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Meta-analysis of the effects of furosemide combined with hydration therapy on contrast-induced acute kidney injury after coronary intervention

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Abstract. – OBJECTIVE: A meta-analysis was performed to evaluate the effect of furosemide combined with hydration therapy on the incidence and prognosis of contrast-induced acute kidney injury (CI-AKI) in patients after coronary intervention.

MATERIALS AND METHODS: Through the PubMed, EMBASE, Cochrane Library and Web of Science databases, all relevant literature from database establishment until October 1, 2020, was retrieved and screened. Quality evaluation was performed using the risk of bias evaluation tool recommended by the Cochrane Collaboration network, data extraction was performed based on pre-selected effect indicators, and statistics were calculated using Review Manager 5.3 analysis software.

RESULTS: A total of 2084 patients in 9 studies were included in the meta-analysis. The results showed that furosemide combined with hydrotherapy had no effect on the incidence of CI-AKI (OR = 0.85, 95% CI [0.46, 1.60], $p = 0.62$) and can significantly decrease the incidence of major adverse cardiovascular events (MACEs) (OR = 0.43, 95% CI [0.27, 0.67], $p = 0.0003$) and mortality (OR = 0.24, 95% CI [0.08, 0.79], $p = 0.02$) in patients. However, it had no significant impact on the need for postoperative dialysis treatment, postoperative creatinine level or length of hospital stay.

CONCLUSIONS: Furosemide combined with hydration therapy has no significant effect on the incidence of CI-AKI in patients after coronary intervention but can reduce the incidence of MACEs and mortality, thereby providing clinical benefits.

Key Words:
Meta-analysis, Furosemide, Contrast-induced acute kidney injury.

Introduction

With the increasing application of coronary intervention techniques in disease diagnosis, assessment, and treatment, contrast-induced renal injury has also emerged, namely, contrast-induced acute kidney injury (CI-AKI). The pathogenic mechanisms of CI-AKI mainly include renal tubular ischemic/hypoxia injury, oxidative stress and direct toxicity of contrast agent[1]. In most cases, CI-AKI is reversible. Allowing its development will increase the incidence of renal and cardiovascular adverse events, increase patient mortality, prolong hospital stay, and increase the financial burden, especially high-risk patients will have poorer prognosis[2].

Currently, standard hydration therapy has become the cornerstone of the prevention of contrast-induced renal injury. The preventive effect of furosemide combined with hydration therapy on CI-AKI after coronary intervention has become one of the research hotspots currently. As a clinically used loop diuretic, furosemide reduces renal tubular metabolic oxygen consumption and can transiently increase glomerular plasma flow and reduce apoptosis and related gene transcription in ischemia-reperfusion-induced acute kidney injury. On the other hand, Furosemide can reduce the drug concentration of contrast agents in renal blood vessels, thereby reducing renal damage[3] However, the following studies reported different results. Benjamin et al[4] showed that furosemide combined hydration therapy not only did not benefit the prognosis of AKI but also aggravated oxidative stress reactions and led to

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severe adverse reactions. Currently, the effect of furosemide combined with hydration therapy on CI-AKI after coronary intervention is still inconclusive.

This study included randomized controlled trials to perform a meta-analysis to evaluate the effect of furosemide combined with hydration therapy on other important clinical outcomes after coronary intervention, such as the incidence of CI-AKI, mortality, incidence of major adverse cardiovascular events (MACEs), and the need for renal replacement therapy (RRT) rate, thereby to further evaluate the safety and effectiveness of the clinical application of furosemide combined hydration therapy and to better provide a reference for the clinical diagnosis and intervention strategies of CI-AKI.

Materials and Methods

The meta-analysis used in this study strictly followed the regulations and procedures of the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA) and strictly followed the inclusion criteria and exclusion criteria according to the PICOS standards[5]. The registration number of our study in PROSPERO is CRD42020180792.

