Meta-Analysis

Remote Ischemic Preconditioning Reduces the Risk of Contrast-Induced Nephropathy in Patients with Moderate Renal Impairment Undergoing Percutaneous Coronary Angiography: A Meta-Analysis

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Keywords

Remote ischemic preconditioning · Contrast-induced nephropathy · Meta-analysis

Abstract

Background/Aims: This meta-analysis evaluated the effects of remote ischemic preconditioning (RIPC) on the risk of contrast-induced nephropathy (CIN) in patients undergoing percutaneous coronary intervention/coronary angiography (PCI/CA). **Methods:** PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were searched for randomized controlled trials (RCTs) that assessed the effect of RIPC on CIN in patients undergoing PCI/CA. The main outcomes of interest were the incidence of CIN 48–72 h after CA, the levels of serum creatinine, cystatin C, neutrophil gelatinase-associated lipocalin, and estimated glomerular filtration rate (eGFR), mortality, and requirement of hemodialysis and rehospitalization. The analysis was conducted using the random-effect model due to the expected heterogeneity among different studies. **Results:** In total, 16 trials covering 2,048 patients were identified. By assessing the methodological quality of the included studies through the Cochrane risk of bias, we found that of the 16 RCTs, 3 had a low risk of bias, 6 a high, and 7 an unclear risk. The application of RIPC decreased the incidence of CIN (relative risk, RR, 0.50, 95% confidence interval, CI, 0.39–0.65; $p < 0.001$). Subgroup analyses showed that RIPC decreased the incidence of CIN in patients with eGFR < 60 mL/min/1.73 m² (RR 0.53, 95% CI 0.38–0.75;

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$p < 0.001$) but not in patients with eGFR ≥ 60 mL/min/1.73 m² (RR 0.82, 95% CI 0.35–1.94; $p = 0.66$) at baseline. Furthermore, the increase in serum creatinine was significantly lower in patients with RIPC compared to control patients (standardized mean difference -1.41 , 95% CI -2.46 to -0.35 ; $p = 0.009$). **Conclusions:** Based on 16 RCTs, this meta-analysis shows that RIPC can reduce the risk of CIN in patients with moderate renal impairment undergoing PCI/CA. However, this needs to be confirmed by further high-quality evidence.

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Introduction

In recent years, the number of percutaneous procedures requiring contrast medium administration has increased exponentially [1]. Contrast-induced nephropathy (CIN) is a common iatrogenic complication of percutaneous coronary intervention (PCI)/coronary angiography (CA), and it is associated with poor cardiovascular and renal outcomes [2, 3]. The most common definitions of CIN in use are an absolute rise of >0.5 mg/dL and/or a relative increase of $>25\%$ in serum creatinine compared with baseline within 48–72 h after contrast administration without an alternative cause of kidney injury [4]. The incidence of CIN varies from 2% in the general population to $\geq 50\%$ in high-risk groups [5]. Clinical surveys have revealed that patients with renal dysfunction are more likely to develop CIN compared to those with normal renal function. Several concomitant risk factors such as old age, diabetes, congestive heart failure, hypertension as well as the type and amount of the contrast agent contribute to the occurrence of CIN [6–8]. As the third most common cause of acute kidney injury (AKI), CIN has been closely linked with the need for dialysis and intensive care unit support, prolonged hospital stay, and significant mortality [9]. There are 2 main pathways to prevent CIN: optimal hydration and use of lower volumes of contrast medium. N-acetylcysteine was probably the most investigated adjunctive therapy, so far failing to prove a significant clinical benefit of preventing CIN [10–13].

Remote ischemic preconditioning (RIPC) seeks to stimulate endogenous protective mechanisms by inducing short intermittent periods of ischemic reperfusion by blocking blood flow in nontarget tissues such as limbs before subsequent episodes of ischemia-reperfusion injury [14, 15]. In 1993, Przyklenk et al. [16] found that preconditioning of the heart confers protection not only to coronary perfusion vessels, but also to remote tissues. Since then, several studies have demonstrated that ischemic preconditioning can protect distal organs or tissues, such as the kidney, small intestine and extremities [17–19]. Therefore, it can be used to protect vital organs that are susceptible to ischemic damage [20]. In recent years, RIPC has emerged as a novel nonpharmacological approach used to prevent CIN. Given that findings from previous investigation on the use of RIPC on CIN have been inconsistent, we designed this meta-analysis to provide a more comprehensive analysis of the previous literature and to determine whether RIPC confers protection to patients undergoing PCI/CA.

