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The efficacy of sodium bicarbonate preventing contrast-induced nephropathy in patients with preexisting renal insufficiency: a meta-analysis

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ABSTRACT

Objective: The primary objective of this meta-analysis was to explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy (CIN) and assess if it could reduce the risks of dialysis and mortality, thus improving the clinical prognosis of patients with CIN.

Methods: A comprehensive literature search of PubMed, Medline and Cochrane Library was conducted through August 2014.The effect estimate was expressed as pooled odds ratio(OR) with 95% confidence interval(CI),using the random-effects model.

Results: A total of 20 clinical trials consisting of 4,280 patients were absorbed into this study. Pre-procedural hydration with sodium bicarbonate was associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency(OR 0.67; 95%CI 0.47-0.96; P=0.027).However, moderate heterogeneity was noted among the included trials(I^2=48%;P=0.008).Therefore, we performed subgroup analyses and indicated a more pronounced effect of sodium bicarbonate in studies using low-osmolar contrast agents(OR 0.59; 95%CI: 0.37-0.93,P=0.024) compared with those using iso-osmolar ones(OR 0.76; 95%CI: 0.43-1.34,P=0.351). Similarly,a lower odds of CIN with sodium bicarbonate occurred in studies including exclusively patients undergoing emergency procedures (OR 0.16; 95%CI: 0.05-0.51, P=0.002)compared with those undergoing elective ones (OR 0.76;95%CI:0.54-1.06, P=0.105). Furthermore, sodium bicarbonate played a more active role in patients given bolus injection before procedures (OR 0.15; 95%CI: 0.04-0.54, P=0.004) compared with continuous infusion(OR 0.75; 95%CI:0.53-1.05,P=0.091).

Sodium bicarbonate plus N-acetylcysteine (NAC) (OR 0.17; 95%CI:0.04-0.79,P=0.024) outweighed sodium bicarbonate alone (OR 0.71;95%CI:0.48-1.03,P=0.071).The effect of sodium bicarbonate was considered greater in papers published before 2008(OR 0.19;95%CI:0.09-0.41,P=0.000) than after 2008(OR 0.85; 95%CI: 0.62-1.16, P=0.302).

However, no significant difference was found in the mortality (OR 0.69;95%CI:0.36-1.32,P=0.263)and need for dialysis(OR 1.08;95%CI:0.52-2.25,P=0.841).

Conclusions: Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency. However, it failures to lower the risks of dialysis and mortality and thus cannot improve the clinical prognosis of patients with CIN.

Article summary

Article focus:

- To explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy.
- To assess if sodium bicarbonate could reduce the risks of dialysis and mortality, thus improving the clinical prognosis of patients with CIN.

Key messages:

- Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency.
- Infusion of sodium bicarbonate failures to lower the risks of dialysis and mortality.

Strengths and limitations of this study

- In this updated meta-analysis, we demonstrate that pre-procedural hydration with sodium bicarbonate is associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency.
- In this study, we find that sodium bicarbonate failures to lower the risks of dialysis and mortality and thus cannot improve the clinical prognosis of patients with CIN.
- New Jadad Scale after revision was used to assess the quality of articles.
- No publication bias.
- However,moderate heterogeneity was noted among the included trials.

Keywords: Sodium bicarbonate; Saline; Contrast-induced nephropathy; Renal insufficiency; Meta-analysis

Introduction

Contrast-induced nephropathy is the third leading cause of in-hospital acute kidney injury[1-3], which is a serious complication of angiographic procedures resulting from the administration of contrast media. Although the definition of CIN is various, CIN is usually defined as an increase in serum creatinine level of 25% or an increase of 0.5mg/dl (or 44μmol/L) from baseline within 48-72h of contrast exposure. It results in increased morbidity, prolonged hospital stay, and increased healthcare expenditure and is associated with a higher mortality[4].

The incidence of CIN in the general population is low, but increases exponentially in patients with high-risk factors, such as preexisting renal insufficiency, diabetes mellitus[5]. In a recent study, 21.7% of preexisting chronic renal insufficiency group and 6.3% of no preexisting chronic renal insufficiency group developed CIN[6]. Thus, baseline renal insufficiency was a significant predisposing factor of CIN.

To prevent CIN, sodium bicarbonate-based hydration has been proposed as one of the feasible therapies. According to recent studies, some of them suggested that for prevention of CIN, sodium bicarbonate elicited more protective effect compared with sodium chloride, but others did not [7-17]. Although most previous meta analyses were on the side of sodium bicarbonate with possible publication bias, none of them focused on the patients with preexisting renal insufficiency. Therefore, we performed this meta-analysis to test the efficacy of sodium bicarbonate in preventing of contrast-induced nephropathy among patients with renal insufficiency undergoing various procedures that need contrast agents. What's more, differences in need for dialysis and post-procedural death between two arms were also compared in this study.

