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The Effect of Furosemide in Critically Ill Adult Patients – A Narrative Review

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ABSTRACT

Fluid overload is the common condition in the critically ill patients. This associated with the increased fluid intake and inadequate elimination. The management of fluid overload is by fluid removal with Furosemide as a loop diuretic. However, the utilization of Furosemide in the critically ill reminds a polarizing subject. The purpose of this study is to investigate the impact of Furosemide on patients who are critically ill. The inclusion criteria included randomized controlled trials as well as observational cohort studies. The data sources utilized in this study were PubMed, Science Direct, ProQuest, and Cochrane. We included 13 articles, of which 9 articles about generally critically ill patients with or without acute kidney injury (AKI), 2 articles about heart failure, and 2 articles about post operative. The Furosemide was effective in generally critically ill patients with or without AKI, it can decrease the fluid balance, weight change, and improves the urine output. Furosemide had no harmful effect on kidney function. However, patients without oliguria were not recommended to receive high dose of Furosemide. Critically ill patients with heart failure who received continuous infusion of Furosemide were more susceptible to increased diuresis and greater depression of thoracic fluid content (TFC). Furthermore, it might cause the decrease of renal function. When compared to Furosemide, continuous veno-venous hemodiafiltration (CVVHDF) was more successful at removing excess fluid, reducing weight, relieving symptoms, and improving hemodynamic and cardiac performance. In post operative patients, Furosemide might cause metabolic alkalosis. Urinary electrolyte excretion rates were promptly altered by the use of low dose Furosemide. Based on the patient's clinical data, Furosemide use should be taken into consideration. In general and AKI with oliguria, Furosemide is effective to improve diuresis. However, Furosemide in heart failure might affect renal function. In post operative, it might cause metabolic alkalosis.
Keyword: Furosemide; critically ill; ICU; AKI

INTRODUCTION

In the intensive care unit (ICU), the intravenous fluid is a common therapeutic strategy for patients with critically ill. The objectives of fluid administration encompass the replenishment of hypovolemia and distributive alterations, the resuscitation and reestablishment of circulation to essential organs, and the optimization of hemodynamics (Pfortmueller and Schefold 2017; Emanuel et al. 2001). In the first hours of shock syndromes, crystalloid isotonic fluid is the first option to stabilize the arterial pressure and perfusion (Besen 2015). However, to reach physiological hemodynamic targets, intravenous fluids in large amounts may be required. The accumulation of excess fluid within the body resulting from poor fluid removal and increased fluid intake can lead to fluid overload in patients with critical illness (O'Connor and Prowle 2015). In addition, critically ill patients experience some physiological alterations, including capillary leak, and acute kidney injury (AKI) typically accompanied by oliguria. This condition frequently gives rise to the accumulation of sodium chloride and water, ultimately leading to third space extravasation (Sánchez et al. 2011). Therefore, a significant fluid overload may appear. The adverse effects of fluid overload affected various organ systems, including the central nervous system (CNS) (El-Sharkawy et al. 2014; Veiga et al. 2012) cardiovascular system, the liver, (Marik 2014; Gieling et al. 2004) the gastrointestinal tract (GIT) (Dileep N. Lobo 2004) and skin and soft tissues (Nisanevich et al. 2005; Brandstrup et al. 2003; Rahbari et al. 2009; D. N. Lobo et al. 2002). The appropriate assessment and treatment is important in early management of critically ill patients (Claure-Del Granado and Mehta 2016) The

management of fluid overload include the regulation of fluid intake and the implementation of fluid removal strategies, such as the administration of diuretics and the utilization of ultrafiltration techniques.(O'Connor and Prowle 2015) Furosemide, a loop diuretic, is commonly employed as the primary intervention for managing fluid overload in critically ill individuals. The duration of Furosemide's half-life is rather brief, often ranging from 1 to 1.5 hours. Certain studies did not recommend the utilization of Furosemide in various circumstances, including AKI, due to the potential exacerbation of the illness. However, the efficacy of Furosemide in clinical practice is frequently limited, with minimal observed benefits. Our research aims to investigate the effect of Furosemide on patients who are critically ill.

