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FUROSEMIDE RESPONSE TO INCREASED NGAL VALUES AS A PREDICTOR OF AKI DEVELOPMENT IN ICU PATIENTS

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Abstracts

Background: Response to furosemide (FR) is a parameter that measures the effectiveness of furosemide in increasing urine production. Although the dose of furosemide given varies, FR has proven to be effective as a predictor of progression (AKI), even in patients with high plasma NGAL levels. **Objective:** To determine the response of furosemide to increasing NGAL values as a predictor of AKI development in ICU patients. **Method:** Using specific keywords, a comprehensive search for potential articles was conducted on PubMed, Europe PMC, and ClinicalTrials.gov with inclusion criteria for AKI patients treated in the ICU, cohort, case control, and randomized or nonrandomized clinical trial designs, in English which was published from January 2017 to June 2023. **Results:** Two research results were obtained with a total of 201 patients. It was found that NGAL was able to predict the development of AKI up to stage 3. Furosemide therapy did not have a significant effect on increasing the renal biomarker NGAL ($p<0.05$). **Conclusion:** This study concluded that furosemide therapy did not provide a positive or negative response to NGAL, however furosemide administration reduced mortality in AKI patients...

Keywords: Furosemide; NGAL; AKI; Sepsis.

INTRODUCTION

Acute kidney injury (AKI) is an important complication in hospitalized patients accounting for 10-15% of all admissions and in patients in intensive care units (ICU) where the prevalence can sometimes exceed 50% (1). In fact, it is a disease with a high prevalence in the Intensive Care Unit (ICU) and is closely related to mortality and disability rates. This disorder is generally characterized by a sudden decrease in kidney function which disrupts metabolic, electrolyte and fluid balance over a period of several hours to days. The spectrum of AKI is broad, ranging from small changes in the levels of biochemical markers of renal function to renal injury that is particularly pronounced in the initiation of renal replacement therapy (2).

According to global epidemiological studies, the largest burden of AKI at 85% is found in low and lower-middle-income countries. Every year, around 13.3 million people worldwide are estimated to suffer from AKI, with 10 to 15% of them dying (3). The incidence of AKI in hospitals is around 26.8 per 1000 inpatients (4). The most common cause of AKI in critical patients is sepsis. AKI caused by sepsis has a worse prognosis than non-septic disease. Acute kidney injury (AKI) occurs in 40–50% of septic patients and mortality increases six to eightfold (5).

Prediction of the progression of AKI from mild to severe is clinically important. First, early initiation of renal replacement therapy prevents the development of AKI, although currently there is no consensus on when to initiate renal replacement therapy.

Second, AKI is based on changes in serum creatinine concentration, but it is known that changes in creatinine levels have many influencing factors and diagnosis is usually quite late if waiting for high SCr results (2). AKI is defined as increased serum

creatinine (SCr) and/or lack of urine output such as as described by the Global Kidney Disease (KDIGO) guidelines. SCr is a marker of renal function with some limitations related to age, sex, diet and muscle mass and SCr increases only when 50% of the glomerular filtration rate is lost.

Neutrophil gelatinase-associated lipocalin (NGAL), a 25- kDa protein, is one of the biomarkers of AKI. NGAL messenger RNA expression in the kidney and NGAL protein levels in plasma and urine increase after ischemic injury to the kidney. This increase in NGAL protein is also observed in sepsis, with increases in plasma and urine levels (6).

The Furosemide Stress Test (FST) is a simple tool to identify the AKI population for the development of AKI and the need for Renal Replacement Therapy (RRT), diagnostic FST in the prediction of better RRT in the early AKI population 10. Furosemide has been used for decades.

Its pharmacodynamics, pharmacokinetics, and side effects are well described in patients with chronic kidney disease or nephrotic syndrome, but less data are available regarding its effects in AKI patients. When administering furosemide, a urine output of less than 1200 ml one day after coronary artery bypass surgery is more likely to cause AKI, with a specificity of 97.93% (7).

