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Differences between Continuous Infusion and Intermittent Bolus of Furosemide with Length of Hospital Stay in Patients with Acute Heart Failure in Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: Heart failure is a complication that often occurs in individuals with or without underlying cardiovascular disease. Furosemide serves to reduce preload and improve congestion symptoms. The aim of this study was to determine the difference in length of hospital stay between continuous infusion and intermittent bolus of furosemide in patients with acute heart failure.

Methods: This study was a prospective-single blind-randomized controlled study of 54 people with acute heart failure who entered the emergency room and underwent treatment at the H. Adam Malik Hospital from October 2018 to March 2019. Re-examination of urine production, kidney function, and electrolytes was carried out after 72 hours of treatment. Subsequent subjects were observed during treatment for death during treatment and duration of treatment. Follow-up was carried out for 30-days to assess rehospitalization.

Results: Between continuous infusion group and intermittent bolus group, we found, respectively, length of hospital stay 7.6±3.2 vs. 7.3±4.8 days, p=0.28; urine production 2241±429 vs 2020±368, p=0.048; ΔBUN 3.6 ± 14.5 vs 4.0 ± 10.9, p=0.91; ΔUreum 7.9 ± 31.0 vs 8.5 ± 23.3; p=0.92; ΔCreatinine 0.1 ± 0.61 vs. 0.03 ± 0.33; p=0.56; and ΔGFR -5.5 ± 20.6 vs -2.7 ± 22.7; p=0.64. In terms of mortality during hospitalization, we found that 7.4% vs 11.1%, p=0.63 (HR 0.64; 95% CI: 0.098–4.1) and rehospitalization in 30 days showed 22.2% vs 37%; p=0.23 (HR 0.48; 95% CI: 0.14–1.6) in continuous infusion vs intermittent bolus group, respectively.

Conclusions: In patients with acute heart failure, there is no difference between continuous infusion and intermittent bolus of furosemide in regard to length of hospital stay, changes in renal function and electrolyte, death during hospitalization, and rehospitalization within 30-days. However, continuous administration of furosemide infusion is better in urine production.

INTISARI

Latar belakang: Gagal jantung adalah komplikasi yang sering terjadi pada individu dengan atau tanpa penyakit kardiovaskular. Furosemide berfungsi untuk mengurangi preload dan meningkatkan gejala kemacetan. Tujuan dari penelitian ini adalah untuk menentukan perbedaan lama tinggal di rumah sakit antara infus terus menerus dan bolus furosemide intermiten pada pasien dengan gagal jantung akut.

Metode: Penelitian ini adalah penelitian prospektif acak-tunggal yang dilakukan secara acak terhadap 54 orang dengan gagal jantung akut yang memasuki ruang gawat darurat dan menjalani perawatan di Rumah Sakit H. Adam Malik dari Oktober 2018 hingga Maret 2019. Pemeriksaan ulang

produksi urin, fungsi ginjal, dan elektrolit dilakukan setelah 72 jam perawatan. Subjek berikutnya diamati selama pengobatan untuk kematian selama pengobatan dan durasi pengobatan. Tindak lanjut dilakukan selama 30 hari untuk menilai rawat inap.

Hasil: Antara kelompok infus kontinyu dan kelompok bolus intermiten, kami menemukan, masing-masing, lama tinggal di rumah sakit 7,6 ± 3,2 vs 7,3 ± 4,8 hari, p = 0,28; produksi urin 2241 ± 429 vs 2020 ± 368, p = 0,048; Δ BUN 3,6 ± 14,5 vs 4,0 ± 10,9, p = 0,91; ΔUreum 7,9 ± 31,0 vs 8,5 ± 23,3; p = 0,92; ΔKreatinin 0,1 ± 0,61 vs 0,03 ± 0,33; p = 0,56; dan ΔGFR -5.5 ± 20.6 vs -2.7 ± 22.7; p = 0,64. Dalam hal kematian selama dirawat di rumah sakit, kami menemukan bahwa 7,4% vs 11,1%, p = 0,63 (HR 0,64; 95% CI: 0,098-4,1) dan rawat inap dalam 30 hari menunjukkan 22,2% vs 37%; p = 0,23 (HR 0,48; 95% CI: 0,14-1,6) dalam infus kontinyu vs kelompok bolus intermiten, masing-masing.