METHODS

This is a narrative review about the effects of Furosemide in critically ill adult patients. The outcomes that will be reviewed are: (1) all-cause mortality; (2) renal function; (3) diuresis; (4) electrolytes; (5) acid-base balance; (6) length of stay in the ICU and the hospital; and (7) adverse events.

Literature search and data source. Search using search engines, PubMed, Science Direct, ProQuest, Cochrane Search in PubMed and Cochrane using keyword "Furosemide, ICU". Search in Science Direct and ProQuest using keyword "Furosemide, ICU, injection, bolus, continuous"

Article selection. The inclusion criteria: adult >18 years old, the article is RCT, observational cohort prospective or retrospective; Furosemide alone compared with placebo or no intervention, other diuretics, or other pharmacological therapy, article written in English. Exclusion criteria: case control study, article that has an abstract only.

RESULTS AND DISCUSSION

Results

In this study, 13 articles were included to be reviewed. The characteristics of each article are shown in Table I. 9 articles about general critically ill patients with or without AKI, 2 articles about heart failure, and 2 articles about postoperative patients.

Discussion

Generally critically ill with or without AKI

In the multi center, RCT study by Cinotti *et al* (2021), patients who undergoing mechanical ventilation and positive fluid balance, confirms that the use of diuretics decreased the fluid balance. The safety findings indicate the absence of any known cardiac or renal safety concerns. In the retrospective cohort study by Cote *et al* (2021), were comparing the intermittent loop diuretic monotherapy, continuous loop diuretic infusion, diuretic combination, intravenous albumin. The study confirmed that continuous infusion (CI) of loop diuretic proved to be the most efficacious technique for managing the daily fluid balance, urine output (UO), as well as weight fluctuations at both the 24 and 48-hour. The efficacy was enhanced by combining thiazides or carbonic anhydrase inhibitors with loop diuretics. Nevertheless, there was an elevated likelihood of experiencing metabolic disruption. Therefore, it is necessary to implement monitoring procedures.

The study by Hamishehkar *et al* (2017) in AKI patients, was to determine the effect of Furosemide on kidney function and on gelatinase-associated lipocain (NGAL) in patients with AKI. The findings indicate that Furosemide does not have any detrimental impact on renal function in patients with AKI, suggesting its potential utility in the treatment of AKI patients. There is a prevailing belief that both plasma NGAL (pNGAL) and urine NGAL (uNGAL) are viable indicators of renal function.

The study by Lee *et al* (2017), patients in Group I was survivor's group, and Group II was for non-survivor. Group I consist of patients who still alive at least until they discharge from the ICU. The frequency of initial AKI was higher in Group II (51,1%) compared to Group I (28,9%), p 0,002); initial oliguria was higher (29,8% vs. 13,5%, p 0,003); mechanical ventilation was higher (85,1% vs. 35,1%, p 0,0001); and more CRRT was needed (27,7% vs. 3%, p 0,0001). A relationship was discovered between the death rate in the ICU and the use of high-dose Furosemide as an initial treatment in

