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The Effect of Giving Low Dosage Furosemide in Sepsis Patients with Acute Kidney Injury in Intensive Care Unit of H. Adam Malik General Hospital Medan

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Abstract:-
Introduction: Acute Kidney Injury (AKI) with sepsis is a dominant problem in the management of ICU patients who require Renal Replacement Therapy (RRT). Loop diuretics (LD) such as furosemide are used intensively in emergency medicine and intensive care because they can control hyperhydration. LD has been reported to modulate tubular cell survival beneficially. This study aims to determine the effect of low-dose furosemide on the improvement of acute kidney injury and kidney function in septic patients at the ICU H. Adam Malik Hospital, Medan.

Methods: This study is a prospective cohort observational analytic study to examine the relationship between low-dose furosemide and the improvement of acute kidney injury in septic patients in the ICU of H. Adam Malik General Hospital Medan. A total of 34 samples that met the inclusion and exclusion criteria were included in the study.

Results: Median urea, creatinine, and urine output at ICU admission were 149 mg/dL (26 – 308); 3.35 mg/dL (1.4 – 9.47); 1077.88 mL (SD 298.07). Median urea, creatinine, and urine output on day 3 of ICU admission were 154 mg/dL (45 – 274); 3.89 mg/dL (1.02-12.70); 974.4 mL (600 – 1944). There was no significant median difference between low-dose furosemide and blood urea nitrogen levels (p=0.758), serum creatinine levels (p=0.993), and urine output volume (p=0.634).

Conclusion: There was no significant effect of furosemide administration on the improvement of acute kidney injury and kidney function in septic patients with acute kidney injury in the ICU H. Adam Malik Hospital Medan.

Keywords:- *Low Dose Furosemide, Sepsis, Acute Kidney Injury (AKI), Urea, Creatinine, Urine Output, Kidney Function, Improvement of AKI*

I. INTRODUCTION

Acute Kidney Injury (AKI) is defined as a decrease in kidney function experienced by a patient for several hours, days to weeks. The AKI mortality rate is 50-80% in the Intensive Care Unit (ICU) and has not decreased significantly since the initial benefit of acute dialysis therapy. In one study it was found that 80% of ICU patients who experienced AKI died. The mortality rate remains unchanged even though patient care has made significant progress. This is a consequence of the difficult and often late diagnosis of AKI, old age, other comorbidities, and the large number of invasive procedures that must be performed on the patient. MMR in Indonesia according to the 11th Annual Report of Indonesia Renal Registry in 2018 was 3822 patients (Kes, 2010; Uchino, 2005; Perez, 2015).

This new staging system differs from the RIFLE classification in terms of it reduces the need for initial creatinine but requires at least two creatinine checks within 48 hours, AKI is defined as a sudden decrease in kidney function (within 48 hours), currently defined as an absolute increase in serum creatinine 0.3 mg/dl (≥ 26.4 mol/l), a percentage increase in serum creatinine 50% (1.5 times baseline), or a decrease in urine output (oliguria < 0.5 ml). /kg/hour for > 6 hours), which in the RIFLE classification is classified as Risk for stage 1 in AKIN, and also considers an increase in serum creatinine 0.3mg/dl (≥ 26.4ìmol/l), the RIFLE Injury classification becomes stage 2 and Failure to stage 3 includes patients requiring renal replacement therapy regardless of the stage they are in at the time of renal replacement therapy. Two outcome classes, namely loss, and ESRD were removed from the AKIN classification (Mehta, 2002).

Loop diuretics (LDs) - for example, furosemide - are used intensively in emergency medicine and intensive care, because of their effect in which large amounts of electrolytes and water are lost as long as the kidneys can filtrate. Thus, hyperhydration can be controlled. However, reduced glomerular filtration characterizes AKI of various etiologies. Although LD is often used when fluid retention is due to impaired renal function, it is debatable whether the renal prognosis itself can be improved with medication or not. In theory, LD increases the tubular outflow of the filtrate and thereby reduces tubular obstruction. In addition, by inhibiting tubular electrolyte reuptake, they decrease medullary net oxygen consumption. Finally, such drugs have been reported to even modulate tubular cell survival in a beneficial manner (Silbert BI, Ho KM, 2017).