Kesimpulan: Pada pasien dengan gagal jantung akut, tidak ada perbedaan antara infus kontinyu dan bolus furosemide yang intermitten dalam hal lama tinggal di rumah sakit, perubahan fungsi ginjal dan elektrolit, kematian selama rawat inap, dan rawat inap dalam 30 hari. Namun, pemberian furosemide secara terus-menerus lebih baik dalam produksi urin

Introduction

Heart failure is a complication that often occurs in individuals with or without previous cardiovascular disease. The American Heart Association / American College of Cardiology guidelines define heart failure as a clinical syndrome caused by all structural and functional disorders of the heart that interfere with the ventricular ability to fill or pump the blood. [1-6]

The life expectancy of heart failure patients is still low, 17-45% of heart failure patients admitted to hospital died within a year after being treated, and most died within the next 5 years.[7] Heart failure is a syndrome with high morbidity and mortality.[8] According to Riset Kesehatan Dasar 2013, the prevalence of heart failure in North Sumatra, Indonesia, based on diagnosis and symptoms is 0.3%, with an estimated number of 26,819 people. The prevalence of heart failure in Indonesia is similar to the prevalence in North Sumatra, which is 0.3% and with an estimated 530,068 patients.[9]

Acute heart failure requires faster treatment. Furosemide as a diuresis agent is used to reduce heart preload to overcome symptoms of shortness of breath, peripheral edema, ascites, and other congestive symptoms. The European Society of Cardiology Guideline on treating heart failure in 2016 stated that administration of furosemide can be given to improve symptoms of heart failure by monitoring urine production, kidney function, and electrolytes. The choice of intermittent bolus injections or continuous infusion is recommended.[7, 8, 10]

The aim of this study was to determine the differences between continuous infusion and intermittent boluses of furosemide with regard to length of hospital stay in patients with acute heart failure in H. Adam Malik General Hospital Medan.

Methods

This study was a prospective, single blind, and randomized controlled study, for patients with acute heart failure who entered the emergency room and underwent treatment at H. Adam Malik Hospital in Medan from October 2018 to March 2019. The number of subjects in this study was 54 people, divided into 26 people in the continuous infusion furosemide group and 27 people in the intermittent bolus injection furosemide group.

Primary outcome of this study was the difference between continuous infusion and intermittent bolus of furosemide dose with regard to hospital stay. Secondary outcomes of this study were urine production, changes in renal function and electrolyte, rehospitalization within 30 days, and death from cardiovascular disease during hospitalization.

Inclusion and Exclusion Criteria

Inclusion criteria were patients older than 18 years of age and diagnosed with acute heart failure based on clinical criteria for heart failure (shortness of breath, orthopnea, peripheral edema, fatigue, and at least 2 signs such as rales, radiological signs of pulmonary congestion, increased jugular venous pressure, and third heart sound). Exclusion criteria were patients who have received injections of furosemide 1 month before being admitted to hospital, patients with acute coronary syndrome, patients with chronic renal failure who need renal replacement therapy, patients with serum creatinine levels> 4.0 mg/dl, and patients with systolic blood pressure < 80 mmHg

Study Protocol

The subjects in this study were patients with a diagnosis of acute heart failure. The clinical condition and initial diagnosis were determined by the doctor-in-charge responsible for receiving the patient. When patients entered the RSUP H. Adam Malik emergency room, vital signs such as blood pressure, heart rate, respiratory rate, oxygen

saturation, and drug administration history were measured by physicians. Patients then underwent clinical examination and have the following examined: jugular venous pressure, congestive signs such as rales, ascites, and peripheral edema. Afterward, patients underwent electrocardiography and echocardiography for classification before randomization, filled out informed consent, and underwent serological examinations in the form of routine blood examination, kidney function, and electrolytes. Patients were randomized according to their classification to obtain initial furosemide therapy and advanced furosemide therapy. The time interval when a patient enters an emergency room until the initial injection of furosemide bolus was defined as door to furosemide time.