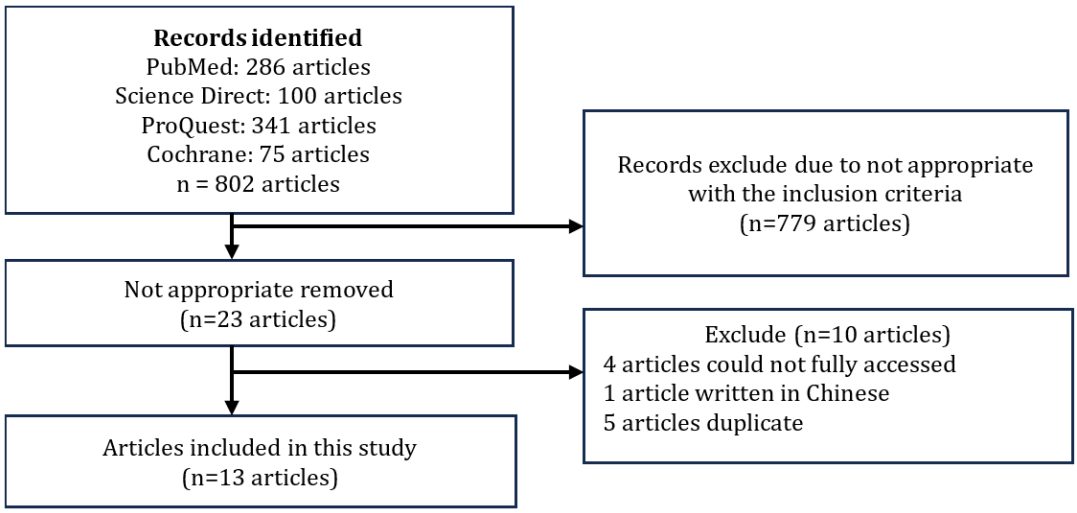

Figure 1. Flowchart of article selection

critically ill patients. The administration of high dose Furosemide to patients who did not exhibit oliguria was found to have the most detrimental effects.

In the study by Ostermann *et al* (2007) in 59 pulmonary edema, or clinical sign of volume overload patients, confirmed that the use of intermittent bolus Furosemide have the same diuresis effect with CI in the first 24 hour. The bolus Furosemide significantly (p 0,0002) need greater dose to achieve target diuresis compared with the infusion. The outcomes of changes in serum creatinine, estimated GFR, 30-day mortality rate were similar in the intermittent bolus and CI. The average duration of ICU stay was shown to be significantly higher in the CI group compared to the bolus group. Based on Furosemide's mechanism of action, the response to Furosemide depends on the amount of drug that reaches the site of action on the thick ascending loop of Henle. The lessened effect of the bolus group in this study may be attributed to the rapid decline in effective concentration and its inability to attain the threshold required to inhibit the reabsorption of sodium ions.

The study by Bagshaw *et al* (2017) in early AKI patients, findings indicated that the administration of Furosemide infusion among critically ill patients experiencing early AKI did not result in a decrease in the occurrence of AKI worsening. However, the administration of Furosemide resulted in a lowered cumulative fluid balance, improved kidney recovery, shorter time to recovery, decreased ICU and hospital mortality rates, lower mortality at 90 days, and a lower incidence of receiving RRT or death at 90 days, but these differences did not reach statistical significance.

In the study by Berthelsen *et al* (2018) in AKI patients were allocated into Group I underwent forced fluid removal, while Group II received standard medical treatment and underwent CRRT. The administration of Furosemide, either alone or in conjunction with CRRT, has demonstrated potential efficacy in achieving a negative fluid balance of 1 mL/kg ideal body weight (IBW) per hour in critically ill patients in the ICU who are experiencing AKI.

The study by Li *et al* (2023) determined the outcome in patients with sepsis-associated acute kidney injury (SAKI). The study showed that patients with SAKI receiving RRT had a net positive fluid balance, but Furosemide therapy was only given to 991 patients (59.6%). The results showed patients receiving Furosemide therapy exhibited reduced fluid retention, decreased in-hospital mortality rates, extended periods without renal replacement therapy, and prolonged periods without the need for mechanical ventilation in comparison to the group not receiving Furosemide.

The study by Zhao *et al* (2020) found that Furosemide reduced short-term mortality in critically ill AKI patients. Furosemide has the potential to facilitate the recovery of renal function. In theory, the prevention of AKI could involve the reduction of GFR and workload of the tubular system,