Materials and Methods

Criteria for Study Inclusion

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this study [21]. All studies that met the following criteria were included: (i) only randomized controlled trials (RCTs) were enrolled; (ii) the studies

contained patients undergoing PCI or CA; (iii) patients were randomized to receive RIPC or sham RIPC therapy; (iv) at least one of the following was reported: the incidence of CIN, the levels of serum creatinine, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), or estimated glomerular filtration rate (eGFR), mortality, and requirement of hemodialysis and rehospitalization. Studies were excluded if the patients received postischemic conditioning.

Search Strategy

We conducted a literature search on Pubmed, Embase, and Cochrane Central Register of Controlled Trials. The search keywords were: “remote ischemic preconditioning,” “ischemic preconditioning,” “ischemic conditioning,” “acute kidney injuries,” “acute renal injury,” “acute kidney failure,” “acute renal failure,” “acute renal insufficiency,” “acute kidney insufficiency,” and “contrast induced nephropathy.” Search strategies are listed in online supplement 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000507330). We scrutinized the reference lists of all included articles to identify additional studies.

Study Selection and Data Extraction

By examining the titles and/or abstracts of all studies, studies that did not meet the inclusion criteria were excluded. The full texts of studies that met the inclusion criteria were reviewed. The following information was extracted: baseline characteristics, patient information, intervention treatment, and the dose of contrast agent. Also, we extracted outcome data such as the incidence of CIN (as defined in Table 1), the levels of serum creatinine, eGFR, NGAL, and cystatin C, and clinical adverse results (the number of hemodialyses, rehospitalization, and mortality).

Assessment of Risk of Bias

The Cochrane handbook was used to assess the quality of the included studies under the following 6 criteria: (1) adequate sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data; (5) selective reporting; (6) other bias. These criteria were graded as low, high, or unclear risk of bias according to the text. We inferred that the unclear risk of bias implied that there was no information or uncertainty on the potential of bias. Studies were considered to have a high risk of bias if they contained one criterion classified as high risk of bias; studies were considered to have a low risk of bias only if all criteria had a low risk of bias; studies were rated to have an unclear risk of bias if there was at least one criterion that was viewed as unclear risk of bias and without high risk.

Statistical Analysis

Relative risk (RR), such as the incidence of CIN, was used to report dichotomous data, while standardized mean difference (SMD) with 95% confidence interval (CI) was used to report continuous outcomes such as eGFR, serum creatinine, NGAL, and cystatin C. The analysis was conducted using the random-effect model due to the expected heterogeneity among different studies. Since $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ is a risk factor for CIN, we conducted a subgroup analysis based on baseline eGFR. Given that the measurement time varied in included RCTs, we conducted a subgroup analysis based on measurement time < 48 or ≥ 48 h after PCI/CA. Since the definition of CIN was inconsistent in the included studies, we performed a sensitivity analysis to confirm the effects of different definitions of CIN on the results. Meanwhile, funnel plots were used to explore publication bias if 10 or more studies were included.