To explore the effect of diuretics on AKI outcome, studies often involve patients using the criteria for Urine Output (UO) and Serum Creatinine (Cr). However, Kellum and colleagues in a study of 23,866 AKI patients found that the mortality of patients with AKI defined by the UO criteria was significantly lower than that defined by the UO and Cr criteria. The study also found that the patient's UO criteria for AKI usually did not match the individual patient's Cr criteria. Because oliguria is the main reason for the use of furosemide

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in clinical practice, AKI patients with oliguria should be considered as the sole population in evaluating the outcome of diuretic effects in AKI patients. In addition, it is known that the association between poor outcome and furosemide was more frequently reported in the group with higher Cr (>3.0 mg/dl) while not significant in patients with mild AKI (<2.0 mg/dl) (Redfors B, Swärd). K, 2009) Therefore, researchers are interested in researching the effect of giving low-dose furosemide in septic patients with acute kidney injury in the ICU H Adam Malik Hospital, Medan.

II. METHODS

This study is a cohort observational analytic study to examine the relationship between low-dose furosemide and the improvement of acute kidney injury in septic patients in the ICU of H. Adam Malik General Hospital Medan. This research was conducted in the ICU of Haji Adam Malik General Hospital Medan. This research takes place from March until the sample is met, since the researcher determines the title of the study, prepares a research proposal, collects research data, and makes a report on research results until the research results seminar, which takes place from March 2021 until the number of samples is met.

The study population was all septic patients who were treated in the ICU of the H. Adam Malik General Hospital Medan, where the study sample was sepsis patients who were treated in the ICU of the H. Adam Malik General Hospital Medan who met the research criteria. The technique of obtaining samples is by consecutive sampling, namely looking for patients who meet the inclusion and exclusion criteria until the required number of samples is met.

The inclusion criteria in this study were patients who met the criteria for sepsis or septic shock and had been treated for one-hour bundle sepsis, aged 18-64 years, had a CVP value of 5-10 cm H20, MAP > 65mmHg, and patients who met the criteria for AKIN Stage 1/ 2/3. While the exclusion criteria in this study were the family refusing to participate in the study, patients with a battery with stage loss and end-stage renal disease, patients with chronic kidney disease, and patients with post-cardiac arrest. Samples were taken using consecutive sampling techniques and obtained a sample size of 34 people.

This research was conducted after obtaining approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital Medan. After obtaining informed consent and approval from the health research ethics committee, all samples were reassessed and included in the inclusion and exclusion criteria. Samples that have been determined to meet the inclusion and exclusion criteria are recorded and given furosemide with an initial bolus of 0.4 mg/kgBW followed by a continuous syringe pump 0.05 mg/kgBW/hour and titrated hourly with a maximum dose of 0.40mg/kgBW with a urine target. output 0.5 – 1 ml/kg/hour for 3 days. Patients are monitored for mean arterial pressure and urine output every 1 hour.

Each patient studied maintained a MAP > 65 mmHg, if the map was < 65 it would be treated with fluid resuscitation or administration of vasopressor drugs. Each patient studied maintained a CVP of 5-10 cmH2o. If CVP < 5, it will be treated with a fluid challenge test. Cvp and Mean Perfusion pressure were checked every 8 hours Every change in urine output was assessed every 1 day T1, 2 days T2, and 3 days T3, and urea and creatinine assessments on the first day of admission and day 3. Collected data were processed and analyzed statistically using the statistical product and service solution (SPSS) Windows program. For numerical data presented in the mean ± standard deviation and statistical tests to compare between statistically significant or significant.

III. RESULTS

This study is a prospective analytic study using an observational cohort design comparing low-dose furosemide with renal and functional improvement in septic patients at H. Adam Malik Hospital Medan. This research was carried out after passing the Ethical Clearance and the number of samples was fulfilled at the Haji Adam Malik General Hospital Medan.