Methods

Data Sources and Searches

We searched PubMed, Medline, Cochrane Library from 2004 through to 1 August 2014. Medical subject headings and keyword searches included the terms "contrast

induced nephropathy", "sodium bicarbonate", "sodium chloride", "saline", "acute kidney injury", "renal failure". Reference lists of selected articles were reviewed for other potentially relevant citations. In addition, top 50 citations for each identified relevant study were searched by using the "related articles" function of PubMed.

Study Selection

Firstly, two investigators(B.Z and L.L) independently reviewed the titles and abstracts of all studies searched to identify all potentially relevant ones. Secondly, the online publications obtained from preliminary selection were reviewed in full text by the same two investigators to assess if studies met the following inclusion criteria: comparison of sodium bicarbonate versus sodium chloride or saline, RCT, age≧18 years, clinical end point assessment included CIN, patients with preexisting renal insufficiency: defined as a serum creatinine concentration of >1.1 mg/dl or estimated glomerular filtration rate(eGFR)<60ml/min[18]or creatinine clearance rate<60ml/min [9]. Reviewers were not blinded to study authors or outcomes. Final inclusion of studies was based on the agreement of both reviewers.

Data Extraction and Quality Assessment

Two reviewers(B.Z and WB.C) extracted relevant information from the literatures including baseline clinical characteristics(mean age, the percentage of males, risk factors other than renal insufficiency, baseline Scr, eGFR, procedures, interventions, type and volume of contrast media , hydration regimen, definition of CIN)(Tab1) and data on primary(the incidence of CIN) and secondary outcomes, such as need for dialysis, mortality. CIN was defined variously in studies, but most of them described it as a absolute or relative increase in the level of serum creatinine. Three studies defined CIN as a rise in serum creatinine by 25% or more within 2-5d of contrast exposure [12,19,20]. Thirteen studies regarded an increase of 0.5mg/dl or 25% in Scr within 2-4d of contrast. Two studies considered a elevated Scr of 0.5mg/dl after the procedures[9, 15]. However, two other trials presented were different from all above,

a decrease in eGFR of 25% within 4d and an absolute increase in Scr of at least 0.3mg/dl or 50% or Urine output<0.5ml·kg^{-1}·h^{-1}(>6h) within 5d were selected to define CIN, respectively[8,17]. We assessed the quality of articles using New Jadad Scale after revision(Tab 2).

Data Synthesis and Analysis

The data from included studies were combined and expressed as pooled OR with 95%CI. All analyses were performed on an "intention-to-treat" basis. Initially, fixed -effects model (Mantel-Haenzel method) was used in this meta-analysis. We evaluated the heterogeneity across studies with the Q and I^2 statistics. If P value<0.1, statistically significant heterogeneity was considered. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0-30%,31-50% and greater than 50% representing mild, moderate and substantial heterogeneity, respectively. The outcome of fixed-effects model analysis demonstrated a statistical heterogeneity, so we selected random-effects model (Dersimonian and Laird method).

Considering of the clinical and statistical heterogeneity across studies, subgroup analyses were performed to assess the effect of sodium bicarbonate in various conditions, such as low-osmolar vs.iso-osmolar contrast agent, emergency vs.elective procedures, article published before vs. after 2008, and continuous vs.bolus infusion of sodium bicarbonate (Tab 3). An influence analysis was carried out to evaluate how robust the pooled estimator is after removal of individual studies(Fig 4). An individual study is suspected of excessive influence if the point estimate of its omitted analysis lies outside the 95%CI of the summary analysis.Publication bias was assessed using Begg' funnel plot and Egger' regression asymmetry test(Fig 5). All statistical analyses were conducted using STATA software, version 12.0(Stata Corp LP,College Station, Texas).

Results

A total of 837 articles were reviewed and 20 studies met the inclusion criteria were absorbed into this study finally(Fig 1).

A detailed description of the baseline characteristics of the included studies is given in Tab 1. Patients in most studies underwent coronary angiography or Interventional procedures. There were also seven studies depicted peripheral procedures, angioplasty, cardiopulmonary bypass and CT[8,18,19,21-24]. The sodium bicarbonate hydration regimen in thirteen studies was described as same as Merten et al: the infusion of sodium bicarbonate at rate of $3ml \cdot kg^{-1} \cdot h^{-1}$ for 1h before and $1ml \cdot kg^{-1} \cdot h^{-1}$ for 6h after the procedure.

Primary Outcome

CIN occurred in a total of 158 patients in the 2,130 patients of the sodium bicarbonate arm compared with that of 217 patients in the 2,150 patients who received saline, a lower overall incidence of CIN was found in the sodium bicarbonate group(Fig 2). The pooled OR was 0.67 (95%CI:0.47-0.96; P=0.027) also in favor of sodium bicarbonate(Fig 2).

