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TOXICITY, SIDE EFFECTS, AND FUROSEMIDE INTERACTIONS IN THERAPY OF HEART FAILURE PATIENTS (SYSTEMATIC REVIEW)

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ABSTRACT

Background: Furosemide as a diuretic loop is one of the main therapies given to heart failure patients with congestion, but in its use furosemide requires a lot of consideration related to toxicity, side effects, and drug interactions. **Objective:** To determine the toxicity, side effects and drug interactions of furosemide on heart failure patients. **Methods:** This research is a Systematic Review. Samples were obtained by searching for journals in the online databases of Pubmed, Scopus and Springer Link then adjusted to inclusion criteria and research questions. Data analysis was based on the PRISMA checklist, then searched for similarities and differences. **Results:** This study found the side effects of furosemide therapy in heart failure patients were: electrolyte disturbance such as: hyponatremia; hypokalemia; and hypomagnesemia, arrhythmia, worsening renal function and worsening of AKI, hypotension, increase of plasma renin, and increased risk of fractures. No incidence of furosemide toxicity. The interaction of furosemide on heart failure patients may occur in several drugs like aspirin, digoxin, ACE-inhibitor, and bronchodilator. **Conclusion:** There is some side effect of furosemide and drug interactions occurred in therapy of heart failure patients.
Keywords: *Furosemide, Toxicity, Side Effects, Interactions, Heart Failure.*

INTRODUCTION

Cardiovascular disease is the main disease that cause of the death in the worldwide.[1] Cardiovascular disease include heart attack, acute myocardial infarction, arrhythmias, stroke, and heart valve defects or heart failure.[2]

Heart failure is a complex clinical syndrome that caused by structural or functional damage of ventricular filling or output by the ventricles, cause the clinical symptoms like dyspnea, fatigue, edema and rales.[3]

Risk factors of heart failure are hypertension, diabetes mellitus, obesity, overweight, congenital heart disease, and hypercholesterolemia.[4]

According to data from RISKESDAS (Basic Health Research) in 2018, the incidence of cardiovascular disease in Indonesia continues to increase. Around 2,784,064 Indonesians suffer from heart disease. The prevalence of heart failure in Indonesia is estimated at 1.5% based on a doctor's diagnosis, or around 29,550 people. Most were found in the province of North Kalimantan with 29,340 people or around 2.2%, and the least in North Maluku with 144 people or 0.3%, in West Java about 96,487 people or 0.3% and the least in the Bangka Islands about 945 people or around 0.15%.[5]

The very important pathophysiology of heart failure is the increase of extracellular fluid volume which leads to increased intracardiac filling pressures cause signs and symptoms of heart failure that referred to as congestion.

Loop diuretics are one of the main therapies given to patients with heart failure.[6] Appropriate use of diuretics requires many considerations, especially when renal function is deteriorated, diuretic resistance occurs, and electrolyte disturbances occur.[7]

Furosemide is a common drug used in patients with heart failure. The diuretic effect of furosemide can cause fluid and electrolyte depletion in the body, influenced by the dose and preparation given.[8]

In the treatment of heart failure patients furosemide use has a risk to interact with other drugs, such as furosemide with ACE-inhibitors, furosemide with aspirin and furosemide with digoxin.[9] Hypokalemia, hyponatremia and hypotension were the side effect that cause from excessive fluid and electrolyte loss. Drug toxicity often occurs in diuretic resistant patients, which is in the form of ototoxicity.[10]

METHODS

The design of this research is Systematic Literature Review (SLR). This study aimed to determine the toxicity, side effects and interactions of furosemide on heart failure patients. The sample was obtained by searching for journals with

keywords in the Pubmed, Scopus, and SpringerLink, then adjusted to the inclusion criteria and research questions.

The inclusion criteria of the study are those published in 2015-2020 with human subject (both inpatients and outpatients), with the keywords "furosemide toxicity", "furosemide side effect" or "furosemide interaction" and "heart failure ", available on Pubmed, Scopus, and SpringerLink, published and in English language version. The exclusion criteria were studies using experimental animals.