This study was followed by 34 samples that have met the inclusion criteria and exclusion criteria. The characteristics of the research sample are shown in the form of frequency, the mean with standard deviation if normally distributed, and the median with minimum and maximum values if not normally distributed and a normality test is performed. Demographic characteristics of the study sample were presented based on age, urea, creatinine, and urine output. The description of the characteristics of this research sample can be seen in Table 1 below.

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Variable	n (%)	Median (min-max)	Mean (± SD)	p-values
Age (years)		50 (25-60)		0.047
Weight (kg)		56 (45-90)		0.007
Gender -Female -Male	 18 (52.9) 16 (47.1)			
Ur1 (mg/dL)		149 (26-308)		0.045
Ur3 (mg/dL)		154 (45-274)		0.014
Cr1 (mg/dL)		3.35 (1.4-9.47)		0.008
Cr3 (mg/dL)		3.89 (1.02-12.70)		0.005
Uo1 (mL/24 hours)			1077.88 (± 298.07)	0.724
Uo2 (mL/24 hours)		938.4 (600-1944)		0.016
Uo3 (mL/24 hours)		974.4 (600-1944)		0.008

Table 1. Demographic Characteristics of the Research Sample

The data listed in Table 1 shows that only urine output data on the first day of admission were normally distributed based on the Shapiro-Wilk test (p>0.05) so that the data presented were the mean (mean) and standard deviation (SD). In addition to urine output on the first day, other data were not normally distributed (p<0.05), so the data presented were median, minimum, and maximum.

Based on the table, the age range of the study samples ranged from 25-60 years, with a median of 50 years. The median bodyweight of the research sample was 56 kg with a range of sample weight ranging from 45-90 kg. The proportion of male and female subjects in our study was almost the same, namely 18 female (52.9%), and 16 male (47.1%). In our study, data on urea levels at ICU admission had a median of 149 mg/dL, ranging from 26 mg/dL to 308 mg/dL. Urea levels on day 3 of ICU admission ranged from 45-275 mg/dL with a median of 154 mg/dL. Serum creatinine levels on the first day of ICU admission ranged from 1.4 to 9.47 mg/dL, with a median of 3.35 mg/dL. Serum creatinine levels on day 3 ranged from 1.02 to 12.70 mg/dL with a median of 3.89 mg/dL. Overall, the median serum urea and creatinine levels in our study sample were higher than normal reference values.

The mean urine output on the first day of ICU admission was 1077.88 (+298.07) mL. Then on the second day, the median urine output was 938.4 mL with a range of 600 – 1944 mL. On the third day of furosemide administration, the median urine output was 974.4 mL and ranged from 600-1944 mL. To obtain the relationship between low-dose furosemide and improvement in AKI in septic patients at H. Adam Malik General Hospital, Medan, the paired T-test was used if the data were normally distributed and the Wilcoxon test if the data were not normally distributed. From table 4.1 it has been stated that the research data are not normally distributed, then the test used is the Wilcoxon test whose results can be seen in Table 2 below.

Wilcoxon test	**Z**	**p-value**
Ur1-Ur3	-0.308	0.758
Cr1-Cr3	-0.009	0.993

Table 2. Association of low dose furosemide with the improvement of AKI

Based on the table, it was found that the p-value of the relationship between low-dose furosemide and improvement of AKI was 0.758 and 0.993, because p-value >0.05, the hypothesis of a relationship between low-dose furosemide and improvement of AKI was rejected. To obtain the relationship between low-dose furosemide and kidney function in sepsis patients at H. Adam Malik General Hospital, Medan, the Annova Repeated Measure test was used if the data were normally distributed and the Friedman test was used if the data were not normally distributed. From table 1 it has been stated that the research data is not normally distributed, then the test used is the Friedman test whose results can be seen in Table 3 below.

Friedman test	Median (Min-max)	p-values
Urine output 0	1038 (540-1728)	0.634
Urine output 1	938.4 (600-1944)	
Urine output 2	974.4 (600-1944)	

Table 3. Relationship of Low-dose Furosemide with Kidney Function

Based on the table, it was found that the p-value of the relationship between low-dose furosemide and kidney function was 0.634 because the p-value was >0.05, the hypothesis of a relationship between low-dose furosemide and kidney function was rejected.