Standard FST protocol, where patients who have not received diuretics receive 1-1.5 mg/kg furosemide with a urine output of 200 ml within 2 hours after administration as a standard measurement value. In subjects with normal renal function or mild AKI, infusion dose and creatinine clearance are major determinants of diuretic response (8).

Detection of AKI with specific biomarkers in ICU patients after cardiac surgery and abdominal surgery. Patients at risk of AKI are identified and intervention is guided by biomarkers of better AKI outcome (9). Specific treatment for AKI currently receives little special attention and only supports supportive therapy. Prevention is therefore of utmost importance, and relies on early identification of patients at high risk for the development of AKI early in intensive care unit (ICU) admission.

Mostly in the ICU, AKI is assessed by looking at the response or lack of response to furosemide administration, this is a clinical assessment of renal tubular function.

Furosemide is excreted from the blood into the urine via the proximal tubule by the organic anion transporter and inhibits the luminal sodium transporter in the loop of Henle from the urinal lumen. If administration of furosemide increases urine output, it can be assumed that the tubules are functioning (10).

Furosemide responsiveness (FR) is determined by urine output after administration of furosemide. Despite administering different doses of furosemide, FR showed favorable effectiveness for predicting the development of AKI even in patients with high plasma NGAL levels.

This suggests that the combination of FR and other biomarkers can stratify the risk of developing AKI, clinically evaluated as the furosemide stress test (FST) to predict the development of acute kidney injury (AKI) (11).

Research conducted by Jayakrishna Murthy S et al. demonstrated that urine output 2 hours after high-dose intravenous furosemide (furosemide stress test; FST) was sensitive in predicting AKI progression to stage 3 in patients with early CKD.

And to better stratify the risk of developing AKI, a combination of functional and renal damage biomarkers is highly recommended. This study explains that the furosemide test can predict the severity of AKI based on urine output (7).

Research conducted by Maatsuraa et al. of 95 AKI patients who received furosemide therapy, it was found that 18 patients developed stage 3 AKI within 1 week. When the plasma NGAL level was <142 ng/mL, only one patient progressed to stage 3 AKI, indicating that plasma NGAL measurements were sufficient to predict the development of AKI.

However, the results of evaluating the performance of FR in 51 patients even with high plasma NGAL levels > 142 ng/mL with an AUC of 0.84 (0.67-0.94), the development of AKI was good. So it can be concluded that the combination of furosemide and the NGAL biomarker can better predict the development of AKI (12).

METHODS

Eligibility Criteria

This systematic review and meta-analysis includes observational research and clinical trials. Meta-analysis is a formal, quantitative, epidemiological study design used to systematically assess previous research (13). One of the characteristics of meta-analysis research is that the data already exists.

Data taken from the results of relevant research that already exists and has been previously tested, scientifically published on a particular topic and related to the research question being conducted.

Systematic Literature Review or what is called SLR is a systematic literature review aimed at identifying, evaluating and interpreting the findings of primary studies (14).

The study protocol of this systematic review and meta-analysis was registered with PROSPERO (CRD42021258750). Based on the research objectives, the research questions in this systematic review are as follows: P: Populations – AKI patients in the ICU with increasing NGAL values; I: Interventions - furosemide therapy; C: Comparator/Control - group of patients who did not receive furosemide therapy Outcomes – AKI criteria (improvement, RRT or death)

Research Characteristics

This research involves cohort research, case-control, and randomized or non-randomized clinical trials. All research other than original research articles (review articles or correspondence), cross-sectional, case-series or case report studies, research other than in English, research on young populations <18 years old were excluded from this study.

Data collection

The following are the steps in collecting data in this research, including: (1). Identifying research questions (meta-analysis research questions); (2) develop a protocol (initial step) for meta-analysis research; (3) determine the location of the search data base for relevant research results as the search area (for example, SINTA, ERIC, Google Scholar, digital repository); (4) selection of relevant research results; (5) selecting quality research results; (6) Data extraction from individual/individual/independent

studies; (7) synthesizing relevant research results with meta-analysis; (8) presenting relevant research results in the form of a research report.