As shown in figure 1, researchers found 1,237 journals that matched these keywords. Then, 341 duplicated journals were reduced using Microsoft Excel, then 896 journals were screened for titles, abstracts, and keywords, so that 828 inappropriate journals were found, including journals that used experimental animals. 68 journals left to be read in full text to determine their eligibility. Total 15 journals were included for data synthesis.

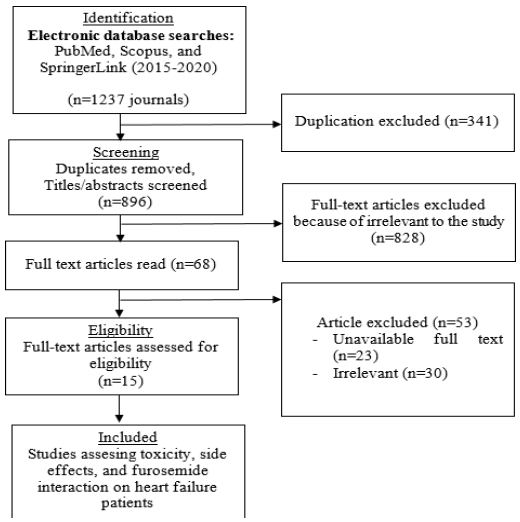

Figure 1. Flow Diagram of Journal Review

Journals that match the inclusion criteria then collected and summary were made. Abstracts and full text journals were examined.

The summary of journals of the research was incorporated in a table. The analysis was carried out based on the PRISMA checklist and SWiM guidelines. The data that has been collected is then searched for similarities and differences and then discussed to draw conclusions.

RESULTS

Results of Journal Selection

The journal articles selected from the Pubmed, Scopus, and SpringerLink databases were listed in a table including the title, name of the researcher, year, country, purpose, research design, method, statistical analysis and research results. Once the journals were collected and incorporated to tabular form (Table 1).

Of the 15 journals that had been reviewed and met the inclusion criteria, the researchers found that side effects of furosemide in the treatment of heart failure patients were electrolyte disturbances, worsening of kidney function and worsening of AKI, hypotension, increased plasma renin, and increased risk of bone fragility and fracture. There were no incidences of toxicity such as ototoxicity and nephrotoxicity, but this is also related to the limitations of the study such as the limited sample and the short duration of the study.

Based on reviewed journals, interactions of furosemide in the treatment of patients with heart failure can occur on some drugs, such as aspirin, digoxin, ACE-inhibitors, aminophylline and albuterol.

Journal Search Quality

Based on the results of extraction of data that met the inclusion criteria, 15 journals were found that were relevant to the topic of this study, toxicity, side effects, and interactions of furosemide in the treatment of heart failure patients. The journals were then read in full text for data synthesis.