However, moderate heterogeneity across studies was observed(I^2=48%,P=0.008) (Fig 2).

Therefore, subgroup analyses were constructed and suggested a more pronounced effect of sodium bicarbonate in studies using low-osmolar contrast media(OR 0.59; 95%CI: 0.37-0.93,P=0.024) (Tab 3). Similarly, subgroup analysis by the setting suggested lower odds of CIN with sodium bicarbonate in studies with patients undergoing emergency procedures (OR 0.16; 95%CI 0.05-0.51, P=0.002) (Tab 3). Before 2008, the effect of sodium bicarbonate was considered greater in articles reported(OR 0.19;95%CI:0.09-0.41,P=0.000)(Tab 3). Furthermore, subgroup analysis according to the manner of sodium bicarbonate administration showed better effect in patients given bolus injection (OR 0.15; 95%CI 0.04-0.54, P=0.004) (Tab 3).Sodium bicarbonate in combination with NAC showed a more salient efficacy in preventing

CIN(OR 0.17;95%CI:0.04-0.79,P=0.024)(Tab 3).

Influence analysis showed no individual study had excessive influence on the overall estimate odds ratios and 95%CI(Fig 4).

Begg' funnel plot and Egger' test(P=0.396) implied no significant publication bias in this study(Fig 5).

Secondary Endpoints

Need for dialysis

The need for dialysis was described in a total of 17 studies(n=3,633). In eight of these studies, there was no dialysis event in both groups[11,12,15,16,18,19,22,24]. Overall, 14 out of 1,809 patients who treated with sodium bicarbonate underwent dialysis compared with 13 out of 1,824 patients treated with saline. No statistical significant difference was observed (OR 1.08; 95%CI 0.52-2.25, P=0.841) (Fig 3a), nonetheless, the OR for the requirement of dialysis suggested that maybe sodium bicarbonate was no better than saline in terms of reducing the dialysis events.

Mortality

Post-procedural death was described in a total of 12 studies(n=2,559), in six studies, there was no death in either group[11,13,14,16,23,24]. There were altogether 15 deaths in the 1,279 patients treated with sodium bicarbonate and 22 in the 1,280 patients treated with saline. Although there was no significant difference between the two arms (OR 0.69; 95%CI 0.36-1.32, P=0.263) (Fig 3b), a trend toward lower mortality risk occurred in sodium bicarbonate arm compared with saline arm.

Discussion

Although CIN is generally regarded as a transient decline in renal function after contrast procedures, it cannot be regarded as a benign complication[25,26]. It accounts for 12% of all cases of acute renal failure[27]. In a observational study, 0.8% of included patients undergoing coronary angiography or Interventional procedures started dialysis and 13% of them needed a permanent one[28]. Furthermore, the

development of CIN is associated with a longer hospital stay, an increased morbidity and mortality, in addition to a higher financial cost. Consequently, we can never be blind to the hazard of CIN.

Various risk factors may contribute to CIN, which are divided into two groups: patient- and procedure-related[29]. Preexisting renal insufficiency and diabetes mellitus are the two main patient- related risk factors. That is one reason why we focus on the patients with a history of renal insufficiency. Renal insufficiency was usually defined as a decrease in eGFR and since the eGFR has to be reduced by 50% before a rise in serum creatinine occurs, an elevated serum creatinine level was used as the cut-off point for the definition for renal insufficiency[21]. In a retrospective review of 938 patients with stable renal insufficiency, the overall incidence of CIN was 6.1%, and the incidence was 4.4%, 10.5%, 10.0% for patients whose eGFR was 45-60, 30-45, and ≤30ml/min, respectively[30]. Hence special care should be taken in patients with renal insufficiency.

In order to prevent CIN, sodium bicarbonate has been proposed by various mechanisms[31,32]. Namely, how does it work remains unknown. Some potential mechanisms are that alkalinizing the tubular urine with sodium bicarbonate may attenuate free radical formation and peroxide injury[28].Oxygen free radicals and peroxide usually generate in acidic conditions, infusion of sodium bicarbonate could increase the PH of local renal tissue to neutral or slightly alkaline, thereby reducing the production of free radicals and peroxide. Merten et al[19] first introduced the administration of sodium bicarbonate in a concentration of 154mmol/L to prevent CIN. In this study, hydration regimens of 13 trials [9-17,19-21,33] were performed similarly to “Merten protocol”. Although most previous systematic reviews and relevant meta-analyses demonstrated that sodium bicarbonate infusion could decrease the incidence of CIN[25,26,34-42], secondary clinical endpoints as diverse as renal replacement therapy and mortality were not ameliorated. Furthermore, a

retrospective cohort study of 7,977 patients at Mayo Clinic got a surprising result: sodium bicarbonate was associated with an increased incidence of CIN[43]. By contrast with a majority of RCTs using creatinine elevations within 48-72h after contrast exposure to define CIN, From et al extended the definition time of CIN to a week based on the fact that creatinine may peak 3 to 7d after contrast. However, this issue remains to be discussed. Because in our study, all the patients with a history of renal insufficiency, the peak of serum creatinine may advance.