Quality Assessment in Research

The quality of each selected article in the research is assessed independently by researchers and other people. The quality of research using clinical trials methodology will be assessed using the modified Jadad scale.

The score for each article can range from 0 (lowest quality) to 8 (highest quality). A score of 4-8 indicates well to very good quality and 0-3 indicates poor to low quality. Critical appraisal was performed by one reviewer and verified by another reviewer.

This scale consists of several assessment items, namely: (1) Assessing the randomized design, (2) Blinding assessment, (3) Withdrawal and dropout, (4) Inclusion and exclusion criteria, (5) Adverse impacts, (6) Statistical analysis. The quality of non-randomized studies (case-control and cohort) was assessed using the Newcastle-Ottawa Scale (NOS).

Assessment is based on three main perspectives, namely: (1) selection; (2) group comparability; and (3) exposure or outcome determination for cohort studies. A maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for results can be awarded to each individual study, for a maximum total of 9 stars per study.

RESULTS

The research results based on searches in databases obtained 2210 studies. After duplication screening, 1532 studies were obtained. A total of 1496 studies were excluded after screening of titles and abstracts, as well as studies that did not meet the inclusion and exclusion criteria.

There were 36 full-text research articles evaluated, of which 20 articles were excluded because they did not have research results, 11 studies did not have a control group or comparison group, 2 articles did not have criteria for the output that was discussed in the research.

In this study, a systematic review was carried out on 2 articles with a total of 201 patients. The research design of the 2 articles consisted of prospective cohort studies and randomized clinical trials (RCT).

The research results show that in both articles with a total of 201 respondents, patients received furosemide intervention during treatment. A total of 95 respondents received 10mg and 106 patients received 40-80mg. The research results explain that NGAL is able to predict the development of AKI to stage three.

However, another article explains that furosemide therapy does not have a significant effect on the renal biomarkers BUN, Cr, and NGAL. However, Hamishehkar40's research showed that furosemide did not have a positive or negative effect on NGAL. This result is the opposite of research conducted by Matsuura.

However, administration of furosemide reduces mortality in AKI patients, although not significantly.

This can be seen in the following table:

Table 1: Research Characteristics of Furosemide Response to Increased NGAL Values as a Predictor of AKI Development

Study	Sample	Design	Output	Furosemide	Control	Development
Matsuura (2018)	95	*Prospective cohort*	*Furosemide Respond;* NGAL; AKI *progression to stage 3*	10mg intravenous while in ICU Before going to ICU 25MG	Without administration of furosemide Standard therapy	FR 0.88(0.75-0.95)3.9 mL/mg/2 h Plasma NGAL 0.81 (0.68–0.89) 199 ng/mL, FR 0.87 (0.73–0.94) 3.9 mL/mg/2 h PNGAL 0.80 (0.67-0.88)199mg/mL Plasma 18 patients experienced AKI stage 3 within 1 week
Hamisehkhar (2017)	106	*Randomized clinical trial (RCT)*	PNGAL BUN, Cr, PNGAL and Urinary NGAL. kem	40–80 mg IV furosemide followed by 1–5 mg/hour infusion	Without administration of furosemide Standard therapy	Patients' serum blood urea nitrogen levels increased in both groups but significantly only in the control group (P = 0.009). Plasma and urine NGAL decreased significantly (P < 0.05) in both groups. The 28-day follow-up mortality findings revealed that 20% and 28% of patients died in the furosemide and control groups, respectively. NGAL was not found to reflect positive or negative effects of Furosemide in patients with AKI.