Table 1. Baseline characteristics of included studies

Study	Inclusion criteria	Number involved, R/C	Sex, M/F	Age, years	eGFR, mL/min/1.73 m ²	Serum creatinine, mg/dL
Hoole et al. [24], 2009	PCI	104/98	R: 84/20 C: 74/24	R: 63.2±10.1 C: 61.8±10.3	–	–
Balbir Singh et al. [15], 2016	PCI	51/51	R: 23/28 C: 25/26	R: 67.8±7.6 C: 69.0±8.6	R: 48.5±12.0 C: 46.6±10.2	R: 1.42±0.58 C: 1.41±0.34
Xu et al. [31], 2014	PCI	102/98	R: 68/34 C: 68/30	R: 69.1±3.8 C: 68.9±2.9	R: 99.1±20.6 C: 100.8±28.2	R: 0.88±0.19 C: 0.84±0.20
Luo et al. [26], 2013	PCI	101/104	R: 78/23 C: 78/26	R: 59.2±10.3 C: 59.3±9.5	R: 101±20 C: 100±20	–
Er et al. [18], 2012	CA	50/50	R: 34/16 C: 37/13	R: 73.2±9.1 C: 72.7±11.4	R: 40.6±8.7 C: 41.3±11.9	R: 1.63 (1.47–1.81) C: 1.62 (1.39–1.93)
Igarashi et al. [25], 2013	PCI or CA	30/30	R: 20/10 C: 23/7	R: 71.3±8.1 C: 70.8±7.6	R: 47.4±9.4 C: 48.9±6.0	R: 1.15±0.29 C: 1.12±0.17
Savaj et al. [28], 2014	CA	48/48	R: 17/31 C: 14/34	R: 63.0±8.9 C: 60.9±9.6	R: 78.2±25.8 C: 94.7±40.2	R: 1.3±0.4 C: 1.1±0.3
Yamanaka et al. [32], 2015	PCI	47/47	R: 34/13 C: 36/11	R: 67.0±12.0 C: 67.0±15.0	R: 73.0±20.0 C: 79.0±33.0	R: 0.82±0.21 C: 0.87±0.44
Zagidullin et al. [33], 2017	CA	26/25	R: 21/5 C: 22/3	R: 60.5 ±1.95 C: 62.96±1.72	–	R: 1.41±0.13 C: 1.21±0.11
Zhou et al. [34], 2018	PCI	50/57	R: 30/20 C: 35/22	R: 69.42±7.07 C: 69.14±7.80	R: 69.99±8.91 C: 68.02±10.17	R: 1.02±0.20 C: 1.06±0.22
Ghaemian et al. [22], 2018	PCI or CA	66/66	R: 51/15 C: 42/24	R: 66.15±8.63 C: 65.27±8.9	R: 41.86±8.16 C: 42.77±9.46	R: 1.5 (1.4–1.73) C: 1.5 (1.4–1.6)
Moretti et al. [27], 2018	PCI	107/116	R: 74/33 C: 80/36	R: 71.8±10.6 C: 72.6±9.6	–	–
Valappil et al. [29], 2018	PCI	50/50	R: 43/7 C: 40/10	R: 62.8±9.1 C: 60.5±8.5	R: 44.3 (39.7–49.7) C: 46.3 (40.2–53.1)	R: 1.5 (1.3–1.7) C: 1.4 (1.4–1.6)
Gholoobi et al. [23], 2015	CA	25/26	R: 18/7 C: 12/14	R: 67.08±12.49 C: 70.31±11.18	–	–
Wojciechowska et al. [30], 2018	PCI	62/61	R: 42/20 C: 42/19	R: 64.4±10.5 C: 62.9±8.60	R: 105.6±36.3 C: 107.3±36.5	R: 0.86±0.27 C: 0.86±0.26
Roubille et al. [35], 2019	PCI or CA	98/104	R: 68/30 C: 72/32	R: 75.6±9.2 C: 76.7±7.6	R: 43±11 C: 42±10	R: 1.69±0.57 C: 1.66±0.50

Results

Study Selection

Initially, 956 relevant articles were identified. Based on the inclusion and exclusion criteria, 869 trials were eliminated because they were duplicates, reviews, and basic research or retrospective studies. After scanning the full text of the remaining 87 studies, 16 studies were deemed to be eligible trials [15, 18, 22–35]. The study selection process is outlined in Figure 1.

Study Characteristic and Evaluation of Study Quality

Table 1 shows the characteristics of the included studies. In total, 2,048 patients were identified, among whom 1,405 were male and 643 were female. There were 1,017 and 1,031 patients in the treatment and control groups, respectively. The risks of bias of the included studies are shown in Figure 2. Three studies had a low risk of bias, 6 had a high and 7 were considered to have an unclear bias.