Table 1. List of articles that made up the systematic review

No	Title	Purpose	Study Design	Method	Statistical Analysis	Result
1.	Randomized pilot trial comparing tolvaptan with furosemide on renal and neuro-humoral effects in acute heart failure. (Kentaro Jujo, et al. ; 2016)	To compare furosemide and tolvaptan side effects	RCT	60 patients hospitalized for heart failure were randomized to 40 mg IV furosemide (n=30)or 7.5 mg oral tolvaptan (n=30).	WRF was higher in the furosemide group (33% ofpatients) than in the tolvaptan group (6.7%; P<0.01), indicated by an increase in serum Cr, BUN, and plasma renin. Hyponatremia more significantly higher in the furosemide group than tolvaptan (30% vs 3.3%, P<0.01) Mortality ratesdid not show asignificant result (P = 0.30).	Side effects in patients that given furosemide include: worsening of kidney function (as seen from the increase in serum Cr, severe decrease in GFR rate and increase in BUN), increase in plasma renin, decrease in systolic blood pressure, and hyponatremia.
2.	The effect of low-dose furosemide in critically ill patients with early acute kidney injury: A pilot randomized blinded control-led trial (the SPARK study). (Sean M. Baghsaw, et al. ; 2017)	To determine the effects of furosemide in ICU patients with heart failure, comorbid diabetes mellitus, and liver disease.	RCT	Patients randomly assigned to furosemide bolus and infusion or 0.9% saline as placebo within 7 days of intervention. The incidence of worsening AKI, electrolyte abnormalities, ototoxicity, heart rhythm, and mortality were observed.	The incidence of worsening AKI in the furosemide group was 43.2% and placebo 37.1%, p = 0.6. No patients had tinnitus(ototoxicity),5 had heart rhythm disturbances, 22 had electrolyte disturbances, 2 had hypomagnesemia and 4 had hypokalemia.	Patients treated with furosemide experienced side effects of electrolyte disturbances, such as hypomag-nesemia, hypokalemia, and heart rhythm disturbances.
3.	High Furosemide Dose has Detrimental Effects on Survival of Patients with Stable Heart Failure. (Chris J Kape-lios, et al. ; 2015)	Compared long-term effects between patients treated with high-dose and low-dose furose-mide.	Cohort Retros-pective	Deterioration of renal function and serum potassi-um levels were measured in 103 patients on low dose and 70 patients with high dose of furosemide.	The incidence of decreased renal function and hypokalemia was higher in high-dose furosemide (73.2% vs. 48.3%, p=0.003, and 43.1% vs. 6.5%, p<0.001).	Side effects of decreased renal function and hypokalemia were significantly higher in high dose furosemide, It is very important to monitor serum electrolytes in all heart failure patients treated with high-dose loop diuretics.
4.	Prognostic Effect of the Dose of Loop Diuretic Over 5 Years in Chronic Heart Failure. Olga (Laszczy ńska, et al. ; 2017)	Compared low and high doses furosemide on the causes of death and side effects such as electrolyte disturbances in heart failure patients.	Cohort Retros-pective	560 out-patients,followed for up to 5 years. Furose-mide exposure was category-zed as low (0–59 mg/ d),moderate (60–119 mg/day), high (120–159 mg/day), and very high (≥160 mg/day). Mortality and electrolyte disturbances were analyzed.	Side effects of hypo-natremia at low, medi-um, high and very high doses were 6.2%, 5.2%, 6.2% and 15.7%. The risk of death in 5 years were; 26%, 32%, 43%, and 56% (P < .001).	Hyponatremia occurred in 37 patients and higher in patients with very high doses of furosemide. Mortality was also increased with very high doses of furosemide, but it was associated with more severe conditions.