In this meta-analysis, underlying sources of moderate heterogeneity should be taken into account, because the study subjects, study settings and type of contrast media were varied. In this case, subgroup analyses were conducted and the results revealed significant differences between emergency and elective procedures, the protective role of sodium bicarbonate played better in the former than latter. In a meta-analysis[42] of the effect of sodium bicarbonate for the prevention of CIN, subgroup analyses also showed a more pronounced efficacy of sodium bicarbonate in 3 trials[18,33,44] included patients undergoing emergency procedures compared with those undergoing elective procedures. But the exact mechanism by which sodium bicarbonate results in a decrease incidence of CIN is still a mystery. Maybe it's related to manner of administration and dosage. Similarly, sodium bicarbonate was more beneficial in patients who received low-osmolar contrast agents[45,46]. However, because of the significantly smaller case number of included patients who received iso-osmolar contrast media (n=1,189) compared with those received low-osmolar ones(n=2,823), the major reason responsible for the more salient effect of sodium bicarbonate is difficult to elucidate.

Although the utilization of N-acetylcysteine(NAC) has been known to reduce the incidence of CIN and the value of it has been the focus of many studies, the definitive effect of NAC is not yet established. Not a few trials and meta-analyses indicated the combination of sodium bicarbonate and NAC is superior to either regimen in

preventing of CIN. Also, three studies[20,44,47] included patients who received NAC in both groups after the infusion of sodium bicarbonate or saline and the results were in favor of sodium bicarbonate. The BINARIO[48]study indicated that hydration with sodium bicarbonate in addition to high-dose NAC in the setting of urgent PCI for STEMI was associated with a net clinical benefit. However, Yang et al[27]and Thayssen et al [49]concluded that use of NAC caused no significant reduction in the incidence of CIN. In our study, because of only one trial[20]using NAC included in the sub-analyses, the effect of which may be overestimated (OR 0.17;95%CI 0.04-0.79, P=0.024). Accordingly, more large-scale and well-designed randomized clinical trials are warranted to determine whether sodium bicarbonate plus NAC is more useful in preventing CIN than either alone.

Many studies have now shown that patients with CIN have a greater risk for the renal replacement therapy and death. In fact, almost all the dialysis and death events occurred in patients with CIN who have high-risk factors. So we could not rely on sodium bicarbonate alone to improve the bad situations caused by CIN together with basic diseases, such as renal insufficiency, diabetes mellitus. Maybe that is one vital reason why we did not find a significant difference in both requirement of dialysis and mortality. However, the lack of power of included RCTs could also be attributed to. In this meta-analysis, not all studies described renal replacement therapy and mortality and sample sizes were relatively small. So this issue needs further research.

Conclusions

Our meta-analysis demonstrates the administration of sodium bicarbonate is superior to the administration of saline in the prevention of CIN in patients with preexisting renal insufficiency undergoing procedures requiring contrast media. However, the use of sodium bicarbonate did not result in clear benefit in regard to reductions in requirement of dialysis and mortality. Therefore, more large sample trials are required to detect the efficacy of sodium bicarbonate in preventing CIN and

improving the clinical prognosis of patients with CIN.

Footnotes

Contributors: B.Z, L.L and WB.C searched the studies. B.Z wrote the manuscript.

L.L ,WB.C, CH.L and SX.Z reviewed, analyzed and helped writing the manuscript.

All authors contributed to the conception and design of this study.

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Tab 1 The baseline characteristics of included studies

