



Utilization of Standard Therapy and Adjunctive Isosorbide Dinitrate Pump with Clinical Outcomes in Acute Heart Failure Patients

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Abstract

BACKGROUND: Acute heart failure is a life-threatening medical condition. Thus, effective therapy is very important for this case. Utilization of standard therapy and adjunctive isosorbide dinitrate (ISDN) pump plays an important role in reducing mortality, length of hospitalization, and national early warning score – NEWS 2. However, the research on the utilization of the ISDN pump as adjunctive therapy is still limited.

AIM: This study aimed to analyze the relationship between utilization of standard therapy and adjunctive ISDN pump with clinical outcomes (mortality, length of hospitalization, and NEWS 2) in patients with acute heart failure.

METHODS: This was a cohort retrospective observational study. The purposive sampling technique was utilized to select the acute heart failure patients in UNS Hospital. All the data were obtained from medical records. Logistic regression was used to analyze the data.

RESULTS: A total of 94 patients were included as the samples. There was a significant relationship between the utilization of standard therapy (OR = 7.9; CI 95% = 3.1–20.4; $p < 0.001$) or ISDN pump (OR = 0.3; CI 95% = 0.1–0.7; $p < 0.001$) with the length of hospitalization. However, there was no significant relationship between the utilization of standard therapy (OR = 1.1; CI 95% = 0.2–6.6; $p = 0.9$) and ISDN pump (OR = 0.2; CI 95% = 0.02–1.6; $p = 0.1$) with NEWS 2 on patients with acute heart failure.

CONCLUSION: There was a significant relationship between the utilization of standard therapy and ISDN pump with the length of hospitalization.

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Introduction

Acute heart failure is a condition of rapid onset and very severe symptoms and signs of heart failure during the first diagnosis or due to worsening congestive heart failure and previous cardiomyopathy (acute decompensated heart failure) [1]. This condition is also accompanied by an increase in fluid and hemodynamic disturbances that can lead to death [2].

Cardiovascular diseases, particularly heart failure, have become a global health problem. Moreover, Indonesia is the country with the highest number of cases in Asia, accounting for 5% of the world's total cases [3]. Based on the latest data in 2018, 1.5% of the Indonesian have a heart failure [4]. The data from the Ministry of Health of the Republic of Indonesia in 2017 showed that Central Java was the province with the highest number of inpatients with heart failure [5]. The increased number of heart failure cases in developing countries is caused by the lack of research and the absence of effective therapy to treat heart failure [6].

In general, the use of standard therapy for heart failure such as angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, beta blocker, loop

diuretic, and mineralocorticoid receptor antagonist can improve mortality rates and also length of hospitalization (LoH), but the mortality rate remains high in patients without adjunctive therapy [7]. The use of isosorbide dinitrate (ISDN) pump as an adjunctive therapy can be significantly beneficial in reducing mortality rates, LoH, signs, and symptoms of acute heart failure, as well as improve the patient's quality of life (QoL) [8]. However, research on ISDN pumps as an adjunctive therapy is limited. Thus, research aims to analyze the relationship between the use of standard therapy and adjunctive ISDN pump with clinical outcomes (mortality, length of stay, and National Early Warning Score (NEWS) – 2) in acute heart failure patients is needed.

Materials and Methods

Study design

This was an analytic observational study with a retrospective cohort approach. The study was conducted at the Universitas Sebelas Maret (UNS) Hospital. The population of this study is all patients with acute heart

failure in UNS Hospital during January–December 2020 period who were selected with purposive sampling. This study was designed to answer the question of whether there is a different result between the treatment with standard therapy and isosorbide dinitrate pump in patients with acute heart failure.

Eligibility criteria

We included all patients who presented acute heart failure patients based on ICD 10 diagnosis, aged over 18 years old, and patients with clear and complete medical records. Patients will be excluded from this study if they are recorded as returning home of their own accord, being transferred to another hospital, and diagnosed with COVID-19.

Data collection

A total of 94 patients with acute heart failure were selected with purposive sampling. Patients' medical records data during January–December 2020 period were collected. The independent variables in this study were standard therapy and adjunctive ISDN pump medication, while the dependent variables were the clinical outcome (mortality, LoH, and NEWS 2).

Data analysis

The data were analyzed descriptively, and the relationship was assessed using a logistic regression test. The study was approved by UNS Hospital and ethical clearance was obtained from the Health Research Ethics Committee of Dr. Moewardi General Hospital (No. 396/III/HREC/2021).

