CLINICAL INVESTIGATION

Comparative effectiveness and safety of bolus vs. continuous infusion of loop diuretics: Results from the MIMIC-III Database

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ABSTRACT

Background: It is unclear whether fluid management goals are best achieved by bolus injection or continuous infusion of loop diuretics. In this study, we compared the effectiveness and safety of a continuous infusion with that of a bolus injection when an increased loop diuretic dosage is required in intensive care unit (ICU) patients.

Methods: We obtained data from the MIMIC-III database for patients who were first-time ICU admissions and required an increased diuretic dosage. Patients were excluded if they had an estimated glomerular filtration rate <15 ml/min/1.73 m^2, were receiving renal replacement therapy, had a baseline systolic blood pressure <80 mmHg, or required a furosemide dose <120 mg. The patients were divided into a continuous group and a bolus group. Propensity score matching was used to balance patients' background characteristics.

Results: The final dataset included 807 patients (continuous group, n = 409; bolus group, n = 398). After propensity score matching, there were 253 patients in the bolus group and 231 in the continuous group. The 24 h urine output per 40 mg of furosemide was significantly greater in the continuous group than in the bolus group (234.66 ml [95% confidence interval (CI) 152.13−317.18, $p < 0.01$]). There was no significant between-group difference in the incidence of acute kidney injury (odds ratio 0.96, 95% CI 0.66−1.41, $p = 0.85$).

Conclusions: Our results indicate that a continuous infusion of loop diuretics may be more effective than a bolus injection and does not increase the risk of acute kidney injury in patients who need an increased diuretic dosage in the ICU.

Keywords: Loop diuretics; Continuous infusion; Bolus injection; Urine output; Acute kidney injury incidence; MIMIC-III database. **[Am J Med Sci 2022;■(■):1–8.]**

INTRODUCTION

Fluid overload is common in patients who are critically ill,[1] and several studies have demonstrated a correlation between fluid overload and adverse outcomes.[2,3] Conservative fluid management can improve the oxygenation index, increase the number of ventilator-free days, and shorten the stay in the intensive care unit (ICU).[4]

Loop diuretics administration is a well-established therapy that can decrease the incidence of fluid overload. Continuous infusion and bolus injection of diuretics are two methods that physicians can use to achieve their fluid management goals. However, there is still not enough evidence to indicate which strategy is better in terms of safety and efficiency. The randomized controlled Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE) study found no significant difference in patients' global assessment of symptoms or in the change in renal function in a large group of patients with decompensated heart failure, when diuretics were administered by bolus as compared with continuous infusion.[5] Other randomized controlled trials have yielded conflicting results in patients with heart failure.[6–8] However, most of the studies only enrolled

outpatients, who were very different from patients in the ICU. A recent meta-analysis reported that the beneficial effect on total urine output was greater when continuous furosemide was administered than when a bolus injection was delivered.[9] However, most of the randomized controlled trials included in that meta-analysis had small sample sizes.

Patients in the ICU have a high incidence of acute kidney injury (AKI) and are more vulnerable and more complicated to manage than the patients in a general medicine ward or outpatient. An appropriate diuretic strategy is needed to help physicians achieve their fluid management goals when a patient needs an increased dose of diuretics. The aim of this study was to compare the efficiency and safety of two diuretic strategies in a relatively large sample of patients who were admitted to the ICU based on the Medical Information Mart for Intensive Care (MIMIC)-III database.

METHODS

Data source and ethical approval

The MIMIC-III database is a publicly available dataset developed by the Massachusetts Institute of Technology Lab for Computational Physiology and includes de-identified health data for approximately 40,000 critical care patients. It includes demographics, vital signs, laboratory tests, medications and other data[10] (https://mimic.physionet.org/). The MIMIC database is approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA), and patient consent is obtained when the data are first collected. Therefore, the need for ethical approval and informed consent was waived for this study. The investigators also completed the required training course before requesting access to the database. The study was performed in accordance with the Declaration of Helsinki.