Patients were randomized to continuous infusion of furosemide and intermittent bolus of furosemide with the A-B-A-B pattern. The patient then underwent treatment, and was evaluated for urine production, kidney function, electrolytes and serial echocardiography after 72 hours of treatment. Other treatments such as vasodilators, ACE-inhibitors or ARBs, MR antagonists, and Beta blockers were given according to guidelines of the European Guidelines for Heart Failure. The two groups were then followed during hospital care for deaths during hospital care and length of stay. Afterwards, 30 days of follow-up were conducted to assess rehospitalization in 30 days. Death during hospital care was defined as occurrence of death from cardiovascular disease. Rehospitalization was defined as the patient's return visit to the emergency department until the patient's re-treatment due to complaints of heart failure. The outcome was measured and observed by second observer.

This study was approved by the Health Research Ethics Committee of the Medical Faculty of the Universitas Sumatera Utara and the Education and Training Division of H. Adam Malik General Hospital in Medan.

Statistical Analysis

Data was presented descriptively by showing frequency distributions and percentages for categorical data. Numerical data was presented by showing mean values and standard deviations for normally distributed data, and median for numerical data that is not normally distributed.

Homogeneity test was carried out by Levene test. Differences in categorical and numerical variables were assessed by conducting independent T-test. If the data were normally distributed, Mann Whitney non-parametric test was used. On the other hand, if the data were not normally distributed, categorical-to-categorical variables were assessed by chi square. P values <0.05 were considered statistically significant. Statistical tests was analyzed using SPSS version 17.0.

Results

The study subjects were generally > 55 years old, or 58 ± 8.9 years for the continuous furosemide infusion group and 56 ± 12.3 years for intermittent furosemide bolus. Most subjects were male, as many as 14 subjects (52%) vs 21 subjects (77%).

Subjects in the continuous furosemide infusion group, compared to the intermittent bolus group, had higher systolic blood pressure at entry (155 ± 44 vs 134 ± 34, p <0.05). For variable heart rate and body weight, there were no significant differences between the two groups (101 ± 14 vs 99 ± 15, p = 0.60 and 62 ± 12.6 vs 65 ± 10.3, p = 0.33). Among risk factor for coronary heart disease, hypertension was most prevalent in both continuous infusion and intermittent bolus group, which amounted to 19 subjects (70%) vs 15 subjects (55%), respectively.

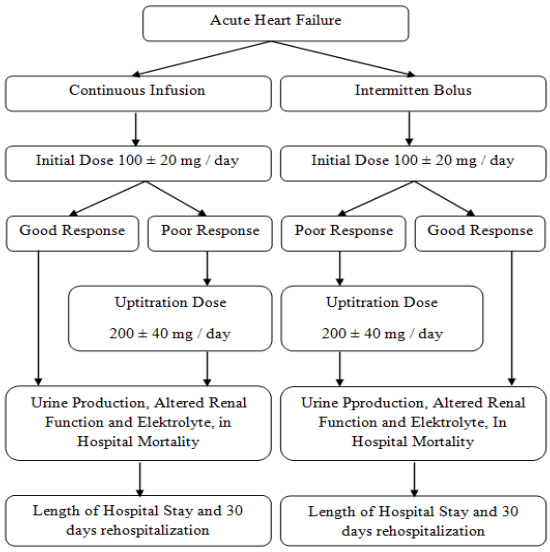

Figure 1. Research Algorithm

Table 1
Baseline Characteristics of Subjects in the Group of Continuou Furosemide Infusions and Intermittent Furosemide Boluses