5.	Increased Fracture Risk with Furosemide Use in Children with Congenital Heart Disease. (Ji Haeng Heo, et al. ; 2018)	To determine the relationship of furosemide therapy with the incidence of fractures in children with heart disease and heart failure.	Cohort Retros-pective	Data were drawn from the database Texas Medica-id 2008-2014. Patients taking furosemide were categorized into adherent and non-adherent groups. (adherent = 254; non-adherent= 724; without furosemide = 2934).	The incidence of fractures was highest in the adherent group (9.1%; 23 of 254), followed by the non-adherent group (7.2%; 52 of 724), both of which were higher than patients who did not received furosemide. (5.0%; 148 of 2934) (P <.001)	Furosemide at any dose, even if inconsistently, was associated with fractures, because furosemide can increase the excretion of potassium, calcium, and magnesium.
6.	Danish register based study on the association between specific cardiovascular drugs and fragility fractures. (Maia Torstensson, et al. ; 2015)	To determine whether drugs used in the treatment of cardiovascular disease that increase the risk of bone fragility and fracture in individuals over 65 years.	Cohort Retros-pective	This study analyzed patient me-dical record, treatment, and their relationship to fracture.	Total of 1,586,554 patients were followed-up for 14 years, 300,135 were given furosemide, and 18,846 patients had fractures A diuretic was significantly associated with fractures in the initial treatment, furosemide with an incidence rate ratio (IRR) of 1.74.	The loop diuretic furosemide was significantly associated with frac-tures in the elderly. Hyponatremia has been shown to increase the risk of related osteoporosis fractures, and to affect cognitive effects leading to impaired balance.
7.	Very High-Dose Furosemide Continuous Infusions: A Case Series. Jessica A. (Wilczyn ski, et al. (2020))	To determine the safety and effectiveness of very high-dose IV furosemide therapy (40 mg/ hr - 240 mg/hr)	Cohort Retros-pective	The data from medical records of 22 patients who used very high-dose infusion furosemide therapy were analyzed and evaluate at 24-48 hours before and after therapy.	Serum creatinine increased 24 hours after therapy but decreased within 48 hours. No electrolyte abnormalities, 2 had hypotensive and there was no ototoxicity.	The side effect of furosemide therapy was hypotension. There were no patients with worsening renal function, electrolyte disturbances, and ototoxicity in this study.
8.	Acquired long QT syndrome in hospitalized patients. (Haixu Yu, et al.; 2017)	To determine the causes and effects of ALQTS on the clinical condition of hospitalized patients	Cohort Retros-pective	This study analyzed 835 electronic medical record and ECG (542 as controls) to identify ALQTS in hospitallized patients	There were 68 patients with severe ALQTS, 59% or 40 of them due to furosemide therapy. In non-survival patients, ALQTS occurred in 68% (13 of 19 patients) who were given furo-semide.	The most common cause of ALQTS was furosemide and also associated with hypokalemia and hypocalcemia, electrolyte disturbances can lead to life- threatening arrhythmia.
9.	Women Hospitalized for Acute on Chronic Decompensat-ed Systolic Heart Failure Receive Less Furosemide Compared to Men.Tyler P. (Rasmus sen, et al.; 2019)	To examined differences in the prescribing pattern of furosemide against the sex and the effects such as the ratio of AKI, respiretory failure, and morta-ity.	Cohort Retros-pective	Data were taken from the electronic medical records of 434 heart failure patients. Initial furosemide dose, first 24 hour, total dose, incidence of AKI, GFR, SBP and mortality related to the dose of furosemide were analyzed.	After adjusting for age, GFR, SBP, DBP, and NT-proBNP, women had more AKI than men (p = 0.0081). Hospital mortality(p = 0.2221), 30 day mortality(p = 0.4106), 1 year mortality(p = 0.2463), intubation (p = 0.2421) and NIV (p = 0.0994) were not	In this study AKI in patients treated with furosemide was more common in women than men. Mortality rates and hospital deaths were not significantly different.

					statistically different between doses (40-80 mg).	
10.	Identification of clinically significant drug-drug interactions in cardiac intensive care units of two ter-iary care hospitals in Peshawar, Pakistan. (Faisal Shakeel, et al. ; 2016))	To identify cardiovascular drug interactions that clinically signifycant and compare them.	Cross-sectiona l	This study was conduct-ed 510 patients,treat-ment chart was evaluated.	From two hospitals, this study found drug interactions with severe degrees 41.4% and 53.1% and mild degrees 4% and 1%. Drug interactions caused patients to stay in the hospital longer with significant relationship (p< 0.0001).	Drug interactions in patients treated with furosemide included: aspirin (108 patients), digoxin (31 patients), and ramipril (40 patients). Heart failure patients who treated with furosemide should be monitored very careful, because significant drug interactions could cause patients to stay longer in the hospital.
11.	Prevalence and Risk Factors Associated with Use of QT Prolo-nging Drugs in Hospitali-zed Older People. (C.Franchi, et al.; 2016)	To evaluate the prevalence of prescription QT-prolonging drugs including furosemide and the risk factors and their effect on electrolyte levels, arrhythmias, and mortality	Cross-sectiona l	Using REPOSI data from 4035 patients. Then the independent risk factors related to drugs that prolong the QT interval were analyzed.	The independent risk factors that prolong the QT interval were age (odds ratio [OR] 1.02, 95% CI 1.01–1.03), multimorbidity (OR 2.69, 95% CI 2.33–3.10), hypokalemia (OR 2.79 , 95% CI 1.32–5.89), atrial fibrillation (OR 1.66, 95% CI 1.40–1.98), and heart failure (OR 3.17, 95% CI 2.49–4 ,05). Furosemide, alone or in combination, is the most widely prescribed drug and is defined as a conditional risk of TdP drug.	The class of drugsthat prolong the QT interval that was most widely prescribed were diuretics (1526 furosemide patients). Hypokalemia due to diuretics is an inde-pendent risk factor for QT prolongation.
12.	Prevalence, predictors and out-comes of potential drug-drug interactions in left ventricu-lar failure: considerable factors for quality use of medicines. (Inamul Haq, et al.; 2020)	To identify drug-drug interactions and assess the effect of various drug interacttions in heart failure patients	Cross-sectiona l	Sample of this study were inpatient patients (n=385). Medications, length of stay in hospital, symptoms, signs and laboratory results were analyzed.	The prevalence of pDDI was 96.4% (n=371). In the interaction of furosemide and ramipril 26 patients had hypotension, 3 nausea, 2 vomited, 1 vertigo, and 9 dizziness. In patients with furosemide and digoxin 5 patients had dizziness, 4 nausea, and 3 vomited. While on aspirin and furosemide the patient still had symptoms of edema.	The most common drug interactions found were furosemide with: aspirin (237 patients), ramipril (132 patients), digoxin (112 patients), albuterol (40patients): aminophylline (23 patients)
13.	Survey on Polypharmacy and Drug-Drug	To assess polypharmacy and potential drug-	Cross-sectional	This study used medical records and clinical charts of 255	There was a significant relationship between heart failure	The most common identified drug combination was