Study population and grouping

The study population comprised 6830 adult patients with data in the MIMIC-III database who had been treated with diuretics during a first ICU stay. The time of diuretic use was divided into 12 h time units, and the total amounts of diuretics used in each time unit were calculated. After comparing the amounts of diuretics used in each 12 h unit with that in adjacent 12 h units, we defined a specific 12 h period as the "start unit", namely, when the amounts of diuretics used were more than that in the previous time unit and the amounts in 24 h were more than 120 mg of furosemide (or more than 60 mg of torsemide or 3 mg of bumetanide). The beginning of this time unit was defined as the "start time". Patients whose start unit occurred during their first ICU stay were subjected to further analysis. Patients who had received renal replacement therapy for end-stage renal disease (estimated glomerular filtration rate $\leq$15 ml/min/m^2) and those with a baseline systolic blood pressure less than 80 mmHg before the start unit were excluded. In total, 878 subjects were enrolled. After exclusion of those with missing data and outliers, 807 subjects were included in the final dataset. Subjects who received continuous intravenous diuretics in "start unit" were assigned into the continuous infusion group, the others were assigned into the bolus group. For those who received both administrations of diuretics, we compared the amounts of diuretics between bolus injection and continuous infusion. And these patients were included into continuous infusion group for the diuretics were dominantly administrated by continuous infusion. A flow chart summarizing the enrollment process is shown in Fig. 1.

Data collection

Demographic characteristics

We collected demographic information, including age, gender, and the last body weight recorded before the start unit. The type of ICU was also recorded.

Vital signs

Vital signs included the most recent systolic blood pressure (SBP) and diastolic blood pressure (DBP) recorded before the start unit.

Laboratory examinations

The most recent serum creatinine, blood urea nitrogen (BUN), blood sugar, and serum sodium level recorded before the start unit were obtained. The maximum serum creatinine level recorded in the 48h after the start time was also obtained to detect changes in kidney function. Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) equation.[11]

Past medical history and risk factors

Past medical history was obtained based on the admitting diagnosis and history of hypertension, diabetes mellitus, chronic kidney disease, and chronic heart failure (CHF). International Classification of Diseases codes were used rather than information on past medical history from the notes. Severity of illness was evaluated using the Simplified Acute Physiology Score (SAPS) III value, which was based on the MIMIC-III GitHub code.[12,13]

Medications

Information on use of spironolactone, thiazide, tolvaptan, norepinephrine, milrinone, and infusions of albumin and plasma during the start unit was recorded. The amounts of loop diuretics used in the previous unit (defined as "previous diuretics") and in the 24 h after the start time were calculated.

