Original Article

Periprocedural Nebivolol for the Prevention of Contrast-Induced Acute Kidney Injury: A Systematic Review and Meta-analysis

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Abstract

Background: Nebivolol provides a protective effect on contrast-induced acute kidney injury (CIAKI) in animal models. However, the reports on the efficacy of nebivolol for the prevention of CIAKI in human remain unclear. **Aims:** The objective of this meta-analysis was to assess the effect of nebivolol for the prevention of CIAKI. **Materials and Methods:** Comprehensive literature searches were performed using MEDLINE, EMBASE, and Cochrane Database from inception through February 2015. Studies that reported relative risks, odd ratios, or hazard ratios comparing the risk of CIAKI in patients who received nebivolol versus those who did not were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. **Results:** Four studies (2 randomized controlled trials and 2 cohort studies) with 543 patients were included in our analysis to assess the risk of CIAKI and the use of nebivolol. Patients in the nebivolol group had an overall lower incidence of CIAKI (14.4%) compared to the control group (18.4%). The pooled RR of CIAKI in patients receiving nebivolol was 0.66 (95% CI: 0.38-1.15, $I^2 = 0$). When meta-analysis was limited only to randomized control trials (RCTs), the pooled RR of CIAKI in patients receiving nebivolol was 0.79 (95% CI: 0.35-1.79, $I^2 = 0\%$). **Conclusions:** Despite no statistical significance, there was a trend toward reduced CIAKI risk in patients receiving nebivolol. The findings of our meta-analysis suggest the need of a large RCT with very careful attention to the balance of benefits and harms.

Keywords: B-Blocker, contrast-induced nephropathy, contrast-induced acute kidney injury, meta-analysis, nebivolol

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Introduction

Acute kidney injury (AKI) is a frequent clinical syndrome in hospitalized patients. Among causes of AKI,[1-6] contrast-induced nephropathy or contrast-induced acute kidney injury (CIAKI) is a common encounter, with an incidence of 2% in the general population without risk factors to more than 40% in high-risk patients.[7-13] In addition, the incidence of CIAKI has been rising in recent years due to the increasing use of cardiac angiography and percutaneous coronary intervention.[14,15] A number of studies have attempted to identify effective interventions to prevent CIAKI including hydration with intravenous isotonic saline, oral hydration, sodium bicarbonate infusion, N-acetylcysteine, nonionic low-osmolar agents, and statin administration.[10,16,17] However, CIAKI is still it is a growing problem worldwide accounting for approximately 150,000 patients each year.[18] Patients

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with CIAKI have also been shown to have longer hospitalizations and higher mortality rates.[19] Thus, further studies to investigate interventions to prevent CIAKI are needed.

Nebivolol, a third-generation beta-blocker, has recently been proposed to be a potentially effective agent to help prevent CIAKI, since it provides nitric oxide (NO)-induced vasodilation and antioxidant properties.[20] Previous studies were conducted to assess the efficacy of nebivolol in humans for CIAKI prevention. The results of several studies trended toward the protective effects of nebivolol for CIAKI prevention.[21-23] Conversely, a study showed no beneficial effect of nebivolol for the prevention of CIAKI.[24] However, these studies included small sample sizes and the findings did not show a significant role of nebivolol in CIAKI. Thus, we performed this meta-analysis to assess the effect of nebivolol for the pharmacologic prevention of CIAKI.

Materials and Methods

Data sources and searches

We performed a MEDLINE search (through February 28, 2015), Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov to identify eligible studies using the Medical Subject Headings database search terms "nebivolol AND contrast- induced nephropathy," "beta-blocker AND contrast-induced nephropathy," "nebivolol," "contrast-induced acute kidney injury," "CIAKI," and "contrast-induced nephropathy." The search is limited to studies in humans aged 18 and older. We also include unpublished studies in the form of posters and abstracts in our search strategy.