Literature Retrieval

In this systematic review, we conducted a comprehensive literature search for studies published in English from database establishment to October 1, 2020. Two researchers independently retrieved published papers written in English containing randomized controlled trials (RCTs) in PubMed, EMBASE, the database of the Cochrane Library and Web of Science. The specified medical subject headings were used, including furosemide, contrast-induced acute kidney injury. The specified MeSH (Medical Subject Headings) terms and key words were used, including furosemide, mortality, contrast-induced acute kidney injury, renal replacement therapy, acute kidney injury, acute renal failure, and renal insufficiency. We searched for all related randomized controlled trials (RCTs) that compared prevention or treatment with furosemide, to a placebo, standard of care or RRT in adult patients with CI-AKI. Moreover, additional relevant studies were searched manually by checking the reference lists of the identified studies or reviews.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) study population – adult patients underwent coronary intervention; (2) intervention measures – furosemide combined with hydration therapy; (3) control group: hydration therapy; (4) outcome – CI-AKI incidence, MACEs incidence, mortality, need for RRT rate, length of hospital stay, and postoperative creatinine level; (5) study design: RCT.

Exclusion criteria: (1) repeated and low-quality studies; (2) could not obtain complete and reliable literature data; (3) publications in the form of review/abstract/letter and comments; (4) publications that were not written in English; (5) Master's or Doctoral thesis.

Literature Screening and Data Extraction

Two researchers independently screened the literature and extracted the data strictly following the inclusion criteria and exclusion criteria by using EndnoteX8 software. The data were first extracted on paper and then input into a standardized Excel file.

Evaluation of the Quality of the Literature

The quality assessment was conducted by two researchers independently. When disagreements were generated, disagreements were resolved by discussion with the third investigator. The criterion for risk of bias in Cochrane Collaboration was used for evaluation.

Statistical Analysis

The Review Manager 5.3 software of Cochrane Collaboration network was used for the quality assessment, heterogeneity test, data merging, forest map plotting, and funnel plot of the included literature. When the data type was a continuous variable and the data unit and measurement method were identical, data were expressed as the mean difference (MD) and 95% confidence interval (CI). The significance level adopted 0.05 as the critical point. Heterogeneity of the included studies was assessed using the I^2 test[6].

Results

Literature Retrieval and Screen Results

A total of 3857 relevant articles were retrieved by searching the above English database. By

carefully reading the full text of the paper and strictly following the inclusion and exclusion criteria, 9 articles were eventually included, with a total of 2084 patients. The literature screening process is shown in Figure 1.

Basic Characteristics of the Included Studies

Among the included studies, only 3 were multicenter trials; AKI data could be obtained in 9 trials, whose definitions were based on those given in the articles; MACE incidence data could be obtained in 4 trials; data of RRT rate could be obtained in 6 trials; mortality data could be obtained in 4 trials; postoperative blood creatinine data could be obtained in 5 trials; length of hospital stay data could be obtained in 4 trials. The characteristics of each included literature are shown in Table I.

Literature Quality Evaluation

Literature quality evaluation was performed using the risk of bias evaluation tool recommended by the Cochrane Collaboration network. The results showed that the overall quality of the included studies was medium, and most of the information came from low or uncertain risk of bias. The risk of bias is shown in Figure 2.

Results of Combined Effect of the Meta-Analysis

Incidence of CI-AKI

The indicator of CI-AKI incidence was included in 9 studies with a total of 2084 subjects. There was a certain heterogeneity among the 9 studies (I^2 = 77%, $p < 0.0001$). Meta-analysis results showed that furosemide combined with hydration therapy had no significant effect on CI-AKI incidence, and the difference was not statistically significant (OR = 0.85, 95% CI [0.46, 1.60], $p = 0.62$) (Figure 3).

Incidence of MACEs

Four studies included the indicator of the incidence of MACEs, with a total of 684 subjects. There was no heterogeneity among the 4 studies (I^2 = 0%, $p = 0.52$). The meta-analysis results showed that furosemide combined with hydration therapy could reduce the incidence of MACEs, and the difference was statistically significant (OR = 0.43, 95% CI [0.27, 0.67], $p = 0.0003$) (Figure 4).