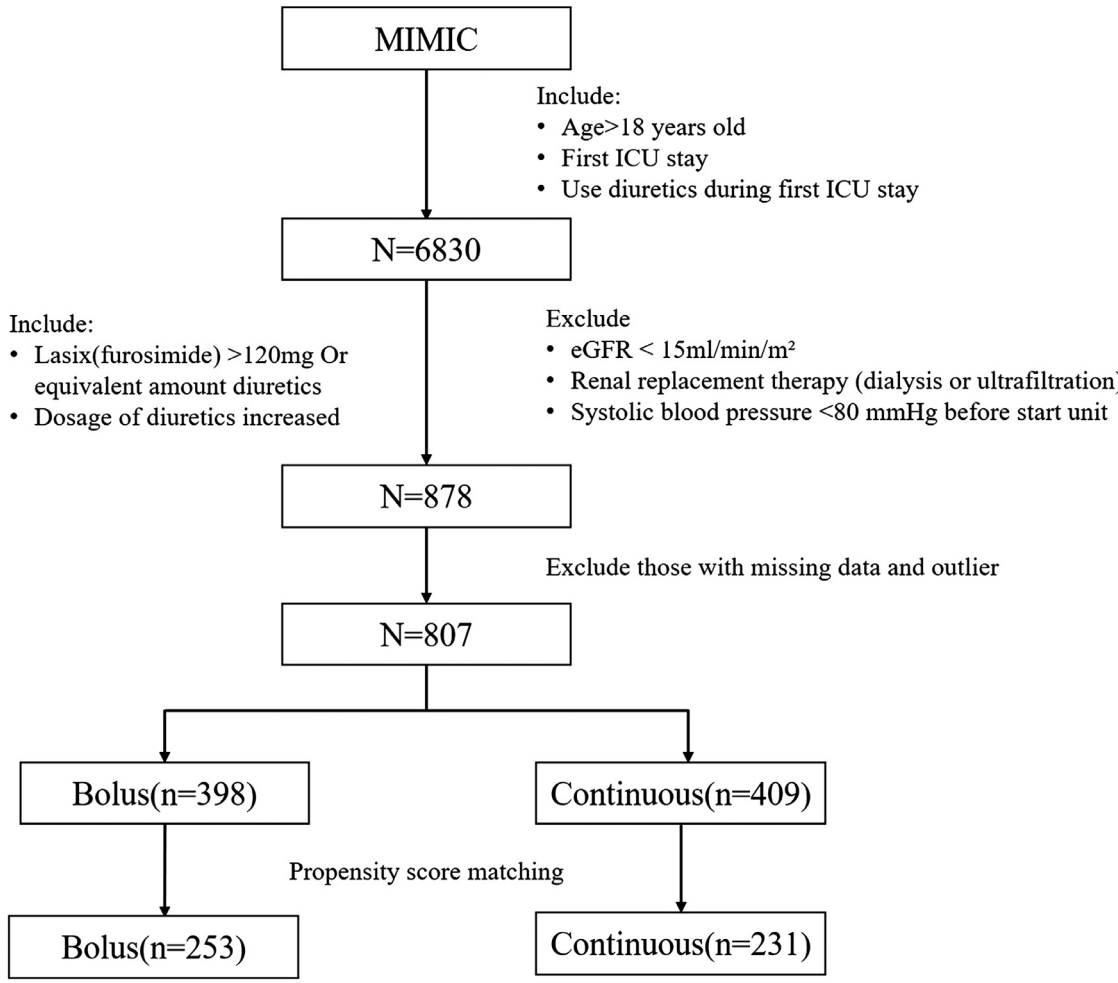

FIG. 1. Flow chart showing the enrollment and propensity score matching procedures.
Abbreviations: eGFR = estimated glomerular filtration rate, ICU = intensive care unit, MIMIC = Medical Information Mart for Intensive Care.

Endpoints

Urine output in the 24 h after the start time was extracted from the database. Urine output per 40 mg of furosemide was calculated using the following formula:

$$\frac{urine\ output(ml)}{amount\ of\ diuretics\ (mg)} \times 40$$

AKI was defined as an increase in the creatinine level of ≥0.3 mg/dl within 48 h in accordance with the 2012 Kidney Disease: Improving Global Outcomes criteria.[14]

Propensity score matching and statistical analysis

We selected variables known to influence the outcome (urine output) in clinical practice, namely, patient age, weight, and sex, SBP, serum creatinine, BUN, and sodium levels, history of chronic kidney disease, history of CHF, SAPS III value, use of spironolactone, thiazide, norepinephrine, and milrinone, infusion of albumin or plasma, type of ICU, previous diuretics and amounts of diuretics in 24h for propensity score matching. We chose 1:1 matching using nearest neighbor matching with a caliper width of 0.05 standard deviation of the logit of the propensity scores without replacement. The propensity score distribution before and after matching was shown in Fig. 2. The value of the C-statistic was 0.78, indicating that the model was of good quality. After propensity score matching, there were 231 subjects in the continuous infusion group and 253 in the bolus group.

Data that were normally distributed were shown as the mean ± standard deviation and data that were not normally distributed were shown as the median (interquartile range). Proportions were compared using the chi-squared test and means were compared using the *t*-test when data were normally distributed and the Wilcoxon test when they were not. Both linear regression and logistic regression were used in the final model. All statistical analyses were performed using STATA 12.0 (StataCorp LLC, College Station, TX, USA) and EmpowerStats software (Greenwood Village, CO). A p-value <0.05 was considered statistically significant.