Characteristics	Furosemide Strategy		*p Value*
	Continuous Infusion	Intermittent Bolus	
	N = 27	N = 27	
Age	58 ± 8.9	56 ± 12.3	0.58
Gender (N, %)			
Male	14 (52)	21 (77)	0.046
Female	13 (48)	6 (23)	
Systolic Blood Pressure	155 ± 44	134 ± 34	0.049
Heart Rate	101 ± 14	99 ± 15	0.60
Body Weight	62 ± 12.6	65 ± 10.3	0.33
Risk Factors (N, %)			
Hypertension	19 (70)	15 (55)	0.26
Diabetes	9 (33)	12 (44)	0.40
Dyslipidemia	3 (11)	5 (18)	0.44
Cause of Heart Failure (N, %)			
Coronary Heart Disease	8 (30)	11 (41)	
Hypertensive Hear Disease	16 (59)	11 (41)	0.38
Valvular Heart Disease	3 (11)	5 (18)	
Heart Failure Classification (N, %)			
Preserved Ejection Fraction	14 (52)	13 (48)	0.58
Reduced Ejection Fraction	13 (48)	14 (52)	
LV Ejection Fraction	49 ± 13	48 ± 12	0.78
BUN	28.8 ± 22.3	24.4 ± 21.6	0.47
Ureum	61.7 ±47.7	52.3 ± 46.3	0.47
Creatinine	1.6 ± 1.3	1.4 ± 0.71	0.69
Glomerular Filtration Rate	62.5 ± 30.4	68.0 ± 42.3	0.85
Sodium Level	131 ± 6.9	131 ± 6.4	0.94
Potassium Level	3.7 ± 0.7	4.0 ± 0.7	0.29
Medical History (N, %)			
ACE-inhibitor	19 (70)	13 (48)	0.091
ARB	4 (14)	7 (25)	0.31
Beta Blocker	17 (63)	22 (81)	0.12
Furosemide	18 (66)	24 (88)	0.048
MRA	13 (48)	20 (74)	0.049
Nitrate	8 (29)	8 (29)	NS
Door-to-Furosemid	50 ± 28	66 ± 33	*0.035*

Both groups have similar left ventricular ejection fraction (49 ± 13 vs 48 ± 12, p = 0.78). In terms of previous treatment history, there was no difference between the two groups given furosemide to the use of ACE-inhibitors, ARBs, Beta blockers, Nitrates, but there were significant differences in previous use of furosemide and oral MR antagonists. (66% vs 88%, p = 0.48; and 48% vs 74%, p = 0.49).

Door-to-furosemide time was found to be significantly different, 50 ± 28 minutes in the continuous furosemide infusion group and 66 ± 33 minutes in the intermittent furosemide bolus group (p = 0.035).

Length of Hospital Stay

In this study, 27 study subjects for each group counted the length of hospital stays, and the results of length hospital stay for continuous furosemide infusion group were 7.6 ± 3.2 days and the intermittent furosemide bolus group was 7.3 ± 4.8 days.

Table 2
Differences in Continuous Furosemide Infusion an Intermittent Furosemide Bolus for Length of Hospital Stay

Parameter	**Furosemide Strategy**		***p Value***
	Continuous Infusion	**Intermittent Bolus**	
	N = 27	**N = 27**	
Length of Hospital Stay	7.6 ± 3.2	7.3 ± 4.8	0.28

With a p value = 0.28, this shows no significant difference in meanings between the two groups on length of stay in the hospital. The same result is shown in Figure 2, where the curves did not differ between the two groups.

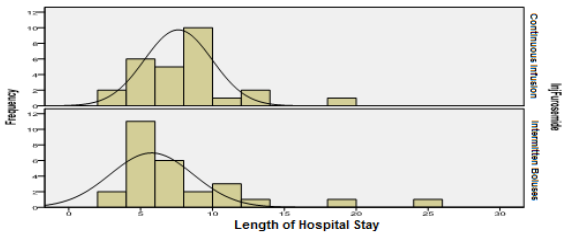

Figure 2. Differences in Continuous Furosemide Infusion and Intermittent Furosemide Bolus for Length of Hospital Stay

Renal Function and Electrolytes

Urine production were significantly different between continuous furosemide infusion and intermittent furosemide bolus (2241 ± 429 vs 2020 ± 368, p = 0.048, respectively).

Table 3
Differences in Continuous Furosemide Infusion an Intermittent Furosemide Bolus to Alteration in Kidney Functio and Electrolyte

Parameter	**Furosemide Strategy**		***p Value***
	Continuous Infusion	**Intermittent Bolus**	
	N = 27	**N = 27**	
Urine Production / 24H	2241 ± 429	2020 ± 368	*0.048*
Δ BUN	3.6 ± 14.5	4.0 ± 10.9	0.91
Δ Ureum	7.9 ± 31.0	8.5 ± 23.3	0.92
Δ Creatinine	0.1 ± 0.61	0.03 ± 0.33	0.56
Δ GFR	-5.5 ± 20.6	-2.7 ± 22.7	0.64
Δ Sodium Level	0.7 ± 5.21	-0.51 ± 8.35	0.52
Δ Potassium Level	-0.2 ± 9.2	-1.3 ± 6.66	0.58