ble I. The characteristic and the outcome of each study

Study	Design	Setting	Intervention and Comparation	Duration of Intervention	Outcome
ndawy nd Fahmy 012	RCT	ICU	Group I: FU CI Group II: CVVHDF	72 h	**Weight loss;** FU= 3,7±3,2**;** CVVHDF= 6,3±3,5*. **LOS in ICU (d);** FU= 19 CVVHDF=12±6*. **30-days mortality rate (%) (NS);** FU=25**;** CVVHDF= **Dialysis dependence at discharge from hospital (%) (NS);** FU=6, CVVHDF= 5,88**. Fluid output:** CVVHDF significantly greater than (p≤0,01)**. CO and SV**: Both groups vs baseline, significantly increase and SV at 72 hours.
gshaw et 2017	RCT (pilot, multicenter)	ICU	Group I: FU Group II: Placebo	48 h	**FU; Placebo** **Worsened AKI (%) (NS):** 43,2; 17,1. **Cumulative fluid balance (NS):** -1081 (-2697 to 467). **Kidney recovery (%)(NS):** 29,7; 42,9. **Time recovery (h) (NS):** OR 4 (-33,5 to 19,4). **Received RRT (%)(NS):** 28,6. **ICU death (%) (NS):** 8,1; 17,1. **Hospital death (%)(NS):** 8,1; 1 **Mortality at 90 days (%)(NS):** 21,6; 30,5. **Received RRT or death 90-days (%)(NS):** 46; 54,3.
rthelsen al. 2018	Pilot RCT (unblinded)	ICU	Group I: FFR with or without CRRT Group II: CRRT	5 days	**The cumulative fluid balance at the time of patient's discharge up death** or day 5, mean ± SD. Group I= -8434 ± 3487; Group II= -641 ± 36 p<0,01. **90-days mortality,** % Group I= 29; Group II= 46; p 0,64
notti et 2021	Multicenter, single-blind, RCT	ICU	Group I: FU Group II: Baseline FU	24 h	**Fluid balance:** Group I (mean difference=− 4.8 CI95 (−7.3 to −2 p<0.001). **Invasive mechanical ventilation (day):** Group I:12(8–2 Group II:14(8–22). **Ventilatory-free days on day-60 (days)**: Group I: (37–57); Group II: 51 (32–56). **Correlation between weight a diuresis** (r^2=−0.43, p<0.001). **Died in ICU (%)**: Group I: 14; Group II: **Safety:** Hypokalemia (%): Group I: 68.8; Group II: 57.3. Duration hypokalemia (day): Group I: 1 (0–4); Group II:1 (0–2). Atrial fibrillat (%): Group I: 17.1; Group II: 19.1. Worsening of AKI (%): Group I: 5 Group II: 75.3; p=0.3.

le I. (Continued)

Study	Design	Setting	Intervention and Comparation	Duration of Intervention	Outcome
nnor et 2020	Observational (Prospective, single center)	Surgical ICU	Group I: CI of FU Group II: No diuretic	72 h	**Baseline; Day1; Day 2; Day 3** **Na:** 141(136–143); 141(134.5–143.5); 141(136.5–145);138 (135 144.5);p 0,371. **K:** 4.3(4–4.8); 4.2(3.7–4.6); 4.1(3.6–4.4); 3.9(3.5–4.2) 0,004. **Cl:** 105(101.5–111.5); 101(97–109); 101 (97.5–111); 99 (9 109.5); p 0,013. **pH:** 7.41 (7.35–7.43); 7.44 (7.35–7.47); 7.44 (7.4–7.4 p 0,032. **PCO2:**50(41.75-52);47(41–53);45(42.5–51.3); p 0,6 **HCO3:**28(26.3-33.3);29(25.5-33.8); 30.5(27-34.8); p 0,180. **BE:** 1.5 (8.3); 4.5 (-1–9.3); 6.5 (2–9); -; p 0,250. **SID:** 44.8 (42.3–47.3); 48.9 (45 49.8); 49.1 (45.6–52.5); 50.8 (44.5–53.3); p 0,001
té et al. 21	Observation al (retrospecti ve, cohort)	CCU, MICU, SICU	I: Intermittent FU monotherapy; II: CI of FU; III: Diuretic combination; IV: IV albumin	24 h	**Dose** above the lowest dose 1,0-2,0mg/ kg day has a greater 24-h compared with the lowest dose (p<0,001). **CI** group: higher 24-h (p<0,001); lower 24-h fluid balance (p<0,001); greater weight loss at 2 h (p<0,001). **Hyponatremia**: frequent when receiving thiaz combination; higher dose of FU; carbonic anhydrase inhibitor; and **Acid base:** Combination: carbonic anhydrase reduce serum bicarbon levels over a 24-hour period. MRA combinations: a significant decrea in serum bicarbonate levels at the 24-hour
mishehk et al. 17	RCT	ICU	Group I: FU Group II: Non-FU	7 days	**FU;Non-FU** **Cr** (mg/dL); day 1: 2,6±0,5; 2,8±0,3, p 0,04; day 3: 2,8±0,9; 3,2±1,2 0,14; day 7: 2,6±1,1; 3,1±1,7, p 0,055. **BUN** (mg/dL): day 1: 46,3±9 41,7±5,7; p 0,04; day 3: 57±20,6;54,4±18,3;p 0,49; day 7: 57,2±34 58,8±32,5; p 0,8. **uNGAL** (ng/mL); day 1: 63,3±9,9; 60,7±9,6; p 0,19; d 3:52,7±20,5;53,6±17,2; p 0,82; day 7: 41,1±27,5;45,6±28,3; p 0, **pNGAL** (ng/mL): day 1: 114,2±26,6; 131±22,9; p=0,00; day 110,3±31,4; 124,4±35,9; p 0,04; day 7: 93,1±50,1; 111±47,4;p 0,07
e et al. 17	Retrospecti ve	MICU	Group I: SUR Group II: Non-SUR	NR	- Total dose of FU: Group II > Group I; p<0,001 - Positive fluid: Group II > Group I; p<0,0001