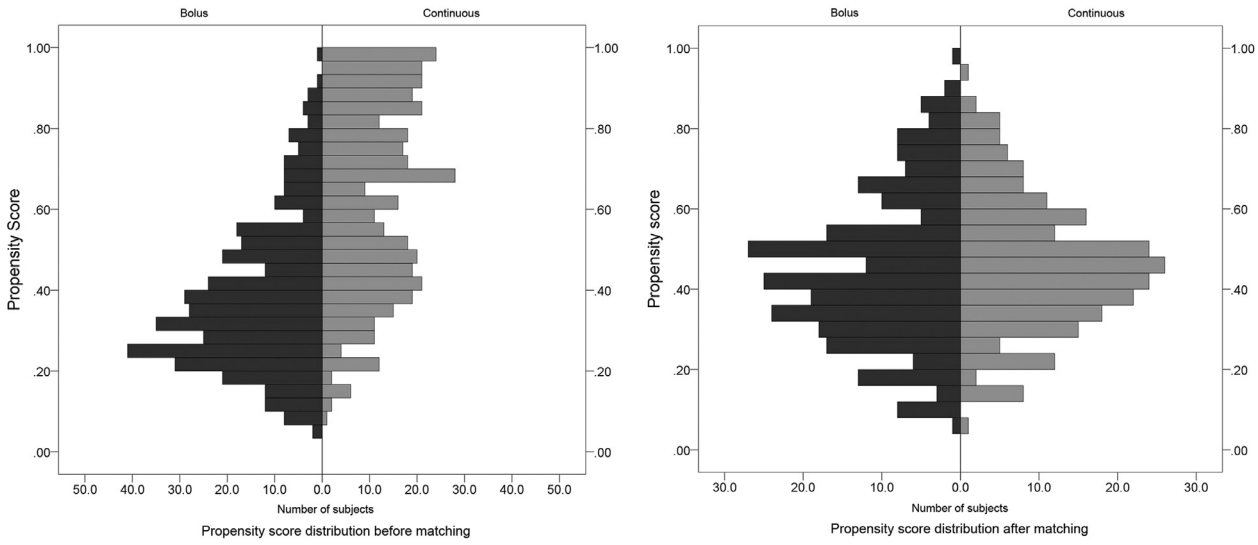

FIG. 2. Distribution of scores before and after propensity score matching in the two study groups. The x axis shows the number of subjects and the y axis shows the propensity score. The bar represents the number of subjects with a propensity score in a certain range.

RESULTS

Table 1 showed the characteristics of the two study groups before and after propensity score matching. Before matching, there were significant between-group differences in body weight, SAPS III value, SBP, serum sodium, BUN, and creatinine levels, previous diuretics, amounts of diuretics in 24h, history of chronic kidney disease, history of CHF, use of spironolactone and thiazides, type of ICU, use of norepinephrine and milrinone, and albumin level. After propensity score matching, the only significant between-group difference was in type of ICU.

Multiple linear regression was used to compare the urine output in 24h after the start time between the two groups. As shown in Table 2, after adjustment for type of ICU, the output in 24h was significantly greater in the continuous group than in the bolus group (by 930.71 ml, 95% confidence interval [CI] 655.51−1205.90, $p < 0.01$), as was urine output in 24h per 40 mg of furosemide (by 234.66 ml, 95% CI 152.13−317.18, $p < 0.01$). Multiple logistic regression showed no significant between-group difference in the incidence of AKI after adjustment for type of ICU (odds ratio 0.96, 95% CI 0.66−1.41, $p = 0.85$).

DISCUSSION

Fluid management is an essential component of health care in critically ill patients. Fluid overload, which can lead to cognitive impairment, systolic and diastolic dysfunction, reduced gas exchange, reduced renal blood flow, impaired absorption and synthesis and is correlated with a poor outcome in these patients.[1] A study by Bouchard et al. demonstrated that patients with AKI and fluid overload had increased 30-day and 60-day mortality rates.[2] Wiedemann et al. found that conservative fluid management could improve the oxygenation index and lung injury score, increase the number of ventilator-free days, and shorten the length of ICU stay in patients with acute lung injury.[4] Moreover, the Vasopressin in Septic Shock Trial demonstrated that a more positive fluid balance was associated with an decreased risk of mortality in patients with septic shock.[3]

