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Global Journal of Medical, Pharmaceutical, and Biomedical Update

Original Article

The Effects of Furosemide usage on Organ System Failure Status based on Modified Sequential Organ Failure Assessment Score in Critically ill Patient

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Received : 18 November 2020
Accepted : 01 December 2020
Published : 18 December 2020

DOI
10.25259/GJMPBU_24_2020

Quick Response Code:

ABSTRACT

Objectives: Eighty-six percent of patients administrated with intravenous fluid resuscitation had positive fluid accumulation. This resulted in fluid overload in 35% of all ICU patients in 2009–2012. Then, the worst consequence is multi-organs failures. Thus, one of the treatments is pharmacological diuresis to solve physiological problems. Despite of its adverse effects and fluid balance decrement on the hypoperfused organ, the organ failure resolution of furosemide usage has not been proven through any research. Hence, a research which analyzed the correlation of organ system failure status based on modified sequential organ failure assessment (MSOFA) score with furosemide usage on intensive care patient and their demographics data has been conducted.

Material and Methods: The research design was a retrospective cohort which analyzed 194 subjects through ICU medical records selected by consecutive sampling method. Data of furosemide usage and MSOFA score changes were recorded. Thereafter, Chi-square test was conducted to analyze the data. Moreover, characteristics of subjects were also recorded and analyzed in this study.

Results: Based on the characteristics of subjects analysis, significant factors on furosemide usage ($P < 0.05$) included total fluid changes, total fluid after therapy, organ system dysfunctions before therapy (including the respiratory and central nervous system), organ system dysfunction after therapy (cardiovascular), and MSOFA score before therapy. Very significant factors ($P < 0.001$) include total fluid before therapy, organ system dysfunction after therapy (central nervous system), and MSOFA score after therapy. There was a significant association between worsening organ system failure with furosemide usage on critically ill patients, especially in the cardiovascular and central nervous system. The relative risk result reported that furosemide usage resulted in higher MSOFA score 1.271 times more than those patients with no furosemide diuresis usage (95% CI 1.108–1.458). Furosemide usage in this research worsens organ dysfunction, especially in cardiovascular and central nervous systems.

Conclusion: The furosemide usage worsens the organ failure based on MSOFA score. Furosemide therapy should be individually adjusted, especially in those who have respiration, cardiovascular, and central nervous system dysfunction.

Keywords: Organ system failure, Modified sequential organ failure assessment score, Furosemide

INTRODUCTION

Intravenous fluid administration has been one of the most common therapies used for a critically ill patient in intensive care. However, 86% of patients got positive-balanced fluid accumulation, which led to fluid overload problems in 35% of patients in ICU in 2009–2012.[1] Moreover,

some observational researches prove the correlation between fluid accumulation increment with multi-system organ dysfunction.[1-6] It is said that every 1% fluid volume increment in fluid overload case leads to 3% chance of mortality.[3] Furosemide is one of the most potent first-line pharmacological therapy for fluid overload cases.[2-7] Diuretic has been proven to lower intra-abdominal pressure, which is one of the early pathophysiologies of fluid overload leading to multi-organ dysfunction.[8,9] The effort to excrete fluid solves the physiology problems but do not solve the main disease.[2,3,10] There is not any research proving the diuretic benefit, while organ hypoperfusion persists. Moreover, furosemide usage as the strongest diuretic has some adverse effects to the patient, including hyperuricemia, hyponatremia, hypokalemia, hypomagnesemia, hypotension, and dehydration. Hence, this research aims to analyze the correlation of organ dysfunctions status changes, shown by modified sequential organ failure assessment (MSOFA) score, with the furosemide administration on ICU patients with fluid overload.

MATERIAL AND METHODS

A retrospective cohort was conducted by analyzing secondary data from patients' medical records. The sampling method was consecutive sampling (nonprobability sampling). This research protocol had been approved by the local Institutional Review Board of Medical Faculty. This research was held in the Intensive Care Unit of a National General Hospital for 12 months.

The research samples included all of the accessible population which fulfilled inclusion criteria (17 years and above ICU patients who used fluid resuscitation therapy was having fluid overload condition based on positive fluid balance status, was using furosemide diuretic therapy for no more than 72 h, and fluid overload patients who did not use any diuretic therapy) and not suitable to exclusion criteria (patients with not complete medical record data and fluid overload patients who were indicated to use mechanic therapy). The sample size was calculated to be 194 patients for demographic descriptive data and categorical comparative hypothesis testing, divided into 97 fluid overload patients with diuretic usage and 97 fluid overload patients without diuretic usage. MSOFA score was recorded on the 1st day and the 3rd day of fluid overload diagnosis on the patients.