Study	Cases	Age(years)		Male(%)	DM	HT	Baseline Scr(mg/dl)		eGFR(ml/min/1.73m²)	
		Bicarbonate	Saline		%	%	Bicarbonate	Saline	Bicarbonate	Saline
Merten	119	66.7*	69.2*	73/76	50/46	NA	1.89*	1.71*	41.0*	45.0*
Ozcan	176	68.0*	70.0*	76/75	42/48	75/81	1.36*	1.40*	NA	NA
Masuda	59	75.0±8.0	76.0±11.0	63/59	27/35	NA	1.31±0.52	1.32±0.65	40.2±15.4	38.7±15.4
REMEDIAL	219	70.0±9.0	71.0±9.0	88/81	49/55	92/87	2.04*	1.95*	32.0±7.0	71.0±9.0
Adolph	145	70.1±8.4	72.7±6.6	75/81	37/28	83/91	1.54±0.51	1.57±0.36	NA	NA
Brar	323	71.0*	71.0*	62/65	43/46	NA	1.49#	1.49#	47.7#	48.3#
Maioli	502	74.0*	74.0*	57/61	25/23	59/57	1.21±0.30	1.20±0.30	NA	NA
Tamura	144	72.3±9.9	73.3±7.7	92/83	60/57	85/83	1.36±0.18	1.38±0.19	40.0±7.5	38.2±0.2
Vasheghani	265	62.9±10.0	63.8±9.0	84/82	22/21	30/41	1.63±0.32	1.66±0.50	46.4±12.0	45.4±12.0
Castini	103	70.0±8.3	72.7±8.2	85/84	35/20	71/78	1.59±0.38	1.49±0.30	46.9±12.8	49.9±10.3
Vasheghani(2)	72	61.4#	62.7#	78/81	33/38	66/71	1.77#	1.71#	42.7#	44.2#
Motohiro	155	71.0±9.0	74.0±7.0	76/64	56/63	86/83	1.54±0.43	1.55±0.44	45.7±12.9	42.8±13.8
PREVENT	382	65.8*	67.5*	71/71	100/100	77/80	1.50*	1.50*	46.0*	46.0*
Ueda	59	77.0±9.0	75.0±10.0	77/79	10/10	NA	1.32±0.46	1.51±0.59	42.4±11.5	38.7±12.6
Klima	176	78.0*	75.0*	66/62	39/34	90/81	1.60*	1.60*	43.1#	43.0#
Gomes	301	64.1±12.0	64.5±12.0	15/75	29/30	77/74	1.50±0.40	1.49±0.50	50.5±13.0	51.9±13
Hafiz	320	74.0*	73.0*	57/57	49/45	95/94	1.65*	1.60*	41.5*	40.5*
Kristeller	92	72.0±11.0	73.0±11.0	64/52	52/38	89/92	NA	NA	48.9#	49.4#
Boucek	120	63.0#	67.0#	75/75	NA	NA	1.92#	1.81#	43.6#	44.6#
Kooiman	548	71.6#	72.5#	60/61	27/27	NA	NA	NA	49.9#	50.9#

Note: DM=diabetes mellitus HT=hypertension eGFR=estimated glomerular filtration rate NA= not applicable
*median value #mean value

Tab 1 Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective diagnostic /interventional procedures	SB vs SC	NA	NA Iopamidol,nonionic,Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥25% within 2d
Elective CAG/PCI	SB vs SC	100* Ioxaglate,ionic,Low-osmolar	100*	1ml·kg^{-1}·h^{-1} for 6h before and after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
Emergency CAG/PCI	SB vs SC	112±89 Iopamidol,nonionic,Low-osmolar	120±61	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
Elective CAG/ PCI /peripheral procedure	SB+NAC vs NS+NAC	169±92 Iodixanol,nonionic,Iso- osmolar	179±9	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑≥25% within 2d
Elective CAG/PCI	SB vs SC	141±50 Iodixanol,nonionic,Iso- osmolar	138±52	2ml·kg^{-1}·h^{-1} for 2h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
Elective CAG	SB vs SC	126* Ioxilan,nonionic,Iso- osmolar	137*	3ml·kg^{-1}·h^{-1} for 1h before and 1.5ml·kg^{-1}·h^{-1} for 4h after the procedure of SB or SC	eGFR↓>25% within 4d
Elective CAG/PCI	SB vs IS	160* Iodixanol,nonionic,Iso- osmolar	170*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h after:IS	Scr↑≥0.5mg/dl within 5d
Elective CAG/PCI	Bolus SB+SC vs SC	82±40 Iohexol,nonionic,Low-osmolar	88±45	Single-bolus SB 20ml for 5min before and SC 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure; 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure of SC	Scr↑>0.5mg/dl or 25% within 3d
Elective CAG	SB+Is vs IS	115±41 Iohexl,nonionic,Low-osmolar	113.2±36	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after in both groups	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB vs SC	179±125 Iodixanol,nonionic,Low-osmolar	196±128	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and after:SC	Scr↑≥25% within 5d

Note：CAG=coronary angiography PCI=percutaneous coronary intervention SB=sodium bicarbonate SC= sodium chloride IS=isotonic saline NAC=N-acetylcysteine NS=normal saline Scr=serum creatinine