	Interactions Among Elderly People with Cardiovascular Diseases at Yekatit 12 Hospital, Addis Ababa, Ethiopia. (Yelbeneh Abayneh Assefa, et al.; (2020)	drug interactions (DDI) in elderly with cardio-vascular disease.		patients in the elderly with cardiovascular disease. Type, severity, level of potential DDI and their effects were analyzed using Med-scape.	and the incidence of drug interactions. The most interactions were pharmacodynamic (73.06%), pharmacokinetics (21.29%) and both (5.65%). The most common pDDI was common (73.29%), minor (19.41%) and serious (7.3%).	furosemide with: enalapril (21.6%), aspirin (19.6%), and digoxin (15.7%).
14.	Impact of short-acting loop diuretic doses and cardiac sympathetic nerve abnormalities on out-comes of patients with reduced left ventricular function. Hisamitsu (Onitsuka, et al.; 2019)	To investigate the relationship between daily dose of furosemide in heart failure patients from the point of view of cardiac sympathetic nervous system abnormalities, renal function and sodium levels.	Observa-tiona	This study involved 137 hospitalized patients with furosemide dose (≥60mg/day, 40–60mg/day and <40mg/day), then observed.	Statistical analysis showed that the use of high-dose furosemide (≥40mg per day) correlated with poor prognosis in patients. Patients treated with furosemide 40mg per day had lower serum sodium (P<0.0001) and eGFR (P=0.011).	From the results of the analysis, it was found that the use of high doses of furosemide (≥40mg per day) correlated with a poor prognosis, patients who were given high doses of furosemide had lower sodium levels and eGFR.
15.	Effect of high-dose furosemide on the prognosis of critically ill patients (Seok Jeong Lee, et al.; 2017)	Determine the effects and prognosis of high-dose furosemide (40 mg) in patients admitted to the ICU.	Retros-pective	This study analyzed the medical records of 448 patients related to length of stay in the ICU, fluid balance, AKI, and furosemide treatment were analyzed.	The use of high-dose furosemide and chronic use increased patient mortality (P=0.028 and OR 2.81, 95% CI 1.16–6.78, P=0.022) and there was significant relationship between furosemide and patient mortality.	High doses of furosemide (in non-oliguric patients) were associated with poor outcomes and there was a significant association between furosemide and patient mortality. (but in oliguric patients also associated with high body fluid volume)

DISCUSSION

Based on the results of data synthesis, it was found that the side effects of furosemide therapy in the treatment of heart failure patients were in the form of electrolyte disturbances, such as[11,12,13,14,15,16]: hyponatremia[11,14]; hypokalemia[12,14,17]; dan hypomagnesemia[12], heart rhythm disturbances[12,15], worsening of kidney function and worsening of AKI[11,12,13,18,16,19], which were characterized by an increase in BUN; creatinine; and decreased GFR; hypotension[20], an increase in plasma renin[11], as well as an increased risk of bone fragility that can lead to fracture.[21,22] The incidence of hypochloremia, hypocalcemia, and dehydration in the study hypothesis, was not identified by the reviewed journals.

