacy of oral indapamide and oral metolazone combination with intravenous furosemide. It is worth mentioning that metolazone was more effective in increasing diuresis in patients with moderately impaired renal function, but both had similar efficacy in severe renal dysfunction with GFR <30. Hypokalaemia was the most common adverse event and observed more commonly in women compared to men.

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References

1. Lloyd-Jones D,Adams R,Carnethon M,De-Simone G,Ferguson TB,Flegal K,et al. Heart disease and stroke statistics–2009 update:a report from American heart association statistics committee and stroke subcommittee. Circulation 2009; 119:e21-181.doi: 10.1161/CIRCULATIONAHA.108.191261.
2. Metra M,Dei-Cas L,Bristow MR. The pathophysiology of acute heart failure – it is a lot about fluid accumulation. Am Heart J 2008;155:1-5. doi:10.1016/j.ahj.2007.10.011
3. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice Guidelines. J Am Coll Cardiol 2009;119:e391-479. doi:10.1161/CIRCULATIONAHA.109.192065.
4. Felker GM, O'connor CM, Braunwald E. Loop diuretic in acute decompensated heart failure:necessary?evil?A necessary evil? Circ Heart Fail 2009;2:56-62. doi: 10.1161/CIRCHEARTFAILURE.108.821785.
5. Peacock WF, Costanzo MR, DeMarco T, Lopatin M, Wynne J, Mills RM, et al. Impact of intravenous loop diuretics on outcomes of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. Cardiology 2009;113:12-9. doi: 10.1159/000164149.
6. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. N Engl J Med 2011;364:797-805.DOI: 10.1056/NEJMoa1005419
7. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96(3-4):132-43. DOI:10.1159/000047397.
8. Dormans TP, Gerlag PG. Combination of high-dose furosemide and hydrochlorthiazide in the treatment of refractory congestive heart failure. Eur Heart J 1996;17:1867-74.
9. Rosenberg J, Gustafsson F, Gelatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of literature. Cardiovasc Drugs Ther 2005; 19:301-6. Doi: 10.1007/s10557.005.3350.2.
10. Hoorn EJ, Ellison DH. Diuretic Resistance. Am J Kidney Dis 2017;69:136-42. doi:10.1053/j.ajkd.2016.08.027.

11. Classes Of Heart Failure, New York Heart Association Criteria Committee, American Heart Association. [online] [cited 2017 May 31].Available from: URL: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure.
12. Kajimoto K, Minami Y, Sato N, Otsubo S, Kasanuki H. Gender Differences in Left Ventricular Ejection Fraction and Outcomes Among Patients Hospitalized for Acute Decompensated Heart Failure. Am J Cardiol 2017;119:1623-30.
13. Yancy CW, Jessup M, Bozkurt B, Butler B, Casey DE, Drazner MH etal. 2013 ACCF/AHA Guideline for the Management of Heart Failure. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128:e240–e327.
14. Sica DA. Metolazone and its role in edema management. Congest Heart Fail 2003;9:100-5.
15. Moranville MP, Choi S, Hogg J, Anderson AS, Rich JD.Comparison of Metolazone Versus Chlorothiazide in Acute Decompensated Heart Failure with Diuretic Resistance. Cardiovascular Therapeutics 2015:33;42-9.
16. Uehara Y, Shirahase H, Nagata T, Ishimitsu T, Morishita S, Osumi S, et al. Radical scavenging of indapamide in prostacyclin synthesis in rat smooth muscle cell. Hypertension 1990;15:216-24.
17. Tanaka T, Okamura T, Miura K, Kadowaki T, Ueshima H, Nakagawa H, et al. A simple method to estimate populational 24-h urinary sodium and potassium excretion using a casual urine specimen. J Human Hypertension 2002.16:97-103.
18. Wile D. Diuretics: a review. Ann Clin Biochemistry 2012; 49:419-31.
19. PROGRESS Collaborative group. Randomized trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischemic attack. Lancet 2001;358:1033-4.
20. Sinha AD, Agarwal R.Thiazide diuretics in chronic kidney disease. Curr Hypertens Rep 2015;17:13.
21. Brater DC. Update in diuretic therapy:clinical pharmacology.Semin Nephrol 2001;31:483–94.
22. Tamargo J, Segura J, Ruilope LM. Diuretics in the treatment of hypertension.Part 2: loop diuretics and potassium-sparing agents. Expert Opin Pharmacother 2014;15:605–21.
23. Zhang JL, Yu H, Hou YW, Wang K, Bi WS, Zhang L, et al. Impact of long-term potassium supplementation on thiazide diuretic-induced abnormalities of glucose and uric acid metabolisms. J Human Hypertension 2018;32:301–10.
24. Wilcox CS, Mitch WE, Kelly RA, Freidman PA, Souney PF, Rayment CM, et al. Factors affecting potassium balance during ferusemide administration. Clin Sci 1984;67:195–203.
25. Jentzer JC, DeWald TA, Hernandez AF. Combination of Loop Diuretics With Thiazide-Type Diuretics in Heart Failure. J Am Coll Cardiol 2010;56:1527-34.
26. Kleinfeld M, Borra S, Gavani S, Corcoran A. Hypokalemia: are elderly females more vulnerable?. J Natl Med Assoc. 1993;85:861-4.