Results

Data collection was conducted between June 2021, at the Medical Record Installation of the UNS Hospital. Out of the 94 acute heart failure subjects, 50 patients (53.2%) were men, and 39 patients (41.5%) were belong to 55 to 64 years old group. All patients with acute heart failure had comorbidities, with three comorbidities (36 patients; 38.3%) which were the most, and cardiovascular was the most common disease (83 patients; 88.3%). The detailed characteristics of the subjects are shown in Table 1.

The majority patients (60 patients; 63.8%) received standard optimal therapy (3–4 drugs) (Table 2). The use of standard combination therapy is also more common in the treatment of acute heart failure and had better effectiveness [9], [10], [11], [12]. A proportional number of patients receiving and not receiving the adjunctive ISDN pump was found in this

Table 1: Characteristics of patients

Characteristics	N	%
Sex		
Men	50	53.2
Women	44	46.8
Age group		
≤54	24	25.5
55–64	39	41.5
65–74	22	23.4
≥75	9	9.6
Number of comorbidities		
1	4	4.3
2	24	25.5
3	36	38.3
4	18	19.1
5	7	7.5
6	5	5.3
Mean (±SD)	3,2 (± 1.2)	
Median (IQR)	3 (4–2)	
Types of comorbidities		
Cardiovascular	83	88.3
Endocrine and metabolism	47	50
Respiration	27	28.7
Kidney and urinary tract	20	21.3
Hematology and immunology	10	10.6
Gastrointestinal tract	4	4.3
Musculoskeletal	2	2.1
Neurology	2	2.1
Malignancy	1	1.1

study (patients; 50%) (Table 2). Alzahri [13] also found that the ISDN pump is a common therapy for patients with acute heart failure [13].

Table 2: Distribution of sample data based on the therapy and clinical outcomes

Variables	N	%
Standard therapy		
Minimal (≤2 drug (s))	34	36.2
Optimal (3–4 drugs)	60	63.8
Adjunctive ISDN pump		
No	47	50
Yes	47	50
Mortality		
No	90	100
Yes	0	0
Length of hospitalization		
<3 day (s)	38	40.4
≥3 days	56	59.6
News 2		
Low	88	93.6
Not low	6	6.4

Low, NEWS 2 score = 0–4; not low, NEWS 2 score = ≥5 or red score.

Table 2 showed that there was no patient's death recorded in this study. However, more than half of patients (56 patients; 59.6%) had LoH of ≥ 3 days. The highest NEWS 2 after hospitalization was in the low category in 88 patients (93.6%).

The results of the logistic regression test show that LoH was influenced by the administration of standard therapy. Patients with optimal standard therapy were 7.9 times more likely to have ≥3 days of hospitalization compared to those with minimal standard therapy (OR = 7.9; 95% CI = 3.1–20.4; $p < 0.001$). In the multivariable logistic regression test, the patient treated with optimal standard therapy had a greater risk of longer LoH (OR = 7.0; 95% CI = 2.5–19.6; $p = 0.0$) (Table 3). There is also a significant influence between the administration of an adjunctive ISDN pump and LoH. The adjunctive ISDN pump had a significant effect in reducing LoH (OR = 0.3; 95% CI = 0.1–0.7; $p = 0.0$). In the multivariable logistic regression test, the patients using adjunctive ISDN pump had a 0.7 times lower risk of ≥3 days of hospitalization compared to those who did not use this method (OR = 0.3; 95% CI = 0.1–0.8; $p = 0.0$) (Table 3).

Table 3: Correlates of length of hospitalization

Predictors	Bivariate analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Standard therapy				
Minimal	1			
Optimal	7.9 (3.1–20.4)	<0.001	7.0 (2.5–19.6)	<0.001
Adjunctive ISDN pump				
No	1			
Yes	0.3 (0.1–0.7)	<0.001	0.3 (0.1–0.8)	<0.001
Sex				
Women	1			
Men	1.8 (0.8–4.1)	0.2		
Age group				
≤54	1			
55–64	0.7 (0.2–1.9)	0.5		
65–74	1.9 (0.6–6.6)	0.3		
≥75	2.5 (0.4–14.7)	0.3		
Number of comorbidities (numeric)	1.8 (1.2–2.8)	<0.001	1.9 (1.1–3.1)	<0.001

However, this study showed that there was no significant relationship between NEWS 2 and standard therapy nor adjunctive ISDN pump ($p > 0.05$) (Table 4).