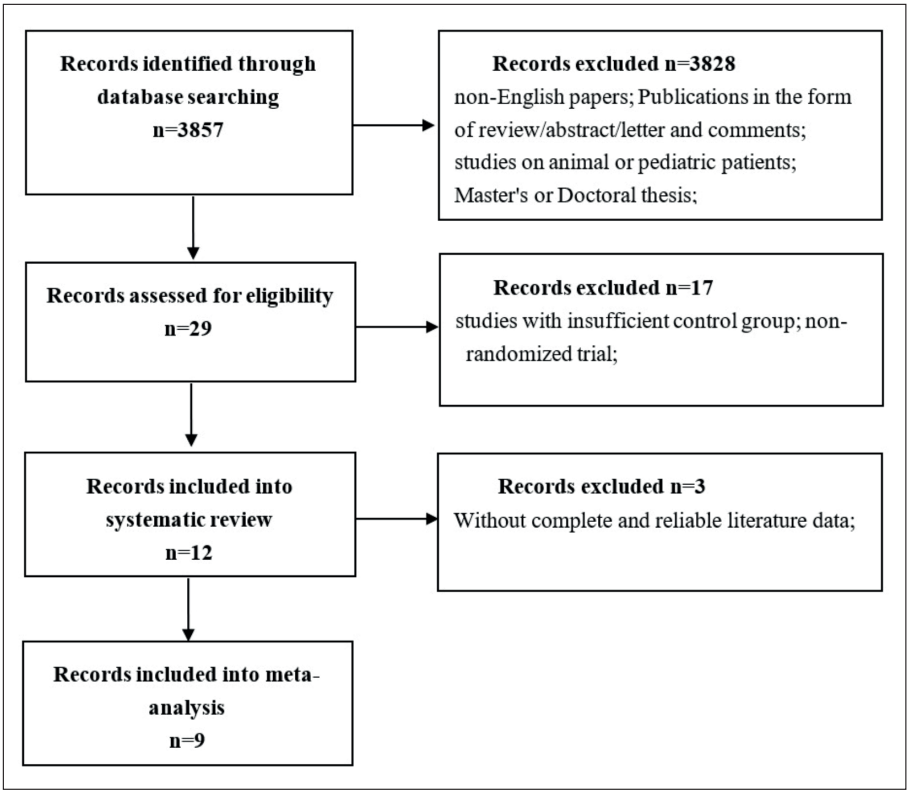

Figure 1. Flow chart of the study selection procedure.

Table I. Characteristics of Included Trials.

Study	Years	Multicenter study	Furosemide intervention	CI-AKI definition	Study endpoints
Usmiani et al[9]	2016	No	IV, 0.5 mg/kg before procedure	SCr > 0.3 mg/dl, at 48 h or > 50 % of baseline in 7 days post-procedure	AKI, MACEs, mortality, RRT, length of in-hospital stay, urinary volume
Gu et al[10]	2013	Yes	IV, 20 mg before procedure	SCr > 25 % of baseline, or > 0.5 mg/dl, at 48 h post-procedure	AKI, SCr, urinary volume
Marenzi et al[11]	2012	Yes	IV, 0.5 mg/kg before procedure	SCr > 25 % of baseline, or > 0.5 mg/dl, at 72 h post-procedure	AKI, MACEs, mortality, RRT, urinary volume
Shemirani et al[16]	2012	No	Oral	SCr > 0.5 mg/dl, at 48 h post-procedure	AKI, SCr
Briguori et al[12]	2011	Yes	IV, 0.25 mg/kg before procedure	SCr > 0.3 mg/dl, at 48 h post-procedure	AKI, MACEs, RRT, length of in-hospital stay, urinary volume
Majumdar et al[17]	2009	No	IV, 100 mg before procedure	SCr >25% of baseline, or > 0.5 mg/dl, at 48 h post-procedure	AKI, mortality, RRT, SCr, length of in-hospital stay, urinary volume
Dussol et al[18]	2006	No	IV, 3 mg/kg just after procedure	SCr > 0.5 mg/dl, at 48 h post-procedure	AKI, RRT, SCr
Stevens et al[13]	1999	No	IV, 1 mg/kg before procedure	SCr > 25% of baseline, > 50% of baseline, >100% of baseline, > 1.0 mg/dl, > 5.0 mg/dl, at 48 h post-procedure	AKI, MACEs, mortality, RRT, SCr, length of in-hospital stay, urinary volume
Solomon et al[19]	1994	No	IV, 80 mg before procedure	SCr >0.5 mg/dl, at 48 h post-procedure	AKI, SCr, urinary volume

AKI: acute kidney injury, CI-AKI: contrast-induced acute kidney injury, IV: Intravenous, MACEs: major adverse cardiovascular events, RRT: renal replacement therapy, SCr: Serum creatinine.