Dependent variable of this research is furosemide usage status on the patients, while the independent variable is MSOFA score changes after the diuretic therapy (categorized into two categories: "good" if MSOFA score decreases and "bad" if MSOFA score increases or persists).

Data were shown as frequencies and percentage for qualitative variables and mean ± standard deviation or medians for quantitative variables. To check the normality of the distribution of the data, we used the Kolmogorov–Smirnov test. Comparisons for clinical and demographic data were performed using Chi-square test, non-paired *t-test,* and Mann–Whitney U-test. Thereafter, comparative hypothesis testing to dichotomy nominal variables was conducting using Chi-square testing in SPSS Application version 20.0. $P < 0.05$ were regarded to be statistically significant.

RESULTS

Of 781 subjects of ICU patients who were eligible to the inclusion criteria of this study, 587 subjects were excluded due to not complete data and indication of mechanical therapy for fluid overload management. Hence, 194 subjects were analyzed in this study.

Clinical and sociodemographic data of the fluid overload patients are reported in Table 1. Significant factors on furosemide usage ($P < 0.05$) included total fluid changes, total fluid after therapy, organ system dysfunctions before therapy (including the respiratory and central nervous system), organ system dysfunction after therapy (cardiovascular), and MSOFA score before therapy. Very significant factors ($P < 0.001$) include total fluid before therapy, organ system dysfunction after therapy (central nervous system), and MSOFA score after therapy.

Furthermore, the association between MSOFA score changes and furosemide usage is shown in Table 2 as a 2 × 2 table. Both groups resulted in a higher percentage of patients with bad organ failure development, depicted by worsening MSOFA score changes. However, there were better MSOFA score changes in patients with no furosemide usage, compared to those with furosemide administration. Based on the Chi-square test, there was a significant association between diuretic usage and MSOFA score changes ($P < 0.05$). The relative risk value was 1.271 (95% CI 1.108–1.458).

DISCUSSION

This study reported significant association between diuretic usage and MSOFA score changes ($P < 0.05$), with a relative risk value of 1.271 (95% CI 1.108–1.458). Therefore, diuretic usage on fluid overload patient causes 1.271 times more multi-organ dysfunction than those without diuretic usages.

The inefficiency of furosemide usage in decreasing body fluid might be correlated to the theory by Shchekochikhin *et al.* about diuretic resistance. Diuretic resistance is caused by macula densa inhibition and negative body sodium balance which stimulates RAAS after diuretic administration.[11] This theory also supports cardiovascular system dysfunction caused by diuretic usage in fluid overload patients. Problem shifting from respiratory system dysfunction to

Table 1: Sociodemographic and clinical data of fluid overload patient in intensive care unit.

Characteristic variable	With furosemide (*n*=97)	Without furosemide (*n*=97)	*P*-value[a]
Gender (%)			NS
Male	47 (48.5)	54 (55.7)	
Female	50 (51.5)	43 (44.3)	
Age (years)	53.62±15.79	51.58±15.12	NS
Admission criteria (%)			NS
Surgical	43 (44.3)	56 (57.7)	
Medical	54 (55.7)	41 (42.3)	
Volume average (ml)	512.42 (−1629.20–5632.22)	605,45 (−723.14–3734.6)	NS
Fluid balance			
Before (ml)	1968.8 (−1557–25,095)	272.4 (9.1–6203)	<0.001
After (ml)	3378.6±4636.48	2279.12±2336.14	<0.05
Fluid balance change (%)			<0.05
Increased	62 (63.9)	78 (80.4)	
Decreased	35 (36.1)	19 (19.6)	
Fluid type (%)			NS
Crystalloid	44 (45.4)	57 (58.8)	
Colloid dan Cristalloid	53 (54.6)	40 (41.2)	
Transfusion (%)			NS
Yes	34 (35.1)	35 (36.1)	
No	63 (64.9)	62 (63.9)	
Vasoactive agent (%)			NS
Yes	89 (91.8)	86 (88.7)	
No	8 (8.2)	11 (11.3)	
MSOFA score before therapy	7±3	6±3	<0.05
System organ status before therapy (%)			
Respiration	96 (99)	89 (91.8)	<0.05
Cardiovascular	37 (38.1)	32 (33)	NS
Central nervous system	82 (84.5)	62 (63.9)	<0.01
Liver	30 (30.9)	21 (21.6)	NS
Kidney	53 (54.6)	45 (45.9)	NS
MSOFA score after therapy	8±3	6±3	<0.001
System organ status after therapy (%)			
Respiration	95 (97.9)	90 (92.8)	NS
Cardiovascular	59 (60.8)	42 (43.3)	<0.05
Central nervous system	89 (91.8)	68 (70.1)	<0.001
Liver	33 (34)	29 (29.9)	NS
Kidney	60 (61.9)	48 (49.5)	NS
Initial creatinine level (mg/dL)	1.3±2.03	1.13±2.09	NS
Post 3 days mechanic therapy indication (%)			NS
Yes	2 (2.1)	4 (4.1)	
No	95 (97.9)	93 (95.9)	