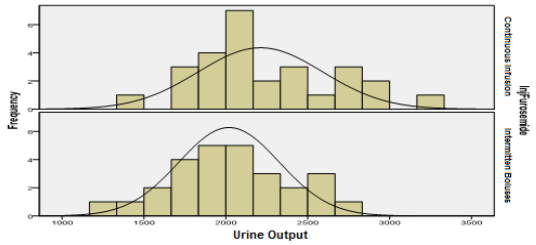

Figure 3. Differences in Continuous Furosemide Infusion and Intermittent Furosemide Bolus to Alteration in Kidney Function and Electrolyte

For kidney function parameters, there were no significant differences in the two groups furosemide administration, with Δ BUN 3.6 ± 14.5 vs 4.0 ± 10.9; p = 0.91, Δ Ureum 7.9 ± 31.0 vs 8.5 ± 23.3; p = 0.92, Δ Creatinine 0.1 ± 0.61 vs. 0.03 ± 0.33; p = 0.56, and Δ Glomelurus Filtration Rate -5.5 ± 20.6 vs -2.7 ± 22.7; p = 0.64. The mean difference in administration of furosemide with changes in electrolyte levels showed that there were no significant differences between the two groups, with changes in sodium 0.7 ± 5.21 vs -0.51 ± 8.35; p = 0.52 and changes in potassium -0.2 ± 9.2 vs -1.3 ± 6.66; p = 0.58. Correlation test results to assess the relationship between administration of furosemide and urine production, found a value of r = 0.27 which indicates a weak correlation between the two variables.

In Hospital Mortality and 30-days Rehospitalization

In continuous furosemide infusion group there were 2 hospital mortality (7.4%) whereas in the intermittent furosemide bolus group there were 3 (11.1%) with a p value = 0.63. Continuous furosemide infusion group had a lower incidence of rehospitalization in 30 days, with 6 events compared to 10 events in the other group.

This data showed no difference in mean groups for continuous infusion or intermittent bolus of furosemide with the incidence of death during hospitalization (HR 0.64; 95% CI: 0.098 - 4.1) and rehospitalization within 30 days (22.2% vs 37%; p = 0.23), (HR 0.48; 95% CI: 0.14 - 1.6).

Table 4
Differences of Continuous Furosemide Infusion and Intermittent Furosemide Bolus for Death Events during Hospital Care and Re-Hospitalation in 30 days

Parameter	Furosemide Strategy		*p Value*
	Continuous Infusion	Intermittent Bolus	
	N = 27	N = 27	
In-Hospital Death	2 (7.4)	3 (11.1)	0.63
Rehospitalization	6 (22.2)	10 (37)	0.23

Discussion

Administration of furosemide injections at the initial patients with presentation of heart failure when entering the emergency room is a first aid for relieving symptoms of acute heart failure such as shortness of breath, pre-tibial edema, and other complaints.[11-12] The basic characteristics of the subjects between the two groups showed no significant differences from the age, but there were significant differences in the gender where the male were more than the female for each group.

Hypertension which triggers the most common acute heart failure and hypertensive heart disease is generally a structural disease underlying heart failure, in which the study subjects showed higher systolic blood pressure at admission in the continuous furosemide infusion group than in the intermittent furosemide bolus group. Heart failure which is triggered by hypertension is also classified as vascular type. In addition to using furosemide as an agent to improve clinical symptoms, the use of nitrate as a vasodilator agent also has an important role. In this study, however, we did not examine the effect of nitrate use in patients with acute heart failure.

Both groups had no different proportions of heart failure classification based on left ventricular ejection fraction. Likewise, in terms of history of the use of previous drugs such as ACE inhibitors, Angiotensin Receptor Blockers (ARB), Beta blockers, and Nitrates, no differences were observed. From the analysis, there were significant differences in the history of use of furosemide and spironolactone, where subjects with the intermittent furosemide bolus group had more oral diuretic use than subjects with the continuous furosemide infusion group. This is thought to be related to the precipitating factor of previous heart failure where the subjects in the continuous infusion group, heart failure was triggered by hypertension with higher systolic blood pressure. In the majority of subjects in the continuous furosemide infusion group, the heart failure symptoms was experienced for the first time or acute de novo.