Table 4: Correlates of NEWS 2

Predictors	Bivariate analysis	
	OR (95% CI)	p-value
Standard therapy		
Minimal	1	
Optimal	1.1 (0.2–6.6)	0.9
Adjunctive ISDN pump		
No	1	
Yes	0.2 (0.02–1.6)	0.1
Sex		
Women	1	
Men	0.4 (0.07–2.4)	0.3
Age group		
≤54	1	
55–64	0.6 (0.04–10.2)	0.7
65–74	5.1 (0.5–49.8)	0.2
≥75	0.00	1.0
Number of comorbidities (numeric)	1.1 (0.6–2.3)	0.7

In addition, there is a significant relationship between the number of comorbidities and LoH. Each additional comorbidity increased the risk of ≥ 3 days of hospitalization by 1.8 times (OR = 1.8; 95% CI = 1.2–2.8; $p = 0.0$) (Table 3). However, there was no significant relationship between sex and age with LoH ($p > 0.05$) (Table 3). Moreover, there was no significant relationship between sex, age, and the number of comorbidities with NEWS 2 ($p > 0.05$) (Table 4).

Discussion

Patients characteristics

This patient's proportion is similar to another study that showed acute heart failure which was more prevalent in men than women [9]. However, several studies showed that a majority of the patients belong to the ≥ 65 -year-old age group [10]. In Table 1, all patients with acute heart failure had comorbidities. It is known that comorbidities are very common in patients with heart failure, even in the younger age group [11].

The majority patients received standard optimal therapy. The use of standard combination therapy is also more common in the treatment of acute heart failure and had better effectiveness [12].

An equal proportional number of patients receiving and not receiving the adjunctive ISDN pump was found in this study. Alzahri (2016) also found that the ISDN pump is a common therapy for patients with acute heart failure [13].

Factors related with length of hospitalization

This finding shows the importance of giving effective standard therapy to reduce the LoH in patients with acute heart failure.

Whellan *et al.* (2011) found that there is a significant relationship between the use of standard therapy and LoH. In their study, the use of standard therapy of < 2 resulted in shorter LoH because there are differences in the severity of acute heart failure [14]. Relatively, mild acute heart failure will have a shorter LoH using minimal amounts and doses. This study finding was consistent with the findings of White and Hill (2014), that showed the combination of standard therapy had shorter LoH compared to monotherapy. The combination use of two standard therapy can reduce LoH from 23.1% to 12.9% [15].

In Table 3, the patient treated with optimal standard therapy had a greater risk of longer LoH. This finding was similar with study by Butler *et al.* (2019) that observed patients with standard combination therapy which had a risk for worsening and longer LoH. Moreover, patients received beta-blocker treatment could have worsening acute heart failure [16].

Moreover, the adjunctive ISDN pump had a significant effect in reducing LoH. This result indicated that adjunctive ISDN pump therapy administration for patients with acute heart failure is important. Study by Ferdinand *et al.* (2014) showed that the use of an ISDN pump can reduce LoH by 39% [17]. Moreover, another study showed a significant relationship between the ISDN pump and LoH. The use of an ISDN pump can reduce LoH, especially in patients who are intolerant to ACE inhibitors [18].

In Table 3, the patients using adjunctive ISDN pump had a lower risk of LoH compared to those who did not use this method. According to study by Ziaeeian *et al.* (2017), the use of the ISDN pump was effective in reducing LoH compared to the use of standard therapy only. The short LoH due to the ISDN pump can prevent the use of intubation in patients with acute heart failure and can significantly reduce LoH [19].

On the other hand, other studies showed no significant relationship between the ISDN pump and LoH. This insignificant result was due to the difficulty of finding samples that used an adjunctive ISDN pump for the treatment of acute heart failure and its infrequent use [20]. In other study, the use of an ISDN pump had a significant result in reducing LoH due to improvements

in hemodynamic function and nitric oxide (NO) balance [21]. Therefore, the use of ISDN pump will help reducing LoH in acute heart failure patients.