Need for RRT Rate

Six studies included indicator for the need for RRT rate. A total of 931 subjects were included, with no heterogeneity among the 6 studies (I^2 = 0%, p = 0.50). The meta-analysis results showed that furosemide combined with hydration therapy had no significant difference in the incidence of postoperative need for RRT rate, and the difference was not statistically significant (OR = 0.47, 95% CI [0.21, 1.04], p = 0.06) (Figure 5).

Mortality

Four studies included mortality indicator with a total of 481 subjects. There was no heterogeneity among the 4 studies (I^2 = 0%, p = 0.61). The meta-analysis showed that furosemide combined with hydration therapy could reduce patient mortality, and the difference was statistically significant (OR = 0.24, 95% CI [0.08, 0.79], p = 0.02) (Figure 6).

Postoperative blood creatinine level

Five studies included postoperative blood creatinine levels, with a total of 1,581 subjects. There was certain heterogeneity among the five studies (I^2 = 62%, p = 0.03). The meta-analysis results showed that furosemide combined with hydration therapy had no significant effect on postoperative creatinine levels, and the difference was not statistically significant (MD = 0.78, 95% CI [-2.23, 3.88], p = 0.62) (Figure 7).

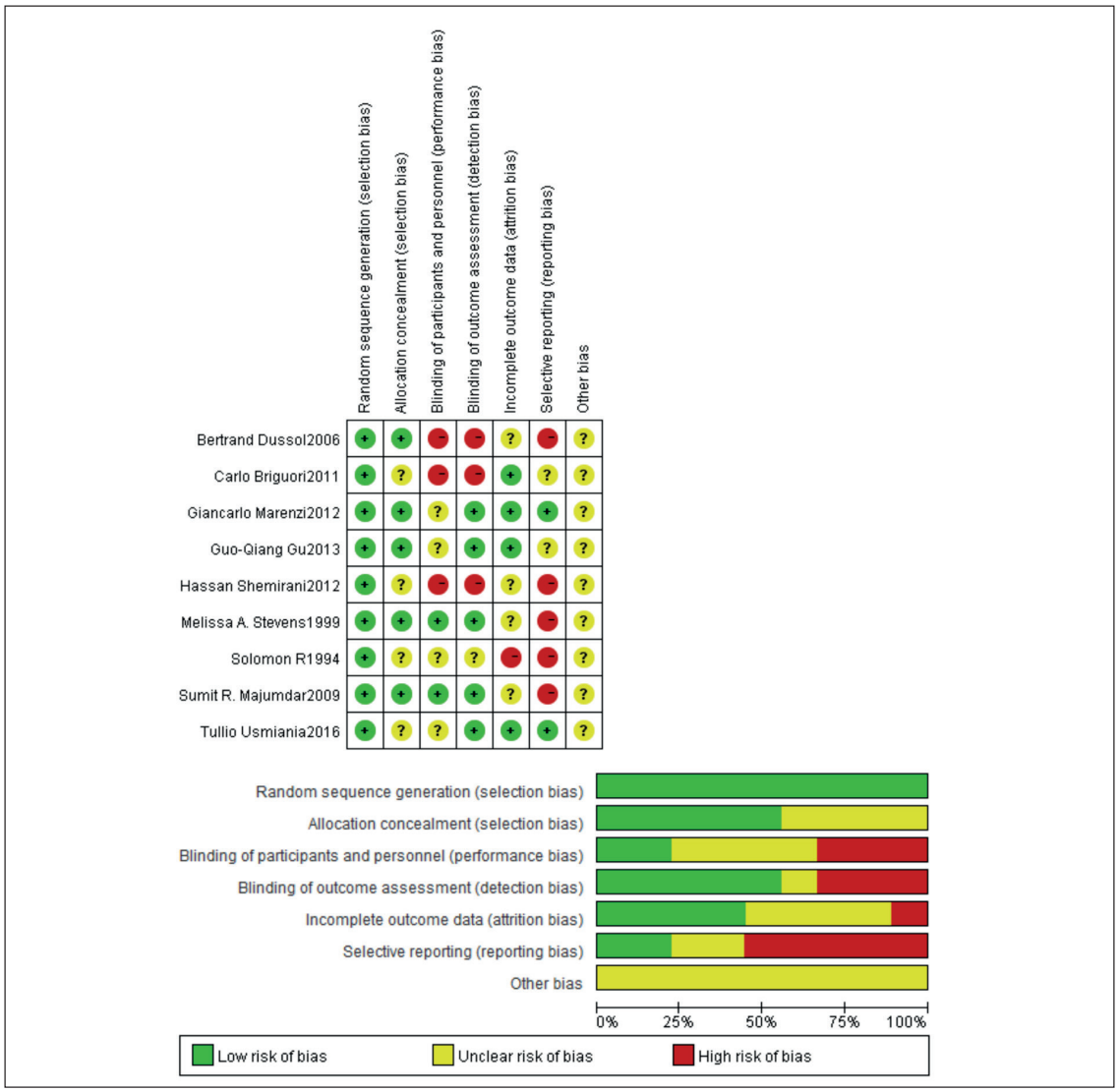

Figure 2. Diagram about the Risk of Bias.

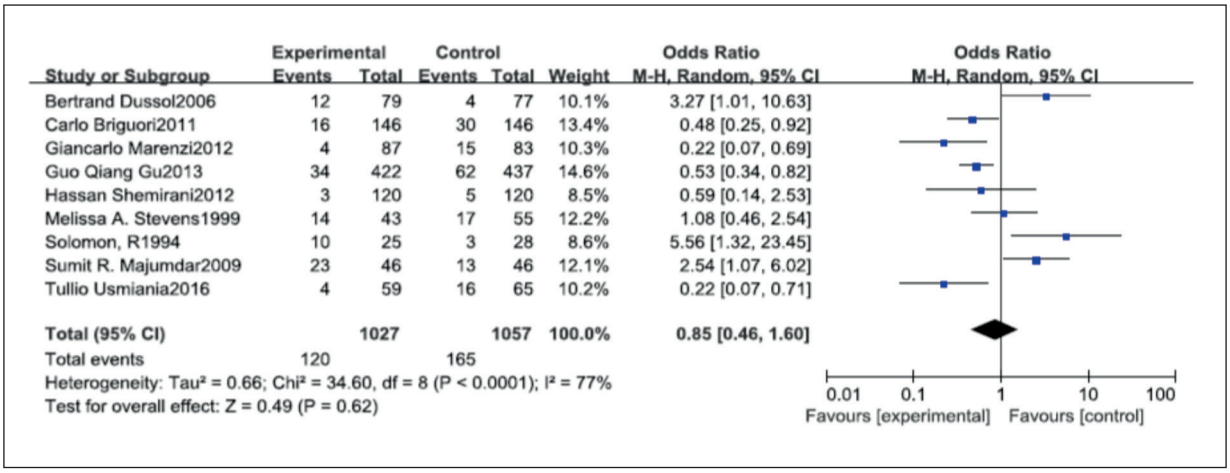

Figure 3. Forest plot effects of furosemide in incidence of CI-AKI.