In a study conducted by Kentaro Jujo et al., Sean M. Baghsaw et al., Chris J Kapelios et al., Olga Laszczyńska et al., and Jessica A. Wilczynski et al., the total sample of patients related to the side effects of furosemide was 888 patients (including control group) and for patients given furosemide alone 822 patients. The most common side effect was electrolyte disturbance. Electrolyte disturbances that occurred in patients who were given furosemide were 105 patients, with details of hyponatremia in 46 patients, hypokalemia in 41 patients, hypomagnesemia in 2 patients, and the rest only mentioned having electrolyte disturbances.

Electrolyte disturbances that occur made heart rhythm disturbances and hypotension that occur in patients.[15,17,18] In the research results of Sean M. Baghsaw et al. of 37 patients who were given furosemide, 5 patients had side effects of heart rhythm disturbances..[12] Studies related to furosemide and QT prolongation were also conducted by Haixu Yu et al. It was found that 53 patients had ALQTS due to furosemide therapy.[15] A total of 2 patients were hypotensive in the study conducted by Jessica A. Wilczynski et al.[20]

Research conducted by Kentaro Jujo et al., Sean M. Baghsaw et al., Chris J Kapelios et al., and Jessica A. Wilczynski et al., also showed that administration of furosemide can cause a decrease in renal function and increase the severity of AKI in patients.[11,12,13,18] In a total of 262 patients treated with furosemide, worsening of kidney function occurred in 127 patients, which was characterized by an increase in BUN, creatinine, and a decrease in GFR. Research conducted by Tyler P. Rasmussen et al. and Hisamitsu Onitsuka et al. also demonstrated that renal function worsened in furosemide-treated patients.[16,19] In the study of Tyler P. Rasmussen et al. it was found that furosemide cause AKI, and in this study female patients suffered from AKI more than men ($p = 0.0081$).[19] Based on the results of the study of Hisamitsu Onitsuka et al, patients treated with furosemide 40mg per day, had low serum sodium ($P<0.0001$) and eGFR ($P=0.011$).[16]

Study about side effects of furosemide and bone fragility and fracture[21,22] has also been performed (Figure 4), both in children and the elderly. Research by Ji Haeng Heo et al. Regarding the effect of furosemide on children with heart disease, it was shown that there were 75 patients receiving furosemide treatment with fractures out of a total sample of 978 patients on furosemide therapy, where the incidence was higher than 2934 patients who did not receive furosemide therapy with a significant relationship ($P < .001$).[21]

The research by Maia Torstensson et al. related to the effect of furosemide on elderly patients who routinely undergo cardiovascular treatment, found that the diuretic furosemide was significantly associated with fractures in treatment, with an incidence rate ratio (IRR) of 1.74 (1.74 per 100 patients).[22] According to the both studies, the administration of furosemide, either adherent or non-adherent, has a significant relationship with bone fragility and fracture incidence, because the mechanism of action of furosemide can cause hypercalciuria and can cause a decrease in BMD which triggers bone fragility and fracture susceptibility.[21] In addition, according to Maia Torstensson et al., the hyponatremia that occurs also affects the patient's cognitive which can cause balance disorders in the elderly.[22]

Toxicity of furosemide therapy such as nephrotoxicity and ototoxicity was not found in the analyzed journals, even in the study of Maia Torstensson et al. who used even very high doses of furosemide (40 mg/hour - 240 mg/hour IV), but in this study the sample was still limited (22 patients only) and monitoring was only 48 hours after the initiation of therapy, so the monitoring of incidence of ototoxicity and nephrotoxicity in patients just limited.[22]

Interaction of furosemide in the treatment of heart failure patients is caused by various conditions such as advanced age and comorbid diseases of the patient, thus requiring various treatments (polypharmacy).[23,24,25] Interaction of furosemide in the treatment of heart failure patients could occur in several drugs, including: aspirin, digoxin, ramipril, enalapril, aminophylline and albuterol.[23,24,25] Among these journals there are no data regarding the interaction of furosemide and beta-blockers in the research hypothesis.