IV. DISCUSSIONS

This In this study, it was found that patients with sepsis at Adam Malik General Hospital had a median age at diagnosis of 50 years. In previous studies, the mean age at diagnosis was 60 years (Levi et al., 2012; Bagshaw et al., 2017; Zhao et al., 2020). This difference may be caused by differences in the sample, namely in our study the research sample was a maximum of 60 years old. In general, the incidence of sepsis increases with age because advancing age is associated with a worsening of the immune system and organ function and the number of comorbid conditions (diabetes, hypertension, malnutrition, COPD, in immunosuppressant therapy), which contribute to the incidence of sepsis. Elderly septic patients (>60 years) are also associated with an increased risk of mortality and morbidity compared to younger patients (Kotfis et al., 2019).

The gender proportions of males and females in our study sample were almost equal with slightly more female patients (52.9%) than males (47.1%). This is by previous research, such as the study conducted by Zhao et al., (2020) which had almost the same proportion of male and female research samples. Gender affects blood urea nitrogen, serum creatinine, and urine output levels. Male gender and older age generally have a higher baseline blood urea nitrogen (BUN) than women (Liu et al., 2021). The median body weight in our sample was 56 kg, in contrast to previous studies with a median bodyweight of 82-83 kg (Bagshaw et al., 2017). This may be influenced by gender, which in this study was dominated by the male sex which is generally heavier than the female.

In addition, the study took samples from abroad, namely Canada and Australia, which have a larger body stature than Indonesia. Bodyweight is a variable that will determine urine output and later determine kidney function and diagnose AKI. In septic patients, using real bodyweight to calculate hourly urine output increases the sensitivity in the diagnosis of AKI compared to using ideal body weight (Katayama et al., 2018).

Blood urea nitrogen levels on the first day of ICU admission had a different median from previous studies, namely in our study the median urea was 149 mg/dL, while in the previous study 34.2 mg/dL (Bagshaw et al., 2017). Our study sample had a median serum creatinine level on the first day of ICU admission of 3.35 mg/dL, this value was higher when compared to previous studies which had an average of 1.3-1.7 mg/dL (Van Der Voort et al. al., 2009; Bagshaw et al., 2017; Zhao et al., 2020).

Elevated blood urea nitrogen and creatinine can indicate kidney disease or disorder, either acute or chronic. Very high blood urea nitrogen levels can indicate decreased blood perfusion to the kidneys or kidney disorders. Increased urea levels can be influenced by many things such as dehydration, a high protein diet, and gastrointestinal bleeding (Hosten, 1990). In addition, the higher serum creatinine in our sample may also be due to damage to the kidneys that reduces creatinine clearance. Daily creatinine production depends on GFR, muscle mass, gender, skin color and ethnicity, age, diet, nutritional status, and chronic disease (Stanga et al., 2013). Serum creatinine and blood urea nitrogen levels before and after furosemide therapy were analyzed to evaluate the improvement of AKI.

In our study, urine output data were analyzed in milliliters every 24 hours. There is a difference in the median urine output with previous studies wherein our study the urine output during the first 24 hours of admission to the ICU was 1077.8 ($\pm$298.07) ml, in contrast to the previous study by Levi et al (2012) whose sample had a mean urine output at the first time. intake of 1600 ml/24 hours. Bagshaw et al (2017) measured the urine output of the sample 6 hours before randomization of drug administration and the median urine output was 210 ml/6 hours.

In our study, the median urine output on the second day after administration of furosemide therapy was 938.4 mg/24 hours, in contrast to the previous study by Bagshaw, et al (2017) which stated that the median urine output after 24 hours of furosemide administration was 3006 mL. This variable urine output value can be caused by several things, namely the amount of the hormone vasopressin, RBF (renal blood flow), and GFR (glomerular filtration rate) (Firsov and Bonny, 2010). Urine output is a rapid kidney function test that can be performed at the bedside, and decreased urine output has long been known as a biomarker of acute kidney injury (Eknoyan, 2002). Oliguria (<0.5 ml/kg/hour) for 1-12 hours is the only predictor of AKI development according to the RIFLE criteria, and mortality rates increase with increasing duration of oliguria. (Md Ralib et al., 2013).