Table 1 (continued)

Study	Contrast dose, mL	RIPC time	RIPC application	Definition of CIN
Hoole et al. [24], 2009	R: 196.7±80.1 C: 187.5±74.2	<1 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr >25% from the baseline at 24 h after PCI
Balbir Singh et al. [15], 2016	R: 197.5±114.3 C: 196.3±118.8	<0.5 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48 h after PCI
Xu et al. [31], 2014	R: 171.8±37.9 C: 163.3±39.0	<2 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline at 16 h after PCI
Luo et al. [26], 2013	R: 154.0±46.0 C: 145.0±41.0	<2 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline at 16 h after PCI
Er et al. [18], 2012	R: 124.0±44.0 C: 103.0±41.0	<45 min before the CA	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline at 48 h after CA
Igarashi et al. [25], 2013	R: 92.9±33.2 C: 91.8±39.4	<2 h before the PCI or CA	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48 h after PCI or CA
Savaj et al. [28], 2014	R: 126.6±77.2 C: 123.8±66.6	<15 min before the CA	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥30% and/or an Scr rise ≥0.3 mg/dL from the baseline at 24 h after CA
Yamanaka et al. [32], 2015	R: 177.0±53.0 C: 199.0±87.0	–	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48–72 h after PCI
Zagidullin et al. [33], 2017	R: 155.8±16.9 C: 148.3±16.7	<1 h before the CA	5-min inflations of a blood pressure cuff to level 50 mm Hg above SBP around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline at 48 h after CA
Zhou et al. [34], 2018	R: 114.76±44.22 C: 108.82±43.25	<1 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48–72 h after PCI
Ghaemian et al. [22], 2018	R: 90 (80–112.5) C: 100 (80–116)	<40 min before PCI or CA	5-min inflations of a blood pressure cuff to level 50 mm Hg above SBP around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An Scr rise ≥0.3 mg/dL from the baseline within 48–72 h after PCI or cCA
Moretti et al. [27], 2018	R: 171.4±78.6 C: 174.4±83.7	<45 min before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48 h after PCI
Valappil et al. [29], 2018	–	<45 min before the PCI	5-min inflations of a blood pressure cuff to level 50 mm Hg above SBP around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 24–48 h after PCI
Gholoobi et al. [23], 2015	–	<1 h before the CA	5-min inflations of a blood pressure cuff to level 50 mm Hg above SBP around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An Scr rise ≥0.3 mg/dL from the baseline within 48 h after CA
Wojciechowska et al. [30], 2018	R: 155.5±76.7 C: 143.7±55.7	<2 h before the PCI	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 3 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 24–72 h after contrast administration
Roubille et al. [35], 2019	C: 73 (45–121) R: 80 (50–111)	–	5-min inflations of a blood pressure cuff to 200 mm Hg around the upper arm, followed by 5-min intervals of deflations, repeated 4 times	An increase in Scr ≥25% and/or an Scr rise ≥0.5 mg/dL from the baseline within 48–72 h after PCI

Data are presented as means ± SD or medians (quartiles Q1–Q3). R, RIPC group; C, control group; CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention; CA, coronary angiography; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; RIPC, remote ischemic preconditioning; SBP, systolic blood pressure; –, not mentioned.

Fig. 1. Flow diagram of study selection. CCRCT, Cochrane Central Register of Controlled Trials.

Effect of RIPC on the Incidence of CIN

All the 16 RCTs reported the number of patients suffering from CIN in the RIPC and control groups. The analysis of outcomes demonstrated that RIPC reduced the incidence of CIN compared to the control group (RR 0.50, 95% CI 0.39–0.65; $p < 0.001$). Subgroup analyses showed that RIPC decreased the incidence of CIN in patients with eGFR < 60 mL/min/1.73 m² (RR 0.53, 95% CI 0.38–0.75; $p < 0.001$), but not in patients with eGFR ≥ 60 mL/min/1.73 m².

Fig. 2. Risk of bias graph: review of authors' judgments about each risk of bias item presented as percentages across all included studies.

Table 2. Sensitivity analysis based on the different definitions of contrast-enhanced nephropathy in the included studies

Study	RR	95% CI	p value
Hoole et al. [24], 2009	0.5	0.38–0.65	<0.001
Xu et al. [31], 2014	0.49	0.37–0.63	<0.001
Luo et al. [26], 2013	0.49	0.38–0.64	<0.001
Savaj et al. [28], 2014	0.51	0.39–0.66	<0.001
Valappil et al. [29], 2018	0.48	0.36–0.64	<0.001
Gholoobi et al. [23], 2015	0.50	0.38–0.65	<0.001
These 6 studies	0.45	0.32–0.62	<0.001

at baseline (RR 0.82, 95% CI 0.35–1.94; $p = 0.66$). The incidence of CIN was lower in the RIPC group compared with the control group in the subgroup of measurement time ≥ 48 h after PCI/CA (RR 0.45, 95% CI 0.33–0.61; $p < 0.001$) but not in the subgroup of measurement time < 48 h (RR 0.64, 95% CI 0.40–1.04; $p = 0.07$). These results are shown in Figure 3. Moreover, sensitivity analysis, based on the different definitions of CIN, revealed that heterogeneity in the definitions of CIN had little effect on the result (Table 2).