Studies conducted by Faisal Shakeel et al., Inamul Haq et al., and Yelbeneh Abayneh Assefa et al., with a total sample of 1150 patients showed that there was a potential drug interaction with furosemide and aspirin as many as 387 patients, with digoxin as many as 177 patients, with ramipril as many as 172 patients, with enalapril as many as 46 patients, with aminophylline as many as 23 patients and with albuterol as many as 40 patients.[23,24,25]

Based on the research results of Inamul Haq et al. who monitored the effect of the potential interaction of furosemide on the treatment of heart failure patients who were hospitalized, the results showed that the interaction of furosemide and ramipril caused 26 patients had hypotension, 3 patients had nausea, 2 patients had vomiting, 1 patient had vertigo and 9 patients had dizziness. While the administration of digoxin and furosemide resulted in 5 patients had dizziness, 4 patients had nausea, 3 patients vomiting, and 2 patients had headaches.[25]

Interaction between furosemide and aspirin (NSAID as an antiplatelet which is a COX-1 inhibitor) is an antagonist pharmacodynamic

interaction, where aspirin can cause a decrease in the effectiveness of furosemide through the action of aspirin that decrease sodium excretion.[23,24,25] The interaction between furosemide and digoxin is a synergistic pharmacodynamic interaction, because furosemide can cause hypokalemia and digoxin's mode of action also inhibits the Na+/K+-ATPase pump (to increase heart muscle contraction), this condition will certainly increase the risk of digoxin toxicity (nausea, vomiting, and cardiac arrhythmias)[23,24].

The interaction between furosemide and ramipril and enalapril as ACE-inhibitor is a synergistic pharmacodynamic interaction, where ACE-inhibitor is a vasodilator and furosemide as a diuresis will reduce blood volume to the heart, so the risk of hypotension will increase. [23,24,25] The interaction between furosemide and aminophylline is that furosemide will increase the excretion of the drug aminophylline (PDE-inhibitor bronchodilator) so that it will decrease its effectiveness. Meanwhile, the interaction between furosemide and albuterol (Bronchodilator group B2-Agonist) can increase the risk of hypokalemia.[25]

Based on the research results of Faisal Shakeel et al. Drug interactions significantly extended the length of stay in the patient's hospital ($P < 0.0001$). [24]

Limitations of this study is this study only conducted journal from Pubmed, Scopus, and SpringerLink. The number of journals that had been reviewed were limited because this study not reached journals published in other media yet, so another review that include another databases may needed.

The data analyzed in the study is also very dependent on the results of the journal research that had been reviewed, so that there were data limitations.

In addition, the research sites reviewed were from outside Indonesia, because data on the toxicity, side effects and interactions of furosemide in the treatment of heart failure patients in Indonesia were limited or there were no recent studies. Then by doing this research, it can provide a reference for researchers in Indonesia to conduct similar research.

CONCLUSION

Based on the review, all journals included in the data synthesis were accordance with the hypothesis of this study, but there were no incidence of furosemide toxicity in the treatment of heart failure patients in this study.

Symptoms due to side effects of furosemide in the treatment of patients with heart failure include electrolyte disturbances were: hyponatremia; hypokalemia; hypomagnesaemia, heart rhythm disturbances, worsening of renal function and worsening of AKI characterized by an increase in BUN; creatinine; decrease in GFR; hypotension, increased plasma renin, and increased risk of bone fragility that can lead to fracture. There were no incidences of furosemide toxicity in the patients in this study. Interactions of furosemide in the treatment of heart failure patients include furosemide with aspirin, digoxin, ramipril, enalapril, aminophylline and albuterol, that associated with advanced age and comorbid disease of the patient.

It is necessary to conduct further and long-term research on the toxicity, side effects and interactions of furosemide in the treatment of heart failure patients. In addition, it is also necessary to conduct additional research using systematic review that includes more journal articles from various journal databases.

ETHICAL APPROVAL

This study received Ethical Clearance from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University with ethical clearance number No. 229/EC/KEPK/FK-UNDIP/VII/2021.

CONFLICTS OF INTEREST

There are no conflict of interest in this study.

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