Based on existing studies, furosemide can prevent and improve AKI by lowering the GFR (glomerular filtration rate) and reducing the workload of the renal tubules, thereby reducing oxygenation of the renal medulla (Epstein and Prasad, 2000; Peixoto, 2016). In addition, some studies state that furosemide can work as a renal vasodilator so that it can treat acute tubular necrosis (ATN) (Kellum, 1997). However, these arguments have only been proven in studies under experimental conditions and have not been proven in direct clinical practice. Several studies and previous meta-analyses did not support the use of furosemide in AKI patients because there was no evidence of an effect of furosemide administration on mortality or the need for RRT (renal replacement therapy) in adult patients with AKI (Ho and Sheridan, 2006; Krzych and Czempik, 2019). The KDIGO Clinical Practice Guidelines so far also do not recommend the use of furosemide for the management of AKI improvement (Levin et al., 2012).

Elevated serum creatinine has been used as a diagnostic criterion for AKI and the growing data to date suggest that even slight changes in creatinine are associated with poorer patient outcomes. So far, the diagnosis of AKI is still based on an increase in serum creatinine or a decrease in urine volume. Unfortunately, creatinine is a suboptimal marker for injury, so the amount sometimes does not reflect GFR because there are renal and non-renal influences on creatinine levels (Vaidya, Ferguson, and Bonventre, 2008). Other studies have suggested that the effect of furosemide on mortality in AKI patients is dependent on serum creatinine levels and the association between mortality risk and furosemide has been reported more in cohort studies with higher serum creatinine (Shen and Wu, 2018).

Another study suggested that furosemide administration was associated with the return of renal function in critically ill patients with AKI and was primarily effective in AKI patients with staging using urine output stages 2 (<0.5 mg/kg/hour for +12 hours) and 3 (<0.3 hours). mL/kg/hour for +24 hours or anuria +12 hours) (Zhao et al., 2020). Oliguria is one of the two main criteria for the diagnosis of AKI and is also a major reason for the use of diuretics. A positive fluid balance is one of the complications of oliguria in AKI patients and furosemide is useful for the management of fluid overload. A multicenter study in ICU patients also

found that in patients with positive fluid balance and decreased urine volume output, the use of diuretics was associated with better survival, so that the mortality benefit of furosemide in oliguric AKI patients was mediated by fluid balance (Teixeira et al., 2013; Zhao et al., 2020).

Limitations in this study include that in our study there was no randomization of furosemide administration and no control, so all septic patients with AKI were given an initial bolus of furosemide. This is because H. Adam Malik General Hospital has not been able to provide ethical feasibility in a randomized control test in the setting of this study. In addition, in our study, there is a limited research sample which makes this study have suboptimal statistical power.

V. CONCLUSION

In this study, the median blood urea nitrogen on the first day of admission to the ICU was 14 mg/dL (26 – 308), and the median on the third day of admission was 154 mg/dL (45 – 274) with data not normally distributed. The median serum creatinine on the first day of admission to the ICU was 3.35 mg/dL (1.4 – 9.47) and the median on the third day of admission was 3.89 mg/dL (1.02 – 12.70) with data not available. normally distributed. The mean urine output on the first day of admission to the ICU was 1077.88 ml/24 hours (SD 298.07) with data normally distributed. The mean urine output on the third day of admission to the ICU was 974.4 m:/24 hours (600 – 1944) with data not normally distributed. There was no significant effect of giving low-dose furosemide with the improvement of AKI and kidney function in septic patients with AKI at H. Adam Malik General Hospital. There was no significant median difference between low-dose furosemide administration and blood urea nitrogen (p=0.758) and serum creatinine levels (p=0.993) There was no significant difference between low-dose furosemide administration and urine output volume (p=0,634).

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