Administration of diuretic agents, in particular loop diuretics, is the strategy most commonly used to manage fluid balance. The main side effects of diuretics are hypokalemia, hypotension, and increased serum BUN and creatinine levels. In theory, compared with bolus injection, continuous intravenous infusion may be more effective because it maintains a consistent rate of drug excretion and inhibits reabsorption of sodium chloride in the loop of Henle over time.[15] Several studies have compared the efficiency of these two strategies but no consistent conclusions have been reached. The DOSE study included 308 patients with acute decompensated heart failure and focused on co-primary endpoints of patient-reported global assessment of symptoms, quantified as the area under the curve (AUC) for the visual analog scale score, and the change in serum creatinine level between baseline and 72h. The investigators found no significant difference in patient-reported symptoms (mean AUC, 4236 ± 1440 vs 4373 ± 1404, $p = 0.47$) or in the mean change in creatinine level (0.05 ± 0.3 mg/dl vs 0.07 ± 0.3 mg/dl, $p = 0.45$) between bolus injection and continuous infusion group.[5] A study by Makhoul et al. found that urine output was higher in patients in the ICU who received diuretics via continuous infusion than in those who received the same amount of diuretics via bolus injection.[16] Furthermore, in a study by Ostermann et al., a significantly higher dose of furosemide was needed to achieve target diuresis in a bolus group than in a continuous infusion group (24.1 mg/h vs. 9.2 mg/h, $p = 0.0002$)

Table 1. Characteristics of two groups before and after propensity matching.

	Before PS matching			After PS matching		
Variables	**Bolus**	**Continuous**	***p***	**Bolus**	**Continuous**	***p***
n	398	409		253	231	
Demographic characteristics						
Age	69.95±14.84	69.35±14.34	0.56	70.05±13.85	69.97±14.65	0.95
Weight	85.37±26.23	90.76±30.27	<0.01	86.84±28.60	86.50±27.00	0.90
Gender			0.47			0.288
Male	203(51.01%)	219 (53.55%)		117(46.25%)	118(51.08%)	
Vital sighs						
SBP	119.00±14.36	112.34±13.68	<0.01	116.85±14.04	115.94±13.29	0.47
DBP	59.15±8.97	59.05±9.17	0.88	58.59±9.13	59.85±9.75	0.14
Laboratory test						
Scr	1.20(0.80–1.60)	1.40(1.00–2.10)	<0.01	1.20(0.80–1.70)	1.30(0.90–1.90)	0.16
MAX Scr	1.20(0.90–1.60)	1.60(1.10–2.20)	<0.01	1.30(0.90–1.90)	1.40(0.90–2.00)	0.54
BUN	26.50(20.00–39.75)	35.00(23.00–57.00)	<0.01	29.00(19.00–44.00)	32.00(20.00–44.50)	0.22
Na	138.91±4.76	138.11±5.27	0.03	138.58±4.97	138.91±4.82	0.45
GLU	139.97±52.82	145.90±55.77	0.12	141.16±54.76	141.81±54.21	0.90
Past history and risk factor						
Hypertension	166 (41.71%)	161 (39.36%)	0.498	105(41.50%)	90(38.96%)	0.57
DM	177 (44.47%)	191 (46.70%)	0.525	108(42.69%)	98(42.42%)	0.95
CKD	122 (30.65%)	144 (35.21%)	0.17	75(29.64%)	74(32.03%)	0.57
CHF	239 (60.05%)	288 (70.42%)	<0.01	161(63.64%)	147(63.64%)	0.79
SAPS III	50.62±19.91	54.37±19.53	<0.01	51.58±20.64	52.27±18.83	0.70
Medications						
Spironolactone	17(4.27%)	19(4.65%)	0.80	9(3.56%)	9(3.90%)	0.84
Thiazide	25(6.28%)	44(10.76%)	0.02	19(7.51%)	22(9.52%)	0.43
Norepinephrine	30(7.54%)	61(14.91%)	<0.01	24(9.49%)	27(11.69%)	0.75
Milrinone	26(6.53%)	57(13.94%)	<0.01	21(8.30%)	18(7.79%)	0.84
Infusion albumin	92(23.12%)	73(17.85%)	0.06	63(24.90%)	55(23.81%)	0.78
Infusion plasma	39(9.80%)	33(8.07%)	0.39	19(7.51%)	20(8.66%)	0.64
Previous diuretics	40.00(20.00–40.00)	60.00(37.50–100.48)	<0.01	40.00(20.00–60.00)	40.00(29.88–60.14)	0.48
24h diuretics amount	160.00(120.00–200.00)	232.06(160.11–349.93)	<0.01	160.00(120.00–240.00)	177.74(133.63–237.70)	0.18
ICU type			<0.01			0.03
Cardiac ICU	86(21.61%)	149 (36.43%)		55(21.74%)	68(29.44%)	
Medical ICU	105(26.38%)	52 (12.71%)		61(24.11%)	39(16.88%)	
Surgery ICU	162(40.70%)	149 (36.43%)		110(43.48%)	86(37.23%)	
Cardiac surgery ICU	29(7.29%)	35(8.56%)		17(6.72%)	20(8.66%)	
Trauma surgery ICU	16(4.02%)	24(5.87%)		10(3.95%)	18(7.79%)	
Endpoints						