Factors related with NEWS 2

NEWS 2 is a scoring system for acute illness based on the assessment of vital signs. Bhimaraj (2013) also found that there is no significant relationship between the use of standard therapy with symptoms and signs as measured by vital signs. In his study, patients who only received standard therapy tend to not experience maximal hemodynamic improvement [22]. Because of that, the use of standard therapy, either monotherapy or combination therapy, did not have a significant impact on improving the clinical outcome in patients with acute heart failure without adjuvant therapy.

On the other hand, a previous research revealed that the use of standard therapy was effective in reducing the signs and symptoms of heart failure which included improving vital signs, hemodynamic, and quality of life. The use of standard combination therapy was found to have a greater effect on improving vital signs than the use of monotherapy. The biggest effect was obtained from a combination of three standard therapies. Improvement of the patient's vital signs will also improve their quality of life [23]. Another study found a significant relationship between the use of standard therapy and the patient's vital signs [14]. Thus, the use of standard therapy will help improve NEWS 2 in acute heart failure patients if it is combined with three standard therapies followed by adjuvant therapy.

In Table 4, NEWS 2 is not influenced using the adjunctive ISDN pump. A previous research also found that there is no significant relationship between the use of an ISDN pump and NEWS 2 [8]. In this study, the use of an ISDN pump did not have a significant relationship with heart rate, blood pressure, and respiration rate due to the unbalanced distribution of the research sample because the use of the ISDN pump is still rare.

The ISDN pump did not have a significant relationship with NEWS 2. It could also be due to the different types of acute heart failure. The use of an ISDN pump can improve blood pressure, heart rate, and respiration rate only in acute systolic heart failure. ISDN pump has no effect in improving hemodynamic and vital signs in patients with acute heart failure without hypertension. Long-term use of the ISDN pump may also decrease the overall tolerance of therapy. The influence of other variables on NEWS 2 – such as epidemiological, clinical, biological, and genetic factors – is presently unclear [24].

According to Ramani *et al.* (2010), the insignificant relationship could be caused by differences of severity level. The ISDN pump is more widely used in severe diseases than in mild ones [25].

In contrast, Freund *et al.* [26] observed that there is a significant relationship between the use of ISDN pump and NEWS 2. The use of ISDN pump has more effective results in improving heart rate, respiration rate, blood pressure, and oxygen saturation than the use of high-dose furosemide. In this study, the use of an ISDN pump did not have a significant result in improving vital sign in acute heart failure patients [26]. Thus, the use of the ISDN pump will not influence the post-therapy NEWS 2 if it is given to patients with mild-severity acute diastolic heart failure and nitrate-intolerant patients.

The influence of other factors on the clinical outcome assessment may explain the difficulty in establishing a significant relationship between standard therapy and ISDN pump and clinical outcomes (LoH and NEWS 2). This finding seems consistent with the findings of Tsujimoto and Kajio (2019), where they found that there was no significant relationship between sex and LoH, because the data only came from one health care center and there was no control over the patient's age, race, and socioeconomic status [27]. Rodriguez *et al.* (2013) also did not find any significant relationship between age and LoH [28]. However, Whellan *et al.* (2011) and Molla *et al.* (2021) suggested a significant relationship between sex and LoH. Women tend to have longer LoH than men [14], [29]. In addition, with the increasing number of age, LoH will be increase and vital signs after hospitalization will be worsen.

The insignificant relationship between sex and age with vital signs in patients with acute heart failure is due to the influence of other demographic and socioeconomic factors [28], [30]. Comorbidities that are relatively non-severe have no significant relationship with vital signs and quality of life [31].

This study has several limitations. First, this was a single center study; thus, the result cannot represent all acute heart failure patients. Second, the data were obtained from medical record not from a direct observation; therefore, there is an issue with the reliability. Finally, several clinical outcomes such as rehospitalization and activity of daily living (ADL), demographic, socioeconomic, and occupational factors were not studied.

Conclusion

The use of standard therapy and adjunctive ISDN pump has a significant relationship with LoH. However, it does not significantly influence NEWS 2 after hospitalization in patients with acute heart failure.

Declaration

This manuscript is based on original work and has not been published in whole or part, in any printed or electronic media, or is under consideration of publication in any printed or electronic media other than as the abstract of conference proceedings.

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Authors' Contributions

RPF, S, and YAM conceptualized the study. S collected the data. RPF and YAM analyzed and interpreted the data. S developed the manuscript draft. RPF and YAM edited the manuscript draft. All the authors approved the final manuscript.

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