DISCUSSION

AKI is common in critically ill patients in the ICU. The mortality rate of AKI is high and AKI is also an independent risk factor for death in critically ill patients (15). The kidney function of AKI patients can be reduced significantly in a short time, and their inability to excrete metabolites and instability of the internal environment. The diagnostic criteria used to identify AKI are: sudden changes in kidney structure or function within 48 hours, with an increase in SCr content greater than 26.4 μmol/l or 50% of the baseline value; urine output below 0.5 ml/(kg·hour) for more than 6 hours, and not due to dehydration or obstructive nephropathy.

A systematic review and meta-analysis found that there was a furosemide response to the stages of AKI as seen from the NGAL value. The NGAL value is able to predict the development of AKI. Identify potential AKI progression to initiate early intervention (more invasive monitoring and RRT) before complications worsen and become life-

threatening. Several AKI biomarkers, including TIMP-2/IGFBP-7, IL-18, and plasma NGAL, are used to predict the development of AKI (16). Neutrophil gelatinase-associated lipocalin (NGAL) is released from renal tubular cells from neutrophils during inflammation. NGAL has been considered the most determining biomarker of acute kidney injury (AKI). NGAL is very stable, making it easy to detect in serum. Under normal conditions, low levels of NGAL expression can be detected in various tissues (lung, kidney, colon, and stomach). High expression levels of NGAL can be induced by cell apoptosis after epithelial cell damage. Several experimental and clinical studies have shown that urinary and serum NGAL values are significantly increased in AKI. In particular, urinary NGAL levels are closely related to the severity of kidney injury, and can be detected earlier than other markers of AKI. Therefore, NGAL has good potential as an effective biochemical marker of early AKI. Research conducted by Andriani et al. explained that plasma NGAL has a sensitivity of 88%, specificity of 81%, positive predictive value of 88%, negative predictive value of 81% and accuracy of 85%. Plasma NGAL examination is more sensitive and specific than serum creatinine examination (6).

The results of other studies showed that serum NGAL levels in the observation group were significantly higher than those in the control group at 2, 8, 12 and 24 hours after surgery ($P<0.05$). The possible mechanism for this phenomenon is that it stimulates renal tubular epithelial cells causing an increase in NGAL expression. NGAL can be absorbed by renal epithelial cells in regulating the expression of apoptosis-related proteins, which in turn promotes cell maturation and induces granulocyte apoptosis (17). Another study described NGAL in early diagnosis, the area under the AKI curve was 0.904, the sensitivity was 90.2% and the specificity was 89.5%; for CysC at early diagnosis, the area under the AKI curve was 0.806, the sensitivity was 79.2% and the specificity was 78.5%; for SCr at early diagnosis, the area under the AKI curve was 0.634, the sensitivity was 64.2% and the specificity was 62.5%. Therefore, NGAL shows satisfactory early predictive value for AKI and can be used as a biomarker for early AKI diagnosis. NGAL is an early predictor of AKI in a heterogeneous adult ICU population. Plasma NGAL allows diagnosis of AKI 48 hours before clinical diagnosis based on RIFLE criteria. Early identification of high risk in AKI patients may allow earlier initiation of therapy and improve patient outcomes (18).

Furosemide causes greater water loss than sodium loss, resulting in the production of hypotonic urine. Apart from that, loop diuretics also cause increased excretion of potassium, calcium and magnesium by inhibiting passive reabsorption of ions (19). Furosemide is excreted from the blood into the urine via the proximal tubule by organic anion transporters and inhibits diluminal sodium transport in the loop of Henle from the urinal lumen. If administration of furosemide increases urine output, it can be assumed that the tubules are functioning properly. Koyner et al., demonstrated that urine output 2 hours after intravenous injection of furosemide (furosemide stress test; FST) was sensitive in predicting AKI progression to stage 3 in patients with early AKI27. Research conducted on 90 patients who received high-dose intravenous furosemide therapy found that serum urea nitrogen, creatinine and potassium levels decreased significantly while pH and oxygenation index increased significantly after six hours of administration ($P<0.05$). After treatment, the renal function of 80 patients (88.9%) recovered completely, with no obvious side effects (20). Another systematic review and meta-analysis explained that administration of furosemide therapy had no impact on mortality or the requirement for RRT. Patients at risk of contrast-induced