Study selection

We included randomized and prospective clinical trials examining the incidence of CIAKI and pre- and post-contrast exposure serum creatinine in a patient with any kind of contrast exposure. Nebivolol was required as the intervention for CIAKI prevention. There were no restrictions on sample size, or study duration. Two authors (NT and WC) independently screened the titles and abstracts of all electronic citations, and full text articles were retrieved for comprehensive review and independently re-screened.

Data extraction and quality assessment

The following data were extracted from the studies examined in the study: Year of publication, study design, sample size, percentage of male subjects, mean age of subjects, incidence of CIAKI, precontrast serum creatinine, 48 h postcontrast creatinine, percentage of diabetes, and interventions of treatment and control groups. Differing decisions were resolved by mutual consensus. Study quality was assessed with a modified version of the Jadad *et al*. scale[25] for randomized control trials (RCTs) and Newcastle-Ottawa quality assessment scale[26] for observational studies.

Data synthesis and analysis

We used random-effects model meta-analyses to assess standardized net changes in continuous outcomes. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird.[27] All pooled estimates are displayed with a 95% confidence interval (CI). Statistical heterogeneity was assessed using the Cochran's Q-test. This statistic is complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0-25% represents insignificant heterogeneity, 26-50% low heterogeneity, 51-75% moderate heterogeneity, and >75% high heterogeneity.[28] The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios versus their standard errors.[29] The meta-analyses were performed with Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).

Results

Characteristics and quality of the studies

A total of 190, potentially relevant studies were identified and screened; 12 full texts were evaluated. Four studies fulfilled our inclusion criteria for the meta-analysis. Finally, 543 patients from 4 studies were included in our analysis to assess the risk of CIAKI and the use of nebivolol.[21-24] Two studies were RCT[23,24] and other two were cohort studies.[21,22] One study was reported as an abstract for poster presentation.[21] The subjects were patients undergoing scheduled coronary angiography. In the above trials, intravenous isotonic saline was administered before contrast exposure in all patients and nebivolol was given to the intervention group. The trials followed patient creatinine before coronary angiography contrast exposure and at 48 h after exposure, and included sample sizes ranging from 90 to 247 patients.

All studies included both diabetic and nondiabetic patients. The mean serum creatinine (SCr) ranged from 0.8 to 1.54 mg/dL and one study was conducted in patients with mild renal insufficiency (SCr >1.2 mg/dL).[22] The mean age of the subjects ranged from 59 to 67 years. Characteristics of the individual trials are displayed in Table 1.

Table 1: Main characteristics of the studies included in this meta-analysis

Characteristics	Avci *et al.*[22]	Gunebakmaz *et al.*[23]	Altunoren *et al.*[21]	Akgullu *et al.*[24]
Country	Turkey	Turkey	Turkey	Turkey
Study design	Cohort study	RCT	Cohort study (abstract)	RCT
Year	2011	2012	2014	2014
Total number	90	120	106	247
Mean age (year)	59	65	67	60
Male sex (%)	61	69	45	53
DM (%)	58	31	56	30
Baseline Cr (mg/dL)	1.5	1.4	1.0	0.8
Procedure/type of contrast	CAG/ioxaglate (low-osmolar, nonionic contrast)	CAG/iopromide (low-osmolar, nonionic contrast)	CAG/iohexol (low-osmolar, nonionic contrast)	CAG/iopromide (low-osmolar, nonionic contrast)
Intervention group	Nebivolol 5 mg/day starting 1 week before angiography and continue at least 48 h and NSS 1 mL/kg/h for 12 h before and 24 h after the procedure. NAC 600 mg 2 times/day at 24 h before and 48 h after	Nebivolol 5 mg/day for 4 days (2 doses before procedure day, 1 dose on the day of the procedure and 1 dose the day after). NSS 1 mL/kg/h 6 h before and 12 h after angiogram	Nebivolol 5 mg/day and NSS hydration (author did not mention the duration)	Nebivolol 5 mg/day at least 2 weeks and maximum at 1 month then continuing until 5 days after angiogram
Control group	Metoprolol 50 mg starting 1 week before angiography and continue at least 48 h and NSS 1 mL/kg/h for 12 h before and 24 h after the procedure. NAC 600 mg 2 times/day at 24 h before and 48 h after	NSS 1 mL/kg/h 6 h before and 12 h after angiogram	NSS hydration	NSS 1mL/kg/h for 12 h before and after the procedure. Subjects were not using beta blocker at least for the last 2 weeks before procedure
Contrast-induced nephropathy definition	Increase in serum Cr of ≥25% within 48 h after procedure compared to baseline	Increase ≥0.5mg/dL or ≥ 25% of serum Cr at day 2 and/or day 5 after the procedure	Increase in serum Cr of 0.5 mg/dL or 25% increase from baseline within 48 h after angiography	Increase in serum Cr of 0.5 mg/dL or 25% increase compared with baseline over 48-h period after contrast when no other viable cause exists
Adjusted OR or RR	0.59 (0.23-1.51)	0.66 (0.23-1.86)	0.51 (0.14-1.87)	1.05 (0.29-3.84)
Quality assessment scale[25]	Selection: 3 Comparability: 1 Outcome: 3	Randomization: 1 Blinding: 0 Follow-up: 1	Selection: 3 Comparability: 0 Outcome: 3	Randomization: 2 Blinding: 0 Follow-up: 1