(*continued on next page*)

Table 1. (*continued*)

Variables	Before PS matching			After PS matching		
	Bolus	Continuous	*p*	Bolus	Continuous	*p*
Urine output 24h	2685.00(1799.25−3503.75)	3309.00(2130.00−4455.00)	<0.01	2495.00(1746.00−−3455.00)	3485.00(2385.00−4840.00)	<0.01
Urine output/40mg Lasix	624.21(359.53−933.33)	544.49(288.20−959.53)	<0.01	524.00(315.62−821.67)	797.75(470.27−−1165.98)	<0.01
AKI	113(28.39%)	155(37.90%)	<0.01	85(33.60%)	77(33.33%)	0.95

AKI, acute kidney injury; BUN, blood urea nitrogen; CHF, chronic heart failure; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; GLU, serum glucose; ICU, intensive care unit; Na, serum Natrium; Previous diuretics, the amount of diuretics used in the last unit before start unit; SAPS III, Simplified Acute Physiology Score III; SBP, systolic blood pressure; Scr, serum creatinine; 24h diuretics amount, the amount of diuretis used in 24h after start time.

Table 2. Multiple linear regression between urine output and inject type[a].

Variables	β	95%CI	p
Urine output in 24h	930.71	655.51−1205.90	<0.01
Urine output in 24h per 40mg furosemides	234.66	152.13−317.18	<0.01

[a]: ICU type was adjusted in this regression model.

with no difference in the change in serum creatinine level.[17] Shah et al. investigated 90 patients in a cardiac ICU and documented significantly greater diuresis in the first 24h (p = 0.002) and a significantly shorter hospital stay (p = 0.023) in the bolus group without any significant difference in renal function.[18] Another study in patients with chronic heart failure and high-risk acute decompensation found that continuous infusion of intravenous furosemide was associated with a better decongestive effect.[19] Moreover, a meta-analysis that included nine studies for a total of 464 ICU patients concluded that continuous infusion of furosemide was associated with a significantly greater total urine output than bolus therapy with no statistically significant change in the creatinine level.[9] However, a more recent meta-analysis found no significant difference in all-cause mortality, length of hospital stay, or electrolyte disturbance between patients with acute decompensated heart failure who received furosemide by continuous infusion and those who received it by bolus injection.[20] Therefore, it is still unclear which strategy is better. One explanation for the inconsistent findings to date is that the target populations have differed from study to study. Therefore, more clinical research is needed to compare these two strategies to guide the diuretics use.

Our present study analyzed data for ICU patients obtained from the MIMIC database and demonstrated that continuous infusion of diuretics was associated with a greater urine output and more urine output per 40 mg of furosemide without an increased risk of AKI. We divided the duration of diuretic therapy into 12 h units to include patients who needed an increased dose of diuretics. Our study population comprised critically ill patients who were already on relatively high doses of diuretics and needed an even higher dose in the ICU. Given that such patients are often encountered in clinical practice, we believe that the findings of this study could be used to assist physicians with clinical decision-making. We also considered that the use of propensity score matching in this study to balance covariates that could otherwise act as confounders improves the credibility of our results. Furthermore, we used the urine output per 40 mg of furosemide to balance the effect of administration of different amounts of diuretics on urine output, which allowed us to demonstrate the sensitivity to diuretics in the two groups.

Our study included patients from cardiac, medical, general surgery, cardiac surgery, and trauma surgery

ICUs with the aim of finding a better strategy for administration of diuretics in a broad range of critically ill patients. These patients were all volume-loaded because they had already used relatively large doses of diuretics. We initially screened the main diagnosis for each patient and found that the diagnoses were too varied to be able to analyze the data on the basis of the type of disease. Therefore, we used the SAPS III value to evaluate the severity of disease in each individual patient; this could have attenuated the effect of type of disease on the endpoint to some extent. After propensity score matching, the SAPS III value was balanced between the two study groups. Mindful of the clustering effect, we included type of ICU as one of the covariates in propensity score matching and adjusted for it in the final regression model. We were unable to confirm the effect of different medical centers because the information in the MIMIC-III database is collected from a single center. Length of ICU stay and mortality were not included as endpoints in view of the large number of factors that could influence these variables, particularly the disease that prompted the ICU admission. We also calculated the incidence of hypotension and found no significant between-group difference.