Tab 1 Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective CAG	SB+half SC vs half SC	112# Iohexol,nonionic, Low-osmolar	123#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of 75ml SB to1L of 0.45%SC; 1075ml 0.45%SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB+SC vs SC	140±50 Iopamidol, nonionic, Low-osmolar	130±40	1ml·kg^{-1}·h^{-1} SC 12h before and 1ml·kg^{-1}·h^{-1} SB from 3h pre-to 6h post-procedure, then 1ml·kg^{-1}·h^{-1} SC for 12h; 1ml·kg^{-1}·h^{-1} SC 12h pre- and 12h post- procedure	Scr↑≥0.5mg/dl or>25% within 2d
Elective CAG/ angioplasty/ endovascular intervention	SB vs SC	113* Iodixanol,nonionic , Low-osmolar	120*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h:SC	Scr↑≥0.5mg/dl or>25% within 2d
Emergency CAG/ PCI	SB vs SC	116±63 Iopamidol/Iohexol, Low-osmolar	104±57	Bolus 0.5mg/ml SB before and SC 1ml·kg^{-1}·h^{-1} for 6h during and after in both groups	Scr↑≥0.5mg/dl or >25% within 2d
Elective CAG/ PCI/ PTA/CT/ PAG	SB vs SC	100* Iopromide/iohexol.etc. Iso/Low-osmolar	100*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 24h:SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB vs NS	124±65 Hexabrix/Loxaglate, Low-osmolar	125±87	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or NS	Scr↑≥0.5mg/dl within 2d
Elective CAG/ PAG/ intervention	SB±NAC vs NS±NAC	110* Iodixanol/Iopamidol/Ioversol, nonionic,Low-osmolar	100*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑>0.5mg/dl or 25% within 2d
Elective CPB	SB vs IS	74# NA	83#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or IS	Scr↑≥0.3mg/dl or 50% or Urine output <0.5ml·kg^{-1}·h^{-1} (>6h) within 5d
Elective CAG/ Lower-limb angiography and /or angioplasty	SB vs NS	115# Iodinated,nonionic , low-osmolar	104#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CECT	SB vs IS	105.7# Iomeprol/Iobitridol/ Iodixanol,Low-osmolar	104.7#	250ml SB for 1h before; 1000ml IS before and 1000ml IS after	Scr↑＞0.5mg/dl or 25% within 4d

Note: PTA=percutaneous transluminal angioplasty PAG=peripheral angiography CPB=cardiopulmonary bypass CECT=contrast-enhanced computerized tomography

Tab 2 Quality assessment of included studies

Included trials	Trial described as randomized (1=yes, 0=no)	Randomized method described & appropriate (1=yes, 0=no)	Allocation concealment described† (1=yes, 0=no)	Allocation concealment described & appropriate (1=yes, 0=no)	Trial described as double blind (1=yes, 0=no)	Double blind method described & appropriate (1=yes,0=no)	Withdrawals & Dropouts described (1=yes,0=no)	Jadad score *
Merten	1	1	0	0	0	0	1	4
Ozcan	1	0	0	0	0	0	1	2
Masuda	1	1	0	0	0	0	1	4
REMEDIAL	1	1	0	0	1	0	1	5
Adolph	1	1	0	0	1	0	1	5
Brar	1	1	1	1	0	0	1	5
Maioli	1	1	1	1	0	0	0	4
Tamura	1	1	0	0	0	0	1	4
Vasheghani	1	1	0	0	1	0	0	4
Castini	1	1	0	0	0	0	0	3
Vasheghani(2)	1	1	0	0	1	0	0	4
Motohiro	1	1	0	0	0	0	1	4
PREVENT	1	1	0	0	0	0	1	4
Ueda	1	1	0	0	0	0	0	3
Klima	1	0	1	1	0	0	0	3
Gomes	1	0	1	1	0	0	0	3
Hafiz	1	1	0	0	0	0	1	4
Kristeller	1	1	1	1	1	0	0	5
Boucek	1	1	1	1	1	0	1	6
Kooiman	1	1	0	0	0	0	1	4

Note: †One point can be obtained from Jadad Score if randomization method of the trial is described &appropriate

*Calculation for quality assessment of included trials:low,1-3;high,4-7

Tab 3 Subgroup analyses: to assess the effect of sodium bicarbonate in various conditions