NS: Non-significant, MSOFA: Modified sequential organ failure assessment. [a]Result of χ^2, non-paired *t*-test, or Mann–Whitney U-test

Table 2: Association between modified sequential organ failure assessment score changes and furosemide administration.

Furosemide Usage	MSOFA score changes		Total	RR (95% CI)	*P*-value[b]
	Bad *n* (%)	Good *n* (%)			
Yes	89 (91.8)	8 (8.2)	97	1.271 (1.108–1.458)	0.001
No	70 (72.2)	27 (27.8)	97		
Total	159	35	194		

MSOFA: Modified sequential organ failure assessment, RR: Relative risk, CI: Confidence interval. [b]Chi-square test result

cardiovascular system dysfunction after therapy might be due to intra-abdominal hypertension alteration after fluid decrement.[8] However, cardiovascular system problem after therapy caused by systemic vasoconstriction after diuretic therapy (correlated to diuretic resistance theory). There is not any research which shows a correlation between furosemide usage to central nervous system dysfunction effects, although it might be caused by hypoperfusion to central nervous system after multi-organ dysfunction.[12]

For respiratory organ system effect from diuretics, a previous study by Libório *et al*., including 14,896 patients, also found that loop diuretic usage in fluid overload critically ill patients was associated with the prolonged mechanical ventilation period.[13] This is because of a serum bicarbonate level 2 mEq/L more than others, in which metabolic alkalosis could also affect the respiratory drive and minute ventilation.[14]

The result of this study is not supported by DOSE-AHF study that shows diuretic benefits on curing organ system dysfunction caused by fluid overload (including cerebral edema, pulmonary edema, myocardial edema, hepatic congestion, renal interstitial edema, and intestinal edema).[8] However, previous research supports the result of the study, stating that diuretic usage causes acute kidney injury and increases the mortality of patients with 1.68 odd ratios.[15] This is explained by apoptosis of distal tubules cells in diuretic usage. Hypokalemia induced in diuretic therapy also causes tubulointerstitial fibrosis and kidney hypertrophy. Besides, tubular necrosis is also caused by systemic vasoconstriction based on diuretic resistance theory.[11] Hence, the patient with vein hypertension caused by mesenteric vein compression might need more fluid resuscitation for tissue perfusion than furosemide therapy. Moreover, the use of diuretics in CKD patients should be carefully evaluated due to the high risk of electrolyte imbalances.[16]

Variation on timing and method of diuretics administration may also affect the effectiveness to cure fluid overload in critically ill patients. It is concluded from a previous study that loop diuretics should be given as early as possible which was associated with the lower mortality. For the method of administration, no difference was seen in the primary endpoint between continuous and bolus infusion.[17]

This study is the first research of diuretic usage on fluid overload ICU patients, evaluating the multi-organ dysfunction status of the patients. This is compared to previous studies which only evaluate specific organ system in each study. However, this research has significant confounding factors, including total fluid changes, total fluid before, and total fluid and after therapy. This may lead to an imbalance of higher MSOFA score in fluid overload patients with diuretic usage. Moreover, this research does not analyze other factors, including side effects of furosemide usage, patients' diseases, and furosemide dosage.

Furosemide therapy should be individually adjusted, especially in those who have respiration, cardiovascular, and central nervous system dysfunction. Further, the research could be conducted to analyze the right time to start diuretic therapy and the correlation between the amount of fluid change to organ dysfunction status.

CONCLUSION

From this research results, we can draw the conclusion that there is a correlation between organ dysfunction status changes and furosemide usage in intensive care patients with fluid overload condition. Furosemide usage in this research worsens organ dysfunction, especially in cardiovascular and central nervous systems. Based on relative risk result, it is proven that furosemide usage causes 1.271 times more patients with organ dysfunction worsening compared to those without any diuretics usage.

Declaration of patient consent

Institutional Review Board permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Marcevianto KV, Aditianingsih D, Pramudita E, Aristya L. The Effects of Furosemide usage on Organ System Failure Status based on Modified Sequential Organ Failure Assessment Score in Critically ill Patient. Glob J Med Pharm Biomed Update 2020;15:8.