DM: Diabetes mellitus; Cr: Creatinine; CAG: Coronary angiogram; NAC: N-acetylcysteine; NSS: Normal saline; OR: Odds ratio; RR: Relative risk; RCT: Randomized controlled trial

The risk of contrast-induced acute kidney injury in nebivolol and control groups

Patients in the nebivolol group had an overall lower incidence of CIAKI (14.4%) compared to the control group (18.4%). The pooled risk ratios (RR) of CIAKI in patients receiving nebivolol was 0.66 (95% CI: 0.38-1.1.15, I^2 = 0). Figure 1 shows the forest plot of the included studies. Sensitivity analysis was limited to only RCTs and demonstrated the pooled RR of CIAKI in patients receiving nebivolol of 0.79 (95% CI: 0.35-1.79) as shown in Figure 2. The statistical heterogeneity was insignificant with an I^2 of 0%.

Evaluation for publication bias

A funnel plot to evaluate publication bias for the risk of CIAKI in patients receiving nebivolol versus a control group is summarized in Figure 3. The graph is fairly symmetric demonstrating insignificant publication bias.

Discussion

Our meta-analysis showed an overall incidence of CIAKI of 5.3% in patients with contrast exposures. Patients in the nebivolol group had a lower incidence of CIAKI (14.4%) when compared to the control group (18.4%). Based on the pooled incidence of CIAKI in the nebivolol and control groups, the number needed to treat (NNT) (the number of patients) to prevent a CIAKI event using nebivolol is 25. Our study also demonstrated a protective effect of periprocedural statins on the incidence of CIAKI.

The kidney disease: Improving global outcomes AKI guideline suggests that intravascular volume expansion, either with normal saline or mixing with sodium bicarbonate, is the most effective way to prevent CIAKI.[30] Despite these preventative measures, CIAKI is still a common clinical problem among hospitalized patients which results in increased length of hospital stay and mortality. Thus, studies have investigated potential pharmacologic agents to reduce the CIAKI risk.

Although the underlying pathogenesis of CIAKI is not completely understood, proposed mechanisms of CIAKI include direct tubular injury mediated by an increase in free radicals and hemodynamic changes of renal blood flow by modulating the actions of dopamine, adenosine, angiotensin II, endothelin, and NO.[31,32] According to the animal studies,[20,33] nebivolol, a selective beta-1 adrenergic receptor blocker can increase the renal NO excretion, enhance NO bioavailability, and prevent deactivation of NO leading to vasodilatation and improved renal blood flow.[34] In addition, nebivolol was found to have a protective role against CIAKI in albino rats.[20] Rats pretreated with nebivolol were found to have significantly less oxidative stress markers and histological abnormalities