Subgroups	Trials/patients	OR(95%CI)	Test for overall effect	Heterogeneity
Type of contrast				
Low-osmolar	14/2823	0.59[0.37,0.93]	Z=2.26(P=0.024)	X^2=26.61,df=13(P=0.014),I^2=51%
Iso-osmolar	4/1189	0.76[0.43,1.34]	Z=0.93(P=0.351)	X^2=4.67, df=3(P=0.198),I^2=36%
Setting				
Elective	18/4162	0.76[0.54,1.06]	Z=1.62(P=0.105)	X^2=29.54,df=17(P=0.030),I^2=43%
Emergency	2/118	0.16[0.05,0.51]	Z=3.11(P=0.002)	X^2=0.07,df=1(P=0.784),I^2=0%
Using NAC or not				
Use	1/219	0.17[0.04,0.79]	Z=2.26(P=0.024)	Not applicable
Non-use	18/3741	0.71[0.48,1.03]	Z=1.80(P=0.071)	X^2=33.13,df=17(P=0.011),I^2=49%
Publication year				
Before 2008	4/573	0.19[0.09,0.41]	Z=4.26(P=0.000)	X^2=1.06,df=10(P=0.788),I^2=0%
After 2008	16/3707	0.85[0.62,1.16]	Z=1.03(P=0.302)	X^2=22.13,df=15(P=0.105),I^2=32%
Manner of administration				
Continuous	18/4077	0.75[0.53,1.05]	Z=1.69(P=0.091)	X^2=30.21,df=17(P=0.025),I^2=44%
Bolus	2/203	0.15[0.04,0.54]	Z=2.90(P=0.004)	X^2=0.23,df=1(P=0.632),I^2=0%

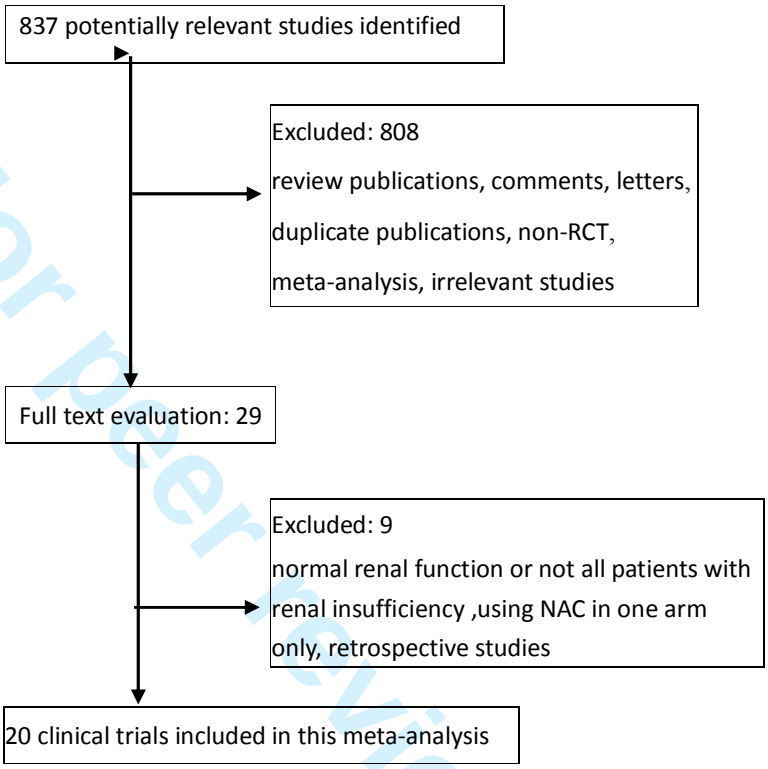


Fig 1 Selecting flow chart showing the number of excluded trials and the reasons, as well as the number of included trials