In this study, we enrolled patients who had received more than 120 mg of furosemide because in clinical practice it is not usually necessary to use a continuous diuretic infusion in patients requiring a furosemide dose lower than 120 mg. Therefore, we were able to minimize the possibility of selection bias. The most important determinant of urine output is the amounts of diuretics administered. As Table 1 showed, the mean dose of previous diuretics was 40mg for bolus group and 60mg for continuous group and 24h diuretics was 160mg for bolus group and 232.06mg for continuous group. So, we included previous amounts and 24 h amounts of diuretics in propensity score model. And after propensity score matching, the difference of previous amounts and 24h amounts of diuretics between two groups were not significant, which reduced the impact to a minimum. The previous amounts of diuretics were much less than the 24h amounts, which made the carry over effect of the diuretics used prior to the start time could be ignored.

Diuretic response is defined as the capacity of inducing natriuresis or diuresis following diuretic administration and diuretic resistance means reduced sensitivity to diuretics because of the reduced natriuresis and diuresis.[21] The measurement of urinary sodium content was proven to be a good indicator for diuretic response.[22] And low natriuresis after furosemide administration was an early marker of poor diuretic response and correlated with higher NT-proBNP and higher incidence of worsening renal function at 72 h.[23] In our study, we tried to include the data of natriuresis to reflect the diuretic response. However, the data of natriuresis was barely recorded in this database.

In this study, patients who received both bolus injection and continuous infusion of diuretics were included. In clinical practice, many of the physicians preferred to using bolus injection before continuous infusion, for rapidly increasing the blood concentration of diuretics to achieve a good diuretic effect. So, we included this part of patients in our analysis. And we also excluded this part of patients and re-do the analysis to investigate the influence of this part of patients. We found the conclusions remained consistent whether we excluded patients who received both diuretic administrations or not. For patients without receiving both diuretic administrations, the characteristics of two groups in patients before and after propensity matching and regression results were showed in Supplementary Tables 1 and 2.

This study had several limitations. First, we could not include every covariate that could potentially influence urine output. We attempted to extract information on other factors that could influence diuretic efficiency, such as plasma albumin, and use of dopamine, but found that the amount of missing data was too large for these additional parameters to be included. Furthermore, we could not include specific doses of inotropes or other types of diuretic agents because of the relatively limited number of subject numbers that remained after propensity score matching. No records of hydration and perspiration could be acquired in the database. We had to not include the amount of hydration and perspiration, though they had effects on the urine output. And this might cause bias. Second, we were unable to investigate the effect of the clinical environment on urine output. Therefore, there could be some deviations. Finally, given the common belief among physicians that continuous infusion is likely to be more effective than bolus injection, continuous infusion of diuretics may have been more common used in more congestive patients. Therefore, patients with greater fluid overload would have a greater diuretic response, which may have introduced a degree of selection bias. Large cohort studies are needed to identify which diuretic strategy is better in the future.

CONCLUSIONS

When there is a need to increase the dosage of a loop diuretic in an ICU patient, continuous intravenous infusion may be more efficient than bolus injection without an increased risk of AKI. The findings of this study are drawn from a relatively large database and should provide physicians with an efficient strategy that will allow them to achieve fluid management goals in their ICU patients.

DECLARATION OF COMPETING INTEREST

None.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Haoyu Weng: Visualization, Writing – review & editing. **Yuxi Li:** Visualization, Writing – review & editing. **Xiaolu Nie:** Formal analysis. **Chunhui He:** Investigation.

Pengbin Feng: Funding acquisition, Writing – review & editing. **Fengxin Zhao:** Funding acquisition, Writing – review & editing. **Qingjie Chen:** Investigation. **Wen Sun:** Writing – review & editing. **Jie Jiang:** Writing – review & editing. **Yan Zhang:** Writing – review & editing. **Yong Huo:** Visualization. **Jianping Li:** Visualization.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjms.2022.12.013.

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