Effect of RIPC on Serum Creatinine

Eight studies reported the changes in serum creatinine. As shown in Figure 4, 5 studies were included in this meta-analysis, suggesting that the increase in serum creatinine was significantly lower in patients with RIPC compared to control patients (SMD -1.41 , 95% CI -2.46 to -0.35 ; $p = 0.009$). Three articles reported the change of serum creatinine in the form of medians with 25th and 75th quartiles. Moretti et al. [27] found that variation in creatinine values at 24 h from baseline showed a statistically significant difference in favor of the RIPC group. However, 2 studies reported that there was no statistically significant difference between the 2 groups in serum creatinine changes 48–72 h after the procedure [22, 35].

Furthermore, 11 studies reported the levels of serum creatinine after PCI/CA. Eight studies were included in this meta-analysis and the results showed that the serum creatinine level after the procedure in the RIPC group was lower than that of the control group, although the difference was not statistically significant (SMD -0.18 , 95% CI -0.37 to 0.02 ; $p = 0.08$). Three articles reported serum creatinine in the form of medians with 25th and 75th quartiles. In the study by Er et al. [18], the level of serum creatinine was significantly higher after 48 h in control patients compared to patients with RIPC. Valappil et al. [29] showed that there was a statistically significant reduction in the serum creatinine at 24 h, 48 h, 2 weeks, and 6 weeks

Fig. 3. Effect of RIPC on the incidence of CIN.

Fig. 4. Effect of RIPC on serum creatinine. **Fig. 5.** Effect of RIPC on eGFR.

in the RIPC group compared to the sham group. However, Ghaemian et al. [22] found that there was no statistically significant difference between the RIPC and control groups in serum creatinine levels 48–72 h after the procedure.

Effect of RIPC on eGFR

Five studies were included in the meta-analysis, and the result showed that there was no difference between RIPC and control groups in eGFR after PCI/CA (SMD 0.10, 95% CI -0.06 to 0.25; $p = 0.23$; Fig. 5). In addition, 3 studies reported serum creatinine in the form of medians with 25th and 75th quartiles. Two studies reported no statistically significant difference between the RIPC and control groups in eGFR after the procedure [24, 35]. In contrast, Valappil et al. [29] found significant improvement in eGFR after the procedure in the RIPC group compared to the sham one at 24 h, 48 h, 2 weeks, and 6 weeks. Moreover, one study compared the maximum decrease in eGFR between the RIPC group and the control group [32]. In this study, the maximum decrease from baseline in eGFR was higher in the control group than in the RIPC group ($p = 0.003$).

Effect of RIPC on NGAL

Four studies reported the levels of NGAL after PCI/CA, and 3 of them were included in the meta-analysis. The results showed that the level of NGAL after PCI/CA in the RIPC group

Fig. 6. Effect of RIPC on NGAL.

Fig. 7. Effect of RIPC on cystatin C.

was lower compared to that of controls (SMD -0.24 , 95% CI -0.49 to 0.00 ; $p = 0.05$, Fig. 6). In the study by Er et al. [18], urinary NGAL increased 6 h after contrast medium use by 244.48% in the control group and 178.28% in the RIPC group ($p < 0.001$). This difference remained after 24 h ($p < 0.001$) and 48 h ($p < 0.001$). In addition, 2 articles reported the changes of NGAL in their RIPC and sham groups. Zagidullin et al. [33] found that the NGAL level was lower from baseline in the RIPC group while it was higher from baseline in the sham group after 48 h ($p = 0.002$). This is inconsistent with Balbir Singh et al. [15] where no significant differences in the changes of NGAL levels were found between RIPC and control groups.