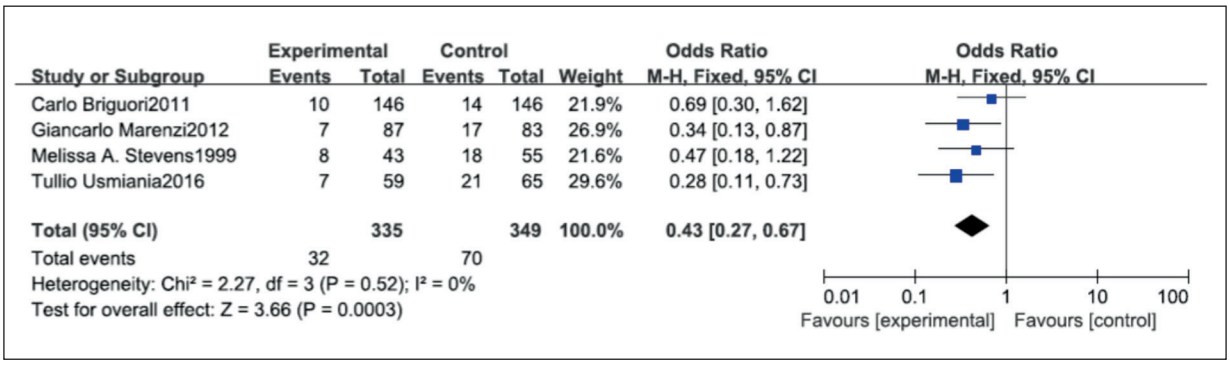

Figure 4. Forest plot of effects of furosemide in incidence of MACEs.

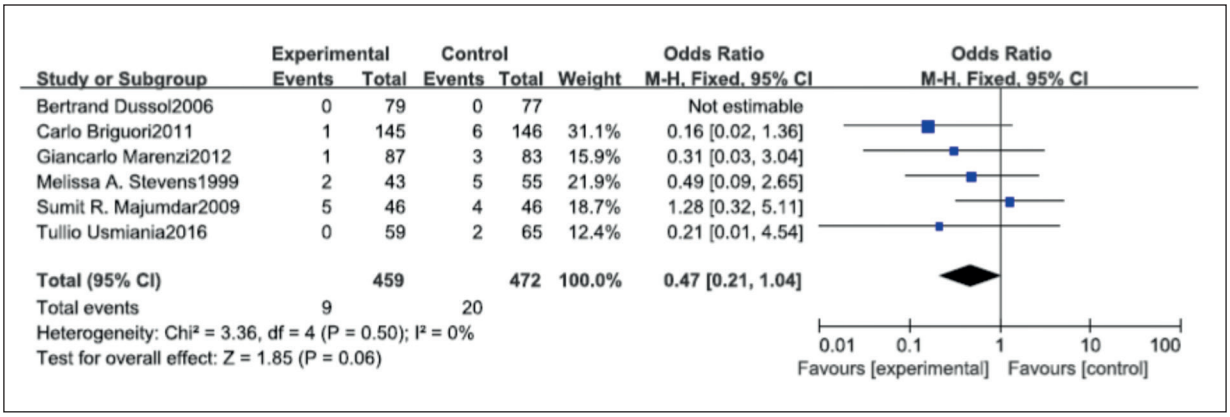

Figure 5. Forest plot of effects of furosemide in receipt of RRT.

Length of Hospital Stay

Four studies included indicator of length of hospital stay, with a total of 606 subjects. The heterogeneity among the 4 studies was moderate (I^2 = 42%, p = 0.16). The meta-analysis results showed that furosemide combined hydration therapy had no significant effect on length of hospital stay, and the difference was not statistically significant (MD = 0.12, 95% CI [-1.26, 1.50], p = 0.87) (Figure 8).

Sensitivity Analysis

By applying one-by-one exclusion of each single study or simultaneously excluding a number