nephropathy (CIN) may benefit from furosemide administration and less frequent need for RRT (OR = 0.218; 95% CI 0.05–1.04; p = 0.055). Furosemide was associated with reduced in-hospital mortality [hazard ratio (HR) 0.67; 95% CI 0.61–0.74; P < 0.001] and 90-day mortality [HR 0.69; 95% CI 0.64–0.75; P < 0.001], and was also associated with recovery of renal function [HR 1.44; 95% CI 1.31–1.57; P < 0.001] in all AKI patients. Furosemide administration is associated with improved short-term survival and recovery of renal function in critically ill patients with AKI. Furosemide is very effective in AKI patients with UO stage 2-3 grade criteria. However, it is not effective in AKI at SCr values stage 2–3 and chronic kidney disease (21).

The results of this systematic review explain that the response to furosemide can be seen from the NGAL biomarker in AKI patients. In this randomized controlled trial, 106 ICU patients with AKI were assigned to furosemide and control groups. Serum and urine NGAL were measured on days 1, 3, and 7 of the study. The results of this study showed that during the study, the patient's serum blood urea nitrogen levels increased in both groups. Plasma and urine NGAL decreased significantly (P < 0.05) in both groups. The 28-day mortality rate showed that 20% of patients died in the furosemide group and 28% in the control group. The mortality rate was lower in the group receiving furosemide therapy (22). The non-significant results in this study may be due to several factors that need to be considered, namely the characteristics of the patients in the study, such as the severity of the disease or other types of comorbidities, may influence the response to furosemide. Additionally natural variability in the body's response to medical interventions is common. Not all patients will respond to furosemide with significant changes in NGAL levels.

Differences in the timing of blood sampling or NGAL measurements during the study may influence the results. The effect of furosemide on NGAL may appear within a certain period of time after administration, and differences in observation time may lead to different results. It is important to remember that a nonsignificant result does not necessarily mean that the effect is absent. Study results could be influenced by various factors, and further studies with larger samples or different study designs may be needed to better evaluate the effects of furosemide on NGAL.

Research conducted by Maatsura et al. explained that FR and NGAL can predict the development of AKI in critical patients. FR can predict the development of AKI in patients with high plasma NGAL levels, while some patients with low plasma NGAL levels show the development of recurrent AKI. These results suggest that functional (furosemide response) and structural (plasma NGAL levels) evaluation of AKI can help predict AKI progression. Furosemide dosage ranges from 10 to 340 mg. Our findings provide information regarding FR at different doses of furosemide that can be used to predict progression of AKI. This is because the dose of furosemide is given individually based on the patient's condition (23).

This retrospective study suggests that plasma FR and NGAL may be significant predictors of the progression of AKI development in ICU patients. In addition, FR can predict the development of AKI even in patients with high NGAL values, indicating that sequential evaluation with FR and plasma NGAL can identify in patients at high risk of progression to severe AKI. Of note, identifying high-risk patients may allow for lowering the potential side effects of furosemide.

CONCLUSSION

These two studies had different focuses and goals, which explains the differences in their findings. The first study focused more on the use of plasma NGAL as a predictor of AKI development, especially in patients with certain plasma NGAL levels. On the other hand, the second study sought to understand the impact of furosemide therapy on renal function and NGAL levels in AKI patients. These two studies used different approaches in analyzing their data, with the first study using ROC analysis while the second study focused more on changes in NGAL levels during furosemide treatment. Due to differences in study design and primary aims, the results of these two studies cannot be directly compared. Therefore, to gain a deeper understanding of the role of furosemide and NGAL in the treatment of AKI patients, further studies with appropriate designs need to be conducted. This will help clarify whether plasma NGAL can truly be used as an indicator of AKI progression or whether furosemide has a significant effect in AKI patients in a different context.

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