Effect of RIPC on Cystatin C

Five studies reported the levels of serum cystatin C after PCI/CA and 4 of them were included in the meta-analysis. According to the result shown in Figure 7, we observed that the level of cystatin C after the procedure in the RIPC group was lower compared to that of control, although the difference was not statistically significant (SMD -0.49 , 95% CI -1.02 to 0.05 ; $p = 0.07$). Er et al. [18] reported that serum cystatin C increment 24 and 48 h after CA reflected major renal injury in the control group compared with patients with RIPC (24 h: $p < 0.001$; 48 h: $p < 0.001$). In addition, 3 RCTs reported changes in serum cystatin C in the sham and RIPC groups. Zagidullin et al. [33] suggested that the cystatin C level was lower from baseline in the RIPC group while it was higher from baseline in the sham group after 48 h ($p = 0.018$). However, 2 studies found no statistically significant difference between the 2 groups in serum cystatin C changes after the procedure [22, 30].

Effect of RIPC on Clinical Adverse Events

Five articles reported the need for hemodialysis and rehospitalization, while 6 articles reported the outcomes of mortality. The result showed that there was no difference between the RIPC and control groups in mortality (RR 0.69, 95% CI 0.34–1.40; $p = 0.31$) and the requirement of hemodialysis (RR 0.87, 95% CI 0.27–2.84; $p = 0.82$) and rehospitalization (RR 0.75, 95% CI 0.49–1.16; $p = 0.19$; Fig. 8).

Fig. 8. Effect of RIPC on clinical adverse events.

Publication Bias

Publication bias was not tested for outcomes except for the incidence of CIN because of the small number of studies (Fig. 9). Funnel plots for the 16 trials exhibited symmetric patterns, suggesting that there was no obvious publication bias for this outcome.

Discussion

The main findings of this meta-analysis can be summarized as follows. First, RIPC reduced the incidence of CIN in patients undergoing PCI/CA. Furthermore, subgroup analyses showed that RIPC decreased the incidence of CIN in patients with eGFR <60 mL/min/1.73 m² but not in patients with eGFR ≥60 mL/min/1.73 m² at baseline, and the incidence of CIN was lower in the RIPC group compared with the control group in the subgroup of measurement time ≥48 h after PCI/CA, but not in the subgroup of measurement time <48 h. Second, the increase in serum creatinine after the procedure was significantly lower in patients with RIPC compared to control patients. And the levels of NGAL and cystatin C after the procedure in the RIPC group were lower compared to that of controls, although the difference was not statistically significant in cystatin C. Third, RIPC did not have any remarkable effect on eGFR and mortality, and the requirement of hemodialysis and rehospitalization.

Although the pathogenesis of CIN is not completely understood, there is increasing evidence that CIN is the result of renal hypoxia injury and the direct cytotoxicity of contrast agents to the kidney [36]. Renal ischemia and reperfusion injury play an important role in the occurrence of CIN [37, 38]. Furthermore, the formation of free radicals, reactive oxygen

Fig. 9. Funnel plot of the incidence of CIN.

species, and inflammatory factors could lead to direct cytotoxicity and renal tubular epithelial apoptosis [39]. Being a novel nonpharmacological approach, RIPC might attenuate the organ damage caused by prolonged ischemia-reperfusion by providing repeated, transient, and mild ischemia-reperfusion in advance. It has been acknowledged that RIPC confers cardioprotection during the ischemia-reperfusion process [40, 41], but at present, its protective effects on renal function are controversial. The results of this study indicate that RIPC can decrease the incidence of CIN in patients undergoing PCI/CA. Furthermore, subgroup analyses showed that RIPC decreased the incidence of CIN in patients with eGFR <60 mL/min/ 1.73 m² but not in patients with eGFR ≥ 60 mL/min/ 1.73 m². It is suggested that patients with moderate renal impairment most likely could benefit from RIPC. And the incidence of CIN was lower in the RIPC group compared with the control group in the subgroup of measurement time ≥ 48 h after PCI/CA but not in the subgroup of measurement time <48 h. It is suggested that the protective effect of RIPC on CIN might be more pronounced over 48 h after PCI/CA. At present, the mechanism of the protective effect of RIPC is still unclear. Some studies have suggested that the mechanism of renal protection by RIPC is that it can play a role in anti-inflammatory, antioxidant, and nerve and humoral pathways by activating a variety of factors [42–44]. Recently studies suggested that RIPC could reduce renal damage in CIN through the activation of the tumor necrosis factor- α /neural factor- κ B pathway and then increases the expression of renal enzymes and plays the role of anti-inflammatory, antiapoptosis, and antioxidant protection of the kidney [45].