From analysis of time of furosemide administration for the first time in the emergency room/door to furosemide, there were significant differences in both groups, where subjects in the continuous furosemide infusion group had faster door to furosemide time than subjects in the intermittent furosemide bolus group. Door to Furosemide is related to better survival during hospital care with a 60-minute cut-off point, but the pathophysiological explanation cannot be explained with certainty.[13]

The length of hospital stay was not significantly different in continuous furosemide infusion and intermittent furosemide bolus in shortening the length of hospital stay with length of stay for continuous furosemide infusion group was 7.6 ± 3.2 days and the intermittent furosemide bolus group was 7.3 ± 4.8 days (p = 0.28). The DOSE Trial provides important information regarding furosemide use in the management of heart failure. In the DOSE Trial, the median length of hospital stay ranged from 5 days. This study did not assess confounding comorbidities that can prolong treatment times, such as infection and stroke. Similar to DOSE Trial, we found no superiority in the use of continuous furosemide infusion and intermittent furosemide bolus, but there is a difference where the intermittent bolus administration was divided into 2 doses while in our study it was divided in several doses with administration of 20 mg per dose.[14]

Significant mean differences were also seen in urine production, where continuous administration of furosemide infusion group, compared to the administration of intermittent furosemide bolus have urine production on average every 24 hours of 2241 ± 429 ml vs 2020 ± 368 ml, p = 0.048, respectively. Then we examined the strength of the relationship between administration of furosemide and urine production, and found the value of r = 0.27 with a weak interpretation of the correlation in this variable. However, in the DOSE Trial where there was no difference in 72 hours urine production both groups 4237 ± 3208 vs 4249 ± 3104, p = 0.89. The increasing of urine production can be possibly due to the administration of continuous furosemide infusion required patients to lie in bed, as urine production could increase if the patient is in a supine position. Continuous infusion also provided stable concentration of furosemide that can maintain urine production.[15-17]

In terms of overall changes in kidney function, such as changes in levels of BUN, Ureum, Creatinine, and changes in electrolytes such as Sodium and Potassium, there were no significant difference between the continuous furosemide infusion group and the intermittent furosemide bolus group. This is consistent with previous studies where in the DOSE trial, there were no significant differences in the efficacy and safety of using furosemide. This may occurred because in the DOSE trial, the daily dose used in the intermittent bolus group can be greater than in the continuous infusion group. In addition, number of subject in this study may be too small.

However, increased kidney function occurred in a previous study by Palazzuoli et al which showed a decrease in kidney function in patients with continuous use of furosemide infusion compared to intermittent bolus furosemide. The declining in kidney function results from a large amount of intravascular fluid loss, reflux of extravascular and interstitial intravascular fluid, and a decrease in blood flow to the kidneys resulting in redistribution between the kidneys and triggered an effective reduction of glomelurus filtration fraction. However, the theory also explains that the use of continuous infusion of furosemide will increase the concentration of the drug in the loop of henle, thereby reducing the energy needed by the kidneys at the level of the medulla and protect against hypoxic state.[17-19]

We found no significant hospital mortality difference between the two groups, but the incidence was more common in the use of intermittent furosemide bolus with a p value = 0.63 (HR 0.64; 95% CI: 0.098 - 4.1). Similarly, there was no significant rate differences of hospitalization within 30 days between the two groups with p = 0.23. (HR 0.48; 95% CI: 0.14 - 1.6).

In this study, the incidence of death during hospitalization and rehospitalization in 30 days was lower in continuous furosemide infusion group compared to the intermittent furosemide bolus group (2 subjects (7.4%) vs 3 subjects (11.1%), p = 0.63) and (6 subjects (22.2%) vs 10 subjects (37%); p = 0.23).