le I. (Continued)

Study	Design	Setting	Intervention and Comparation	Duration of Intervention	Outcome
et al. 23	Observational (retrospective, cohort)	ICU	Group I: FU Group II: Non-FU	72h	**In-hospital mortality** Group I < Group II (OR 0,77;95% CI 0,0 0,93;p<0,05). **Hospital stays**: Group I > Group II; p<0,001. **ICU st** Group I > Group II; p<0,001. **RRT-free time:** Group I > Group II; p<0,0 **Ventilator-free time:** Group I > Group II; p<0,001
termann al. 2007	RCT	MICU, SICU	Group I: FU bolus Group II: FU CI	24h	**Diuresis**: Group I and II: 5,4 and 5.3 liters; p = 0,64). **Dose of FU**: Gro I: 24.1±19.26 mg/h; Group II: 9.2±5.05 mg/h; p = 0.002. Urine volume dose of FU: Group II > Group I: p = 0.014
gab et al. 18	RCT	ICU	Group I: CI of FU Group II: Bolus FU	72 h	The D TFC_1: Group I: 10 (6.3–14.5) kX^1. Group II: 7(3.3–9.8) kX^1, p 0, The D TFC_2: Group I: 8 (6–11) kX^1; Group II: 6 (3.3–8.5) kX^1, p 0,02.
zzeron et 2016	Observational (Retrospective)	Surgical ICU	Group I: FU single dose; II:longterm; III: multiple	8 h	**Decrease in hospital mortality** (HR 0,63;95% CI 0,58-0,69; p<0,001 **Decrease 90-days mortality** (HR 0,66;95% CI 0,61-0,70;p<0,001). **Enhance the restoration of renal function** (HR 1,29; 95% CI 1,21 – 1,38; p<0,001). FU correlated with an extended LOS in ICU (HR 1,44; 95% CI 1,28-1,62; p 0,003) and hospital (HR 1,37; 95% CI 1,12-1,68)
ao et al. 20	Observational	ICU	Group I: FU Group II: Non-diuretic	48 h	**Before; After** **pH;** 7.43 (7.40–7.46); 7.46 (7.43–7.48); p 0,014. **PaCO2 (mmHg):** (38–43) ; 41 (39–45); p 0,36. **HCO3 (mmol/L):** 26.6 (25.3–28.3); 2 (28.5–30.6); p 0,002. **BE (mmol/L):** 2.2 (1.5–4.6); 5.5 (4.2–6.8); p 0,0 **SID (mmol/L):** 31 (31–33); 35 (34–36); p 0,012. **Na^+ (mmol/L):** 1 (135–142); 140 (137–141); p 0,36. **K^+ (mmol/L):** 3.7 (3.5–4.4); 3.8 (3 4.2); p 0,92. **Cl^- (mmol/L):** 110 (106–111); 106 (105–109); p 0,0 **Lactate (mmol/L):** 0.9 (0.7–2.2); 1.0 (0.7–1.2) ; p 0,24

ontinuous Infusion; FU=Furosemide; IV=Intravenous; CRRT=Continuous Renal Replacement Therapy; ICU=Intensive Care Unit; IV=Intravenous; SIRS=Systemic Inflamma onse Syndrome; CO=Cardiac Output; SV=Stroke Volume; NS=Not Significance; Na=Natrium; K=Kalium; Cl=Chloride; BUN=Blood Urea Nitrogen; pNGAL= plasma gelatinase-assoc ain; uNGAL= urine gelatinase-associated lipocain SAKI=Sepsis Associated Acute Kidney Injury; FFR=Forced Fluid Removal; SUR= Survivor