Cystatin C can freely pass through the glomerular filtration and be fully reabsorbed by renal tubular epithelial cells without returning to the blood. Furthermore, renal tubules do not secrete cystatin C. Therefore, it is not affected by factors such as gender, diet, and body weight. Thus, cystatin C has a higher sensitivity and specificity of the predictive power in the identification of AKI compared to serum creatinine and blood urea nitrogen [46, 47]. In this meta-analysis, we found that the level of cystatin C after the procedure in the RIPC group was lower compared to that of controls, although the difference was not statistically significant. NGAL is a protein released from kidney tubular cells after harmful stimuli. It has been shown that NGAL appears earlier and is more sensitive than creatinine and urea for the diagnosis of AKI [48, 49]. In this meta-analysis, we found that the level of NGAL after the procedure in the RIPC group was lower compared to that of controls, suggesting that RIPC may alleviate renal damage in patients undergoing PCI/CA.

Based on the results of the present meta-analysis, RIPC failed to show a significant effect on eGFR, mortality, and requirement of hemodialysis and rehospitalization. The potential

reasons for our negative results about the above outcomes concerned the few studies included in these analyses and the absence of subgroup analyses. Thus, large-scale RCTs are needed to confirm the potential effect of RIPC on eGFR, mortality, and requirement of hemodialysis and rehospitalization during PCI/CA.

So far, 2 meta-analyses have been performed to determine the effect of RIPC on CIN [50, 51]. However, Hu et al. [51] included 10 RCTs with 1,167 patients, and Bei et al. [50] included 7 RCTs with 957 patients, whereas the present study included 16 RCTs with 2,048 patients. Inconsistent with the results of these 2 meta-analyses, 3 recent trials reported that RIPC did not significantly reduce CIN [29, 30, 35]. Here, we included 6 updated additional RCTs to assess the effect of RIPC for CIN in a more comprehensive manner. Since eGFR <60 mL/min/1.73 m² is a risk factor for CIN, we conducted a subgroup analysis based on baseline eGFR. However, Bei et al. [50] performed the subgroup analysis according to whether the mean eGFR was ≥60 mL/min/1.73 m², which would introduce some biases in meta-analysis and tend to confuse the result. In addition, because the measurement time varied across the included RCTs, we conducted a subgroup analysis based on measurement time <48 or ≥48 h after PCI/CA. Furthermore, given that the definition of CIN varied in the included studies, we performed a sensitivity analysis to confirm the effects of different definitions of CIN on the result. Sensitivity analysis revealed that different definitions of CIN had little effect on the result. Finally, the present study explored the effects of RIPC on NGAL and cystatin C, which are crucial for the early diagnosis of kidney injury.

Despite the above strengths, there are some limitations. First, there was heterogeneity in eGFR and serum creatinine across the included RCTs as well as heterogeneity in the definition of CIN, which may weaken the results of this meta-analysis. Second, only a few studies were included in analyses for NGAL, cystatin C, eGFR, mortality, and requirement of hemodialysis and rehospitalization. Third, subgroup analysis was performed only for CIN because of inadequate data. Fourth, only 3 articles involved in this study had a low risk of bias and 6 had a high risk. Thus, further large-scale RCTs are needed to confirm these findings.

Conclusion

The application of RIPC to patients with moderate renal impairment undergoing PCI/CA may be an effective method to reduce the risk of the occurrence of CIN. However, this needs to be confirmed by further high-quality evidence.

Statement of Ethics

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this study.

Conflict of Interest Statement

All the authors declared no competing interests.

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Author Contributions

J.D., J.O., and H.X. designed the study. Y.L. and J.D. were responsible for acquisition and analysis of data. X.W. and X.S. were responsible for data interpretation. Y.L. and J.D. wrote the manuscript. All authors critically revised the paper and approved the final version.

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