In contrast to DOSE Trial, the incidence of death, rehospitalization, and admission to the emergency unit due to complaints of heart failure at 6 months follow-up reached 42% with 67 events vs 63 events (Hazard Ratio for continuous furosemide infusion 1.15; 95% CI, 0.83 - 1.60; P = 0.41)).[14, 20]

Likewise, the study by Palazzuoli et al. showed a higher incidence of rehospitalitation and mortality in the continuous furosemide infusion group compared to the intermittent furosemide bolus group. This event may be due to a decrease in glomelurus filtration rate, hyponatremia and hypotension and a longer duration of treatment in the continuous furosemide infusion group. It showed that this study required a larger sample size and a longer follow-up time.[17]

Limitation

The number of samples of this study was smaller than previous studies and was only in single center, necessitating further research to be conducted with a larger sample size. This study did not excluded comorbidities such as infections and strokes which could confound length of stay. The follow-up in this study was short, i.e. only 30 days post-treatment. Longer follow-up was needed to assess better outcomes.

Conclusion

We found no significant difference between the administration of continuous infusion and intermittent boluses of furosemide with length of hospital stay in patients with acute heart failure at H. Adam Malik General Hospital in Medan.

There were significant differences in the administration of continuous infusion with intermittent bolus of furosemide doses with urine production with a weak correlation (p value = 0.048, r = 0.27) but there was no difference between administration of continuous furosemide infusion doses and intermittent furosemide bolus in alteration of renal function and electrolyte, death during hospitalization, and rehospitalization within 30 days.

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References

1. Filippatos G, Zannad F. An introduction to acute heart failure syndromes: defenition and classification. *Heart Fail Rev* 2007;12:87-90.
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of

heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–259.
3. Alla F, Zannad F, Hipastos G. Epidemiology of acute heart failure syndromes. *Heart Fail Rev* 2007;12:91-5.
4. Yancy CW, Jessup M, Bozkurt B, dkk. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128: 1810–52.
5. Janani AP. 2017. "The Correlation Between Proportional Pulse Pressure and Ejection Fraction in Heart Failure Patients". Available at : Repository-tnmgrmu.ac.in/1161/1/2001495jananiap.
6. Hasenfus G and Mann DL. Pathophysiology of Heart Failure. In: Mann DL., Zipes DP., Libby P., Bonnow RO., and Braunwald E. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed*. Elsevier-Saunders. 2015; 454-472.
7. Ponikowski P, Voors AA, Anker SD, dkk. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891–975.
8. Martins QCS, Aliti GB, Linhares JC, dkk. Excess Fluid Volume: Clinical Validation in Patients with Decompensated Heart Failure Revista Latino-Americana de Enfermagem Volume 19 number 3.
9. Riset Kesehatan Dasar 2013, RisKesDas 2013 available at:http://www.depkes.go.id/resources/download/general/Hasil%20Riskesdas%202013
10. Douglas LM, Management of Patient with Heart Failure with Reduce Ejection Fraction: Braunwald's Heart Disease, a text book of Cardiovascular Medicine 10th Edition. Elsevier. 2015. 25 : 522
11. Nieminen MS, Bohm M, Cowie MR, dkk. ESC Committe for Practice Guideline: Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. *Eur Heart J* 2005, 26:384-416.
12. Adams KF, Fonarow GC, Emerman CL et al. Characteristics and outcomes of patients hospitalized for heart failure in United States: rationale, design, and preliminary observations from the first 100.000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*.2005;149:209-216.
13. Yuya Matsue, Kevin Damman, Adriaan A. Voors, et.al. *Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure*. JACC vol . 69 , no. 25 , 2017
14. Felker GM, et.al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. N Engl J Med 2011; 364:797-805.
15. Abildgaard U, Aldershvile J, Ring- Larsen H, et al. Bed rest and increased diuretic treatment in chronic congestive heart failure. Eur Heart J 1985; 6:1040-6.
16. Dormans TPJ, Vanmeyel JJ, GerlagvPG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996; 28:376-82.
17. Palazzuoli et al. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial Critical Care 2014, 18:R134
18. Salvator DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev 2005; 3:CD003178.
19. Yilmaz MB, Gayat E, Salem R, Lassus J, Nikolaou M, Laribi S, Parissis J, Follath F, Peacock WF, Mebazaa A: Impact of diuretic dosing on mortality in acute heart failure using a propensity matched study. Eur J Heart Fail 2011, 13:1244–1252.
20. Ouwerkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart-failure hospitalization in patients with heart failure. JACC Heart Fail 2014;2:429–436.1244–1252.