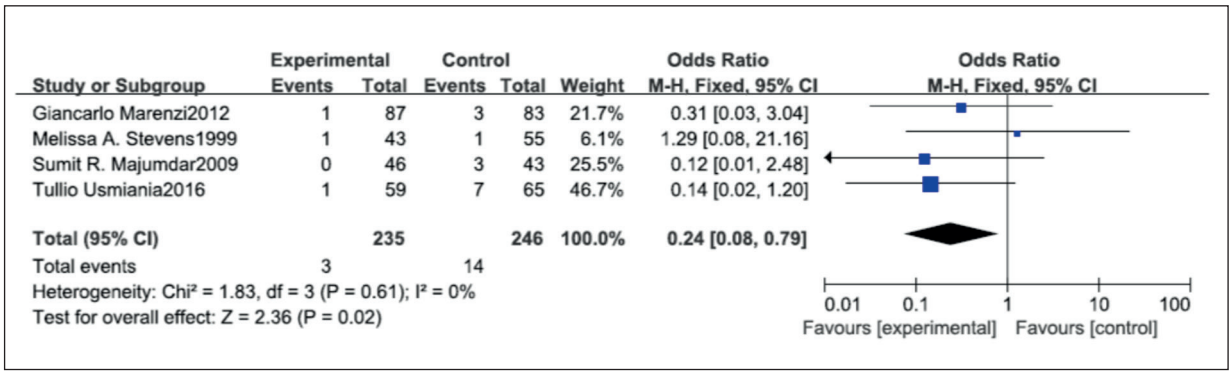

Figure 6. Forest plot of effects of furosemide in mortality.

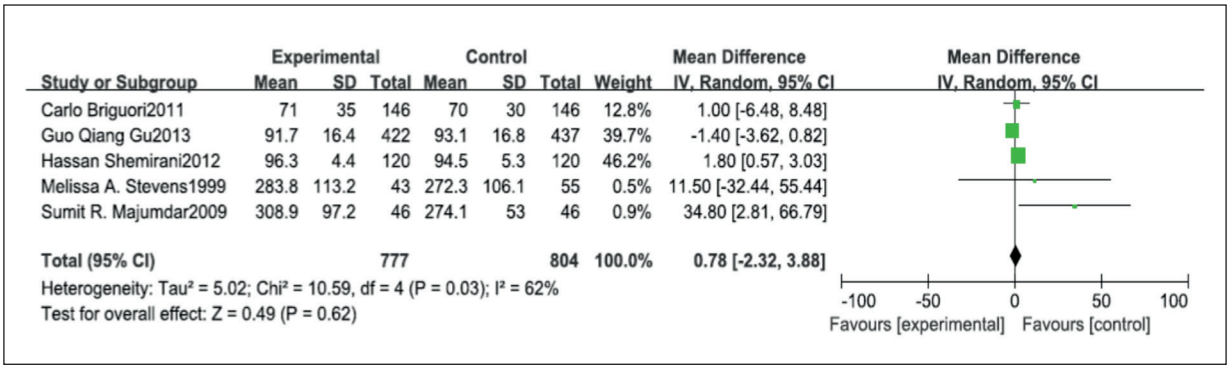

Figure 7. Forest plot of effects of furosemide in SCr.

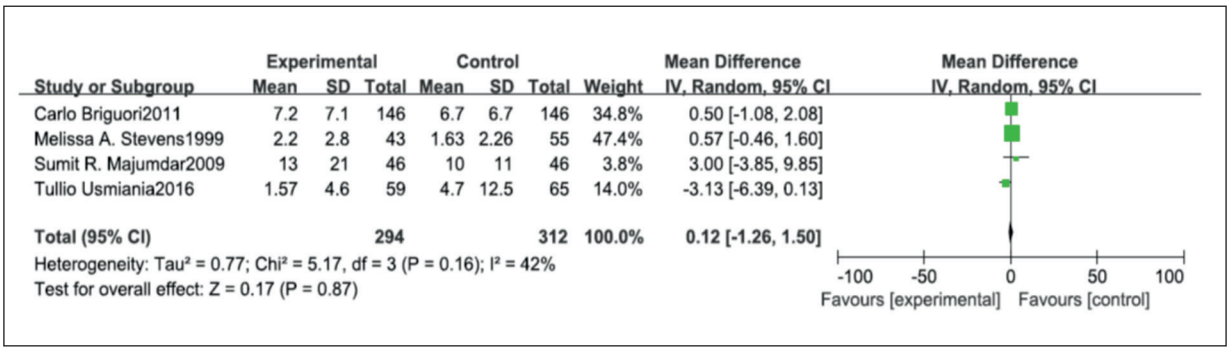

Figure 8. Forest plot of effects of furosemide in length of in-hospital stay.

of studies with small sample size that might affect the results, as well as changing the statistical effect model for analysis, the comparison of the results showed there were essentially no changes, indicating that the meta-analysis results are stable and reliable.