Prasad 2000; Peixoto 2016). The previous studies and KDIGO clinical practice guidelines for AKI did not recommend the use of diuretics in AKI management (KDIGO, 2012). However, it is necessary to perform a more comprehensive analysis of the impact of Furosemide on various subsets of individuals with AKI. In this study, 7244 (82%) patients had AKI due to oliguria, and this is the main consideration for clinicians to use diuretics Furosemide demonstrates a favorable impact in mitigating the fluid overload, resulting in a reduction of positive fluid balance to a degree categorized as stage 2-3, but not helpful in AKI SCr stage 2-3 and CKD. Furosemide associated with longer LOS in ICU and hospital.

Heart Failure

In the study by Badawy and Fahmy (2012), in stages III to IV CHF (NYHA), with edema in the lower limbs patients. The experimental group receiving Furosemide, an initial intravenous loading bolus of 1 mg/kg Furosemide was provided, followed by a CI of Furosemide at a rate of 20 mg/h. To sustain a UO of N1 mL/kg per hour, it is possible to augment the rate of Furosemide CI. The findings indicated that there was a more quicker improvement in the heart functions of patients belonging to the CVVHDF group. The findings for LOS in the intensive care unit (ICU), total fluid output, and weight loss, which were shown to be considerably higher in the CVVHDF group. The study by Ragab *et al* (2018) in acute decompensated heart failure (ADHF) was analyzed. The administration of CI of Furosemide resulted in a significant reduction in thoracic fluid content (TFC) within the initial 48 hours. In summary, the findings of this study indicate that the utilization of CI of Furosemide in ADHF may improves diuretic effects and more pronounced reduction in TFC levels. Nevertheless, it is crucial to acknowledge that this particular methodology could potentially result in a deterioration of renal function.

Postoperative

The study of Connor *et al* (2020), 10 patients who clinically stable, underwent general, vascular, or liver transplant surgery, showed the effect of CI Furosemide compared with no diuretic. During the 72-hour trial period, the administration of Furosemide through CI resulted in improvements in base excess (BE), pH, and plasma strong ion difference (SID), while simultaneously reducing plasma chloride levels. The etiology of this metabolic alkalosis can be attributed to the depletion of chloride ions and an elevation in plasma SID. Metabolic alkalosis is a common ailments among critically ill patients in the ICU. The condition is commonly characterized as either chloride responsive or chloride resistant, primarily observed within ICU) (Guffey et al. 2018). Chloride responsive is condition which referred to chloride-depletion metabolic alkalosis, it is caused by the large of volume excretion of ion chloride because of Furosemide administration (Adrogué and Madias 1998; Webster and Kulkarni 1999).

The retrospective analysis conducted by Zazzeron *et al* (2016) in the setting of postoperative major surgery. Furosemide at low doses promptly alters the rates of excretion of electrolytes in urine. The study indicated the utilization of real-time urinary electrolyte monitoring as a means to assist patients undergoing diuretic and hemodynamic therapy.

CONCLUSSION

This study offers additional information on the effectiveness and safety of Furosemide administration in critically ill patients. The consideration of Furosemide administration should be dependent upon an evaluation of the patient's clinical data. Furosemide has demonstrated efficacy in critically ill patients, irrespective of the occurrence of AKI. Its administration has been associated with reductions in fluid balance and weight, as well as improvements in UO. There is little proof to suggest that Furosemide has any detrimental impact on renal function. Furosemide is not advisable to administer high-dose Furosemide to patients who do not have oliguria. In heart failure patients may develop enhanced diuresis and a more depression of the TFC when they are administered CI of Furosemide. Nevertheless, it is possible that it could result in a decline in renal function. CVVHDF has been found to have superior efficacy in terms of fluid evacuation, reducing weight, relieving symptoms, and improving hemodynamic and cardiac performance. In postoperative patients,

Furosemide has the potential to induce metabolic alkalosis. The administration of low-dose Furosemide promptly alters the rates at which electrolytes are excreted in urine. Monitoring diuresis, electrolytes, and acid-base status are required when administering Furosemide.

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