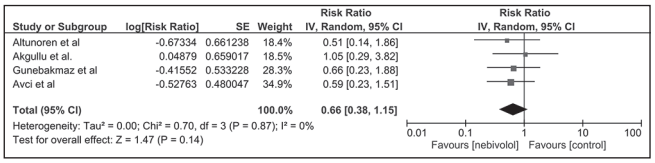

Figure 1: Forest plot of the meta-analysis of all included studies comparing the risk of contrast-induced acute kidney injury in patients who received nebivolol and those who did not; square data markers represent risk ratios; horizontal lines, the 95% confidence intervals with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall risk ratio and 95% confidence interval for the outcome of interest. IV: Inverse variance; SE: Standard error

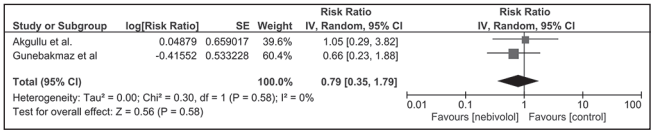

Figure 2: Forest plot of the meta-analysis of randomized controlled trials comparing the risk of contrast-induced acute kidney injury in patients who received nebivolol and those who did not; square data markers represent risk ratios; horizontal lines, the 95% confidence intervals with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall risk ratio and 95% confidence interval for the outcome of interest. IV: Inverse variance; SE: Standard error

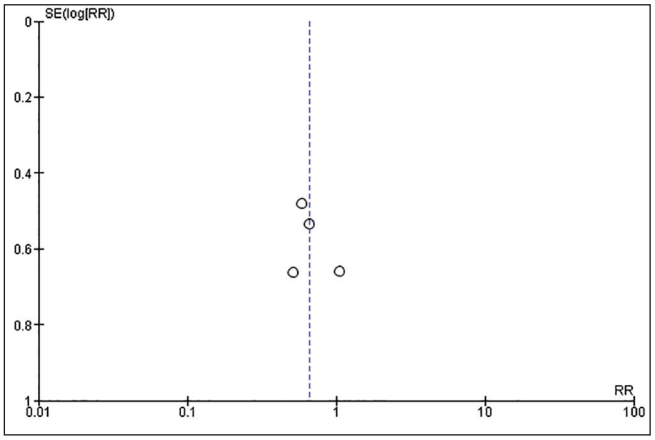

Figure 3: Funnel plot of 4 studies included in the meta-analysis for the risk of CIAKI in patients who received nebivolol. The graph is slight asymmetric and suggests the presence of publication in favor of negative studies. RR: Risk ratio; SE: Standard error.

compared to the control rats. Our study compared the risk of CIAKI between nebivolol group and standard treatment, which is normal saline infusion. Based on the meta-analysis, nebivolol reduces the incidence of CIAKI (18.4% vs. 14.4%). Despite the statistical insignificance of the complete analysis, there was a trend toward the reduction of CIAKI risk in nebivolol treated patients without significant heterogeneity. The insignificant result is likely due to underpowered studies with relatively small sample sizes, especially since the NNT to prevent a CIAKI event using nebivolol in our meta-analysis was

25. Therefore, the findings of our meta-analysis suggest the need of a large RCT.

Despite no significant heterogeneity or publication bias in our complete analysis, there are several limitations in our study. First, a causal relationship needs to be cautiously interpreted because observational studies were included in our meta-analysis. However, a trend toward the reduction of CIAKI risk in nebivolol existed in the sensitivity analysis limited to the only RCTs. In addition, all included studies were conducted in Turkey. Therefore, the generalizability of potential benefit of nebivolol to different populations is limited and future studies are required.

In summary, our meta-analysis demonstrated a trend toward reduced CIAKI risk in patients receiving nebivolol. A large RCT-with very careful attention to the balance of benefits and harms is needed.

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Conflicts of interest

There are no conflicts of interest.

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