Assessment of Publication Bias

Among all the indicators, a meta-analysis funnel plot was performed for the incidence of CI-AKI. Visual inspection showed that the funnel plot was symmetrically distributed on both sides, indicating that there was no significant publication bias (Figure 9).

Discussion

Currently, standard hydration therapy is one of the effective measures recommended by the latest guidelines to prevent CI-AKI[7]. The optimization of the hydration scheme has become the research focus of scholars worldwide, aiming to further reduce the occurrence of CI-AKI and reduce the long-term adverse events based on individualized precision therapy, thereby better improving the quality of life of patients after intervention[8]. This study used a meta-analysis to quantitatively evaluate whether furosemide combined with hydration therapy is better than hydration therapy alone in preventing and treating CI-AKI and had better long-term prognosis in patients after coronary intervention.

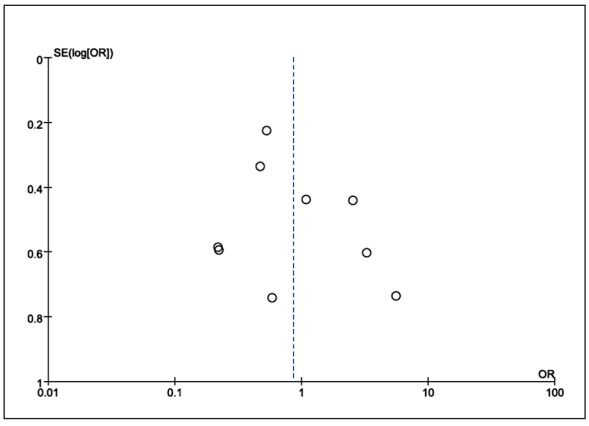

Figure 9. Funnel plots.

The results showed that furosemide combined with hydration therapy had no significant effect on the incidence of CI-AKI in patients after coronary intervention, and the difference was not statistically significant (OR = 0.85, 95% CI [0.46,1.60], p = 0.62). Five out of 9 studies included[9-13] demonstrated that furosemide combined with hydration therapy significantly reduced the incidence of CI-AKI in the patients, and the different results may be related to the subjects enrolled in the study and the administration method in the study design. The conditions of basal renal function of patients included in the studies were different, and the assessment criteria and staging were different, which may result in different sensitivities and efficacies of furosemide treatment. Differences in the timing, dose, and mode of administration of furosemide may lead to differences in drug concentrations, renal blood perfusion, renal medullary oxygen consumption, and oxidative stress responses[14]. The difference in capacity control will directly affect the patients' effective circulation of blood volume and even renal perfusion, which may affect the study results[15]. In addition, in the long-term prognosis analysis of patients, we found that furosemide combined with hydration therapy can reduce the incidence of MACEs and mortality in patients and bring significantly benefit to important clinical outcomes, which has important clinical reference value. Disease prevention and treatment requires a long-term and overall strategy. Although there is still a lack of evidence to support that furosemide combined with hydration therapy can effectively prevent CI-AKI and the relevant evidence is still limited, the improvement of clinical outcome is still the ultimate objective of our study. In the future, multicenter joint research can be carried out to effectively control confounding factors. We may also find beneficial trends in the prevention of CI-AKI by furosemide combined hydration therapies.

As a secondary research, this study also had some common limitations of secondary research, including differences in the clinical characteristics of the study population, different initial and final doses of diuretics, duration of different trials, different drug administration regimens, and differences in some small sample studies.

Our study find that furosemide combined with hydrotherapy can significantly decrease the incidence of MACEs and mortality in patients but had no effect on the incidence of CI-AKI and had no significant impact on the need for postoperative dialysis treatment, postoperative creatinine level or length of hospital stay.

Conclusions

Furosemide combined with hydration therapy did not significantly improve the incidence of CI-AKI after coronary. However, it could reduce the MACE incidence and mortality in patients and provides clinical benefits. Therefore, the efficacy and uncertainty of the furosemide combined hydration therapy strategy still need to be further validated with high-quality large-sample clinical randomized controlled trials in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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