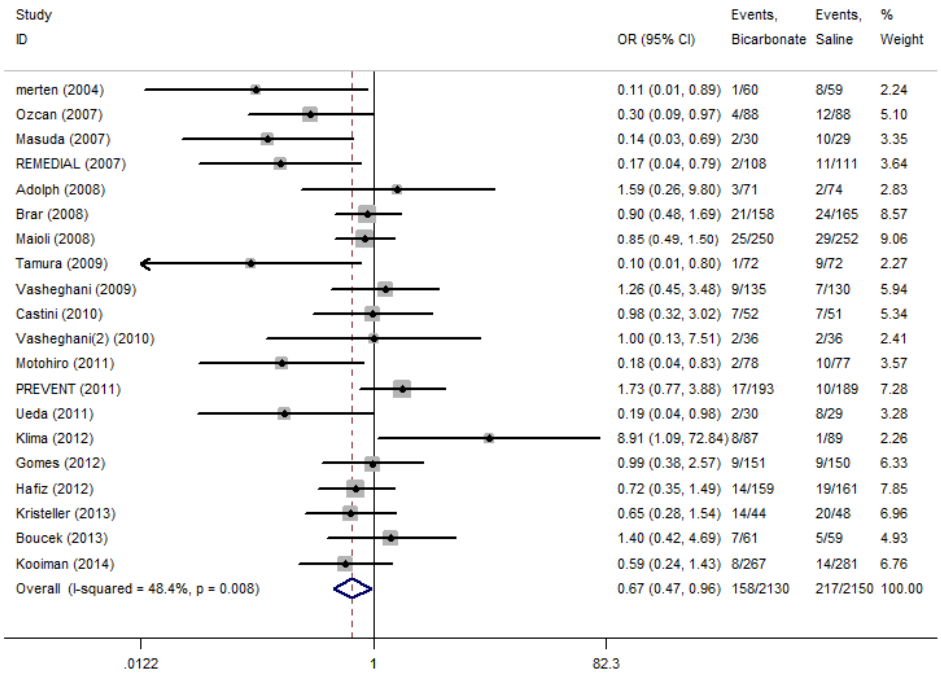


Fig 2 The Forest plot of odds ratios of contrast-induced nephropathy

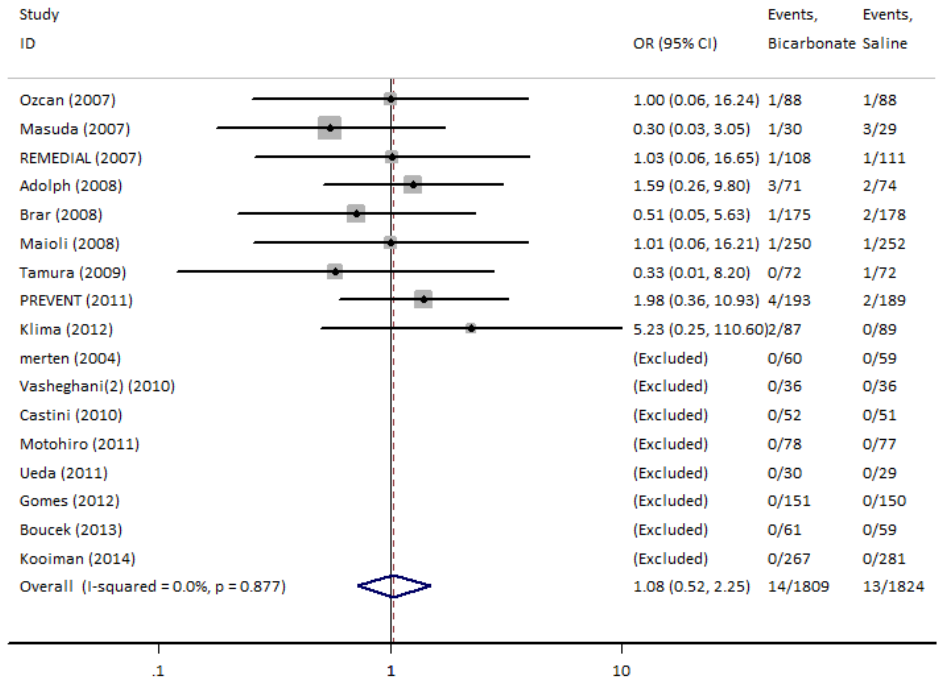


Fig 3a Need for dialysis

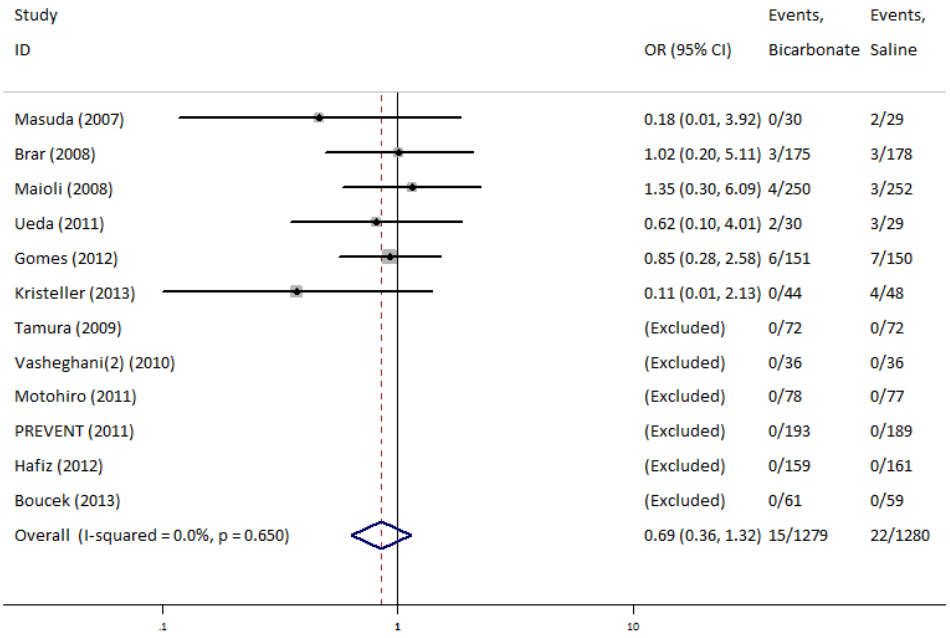


Fig 3b Mortality

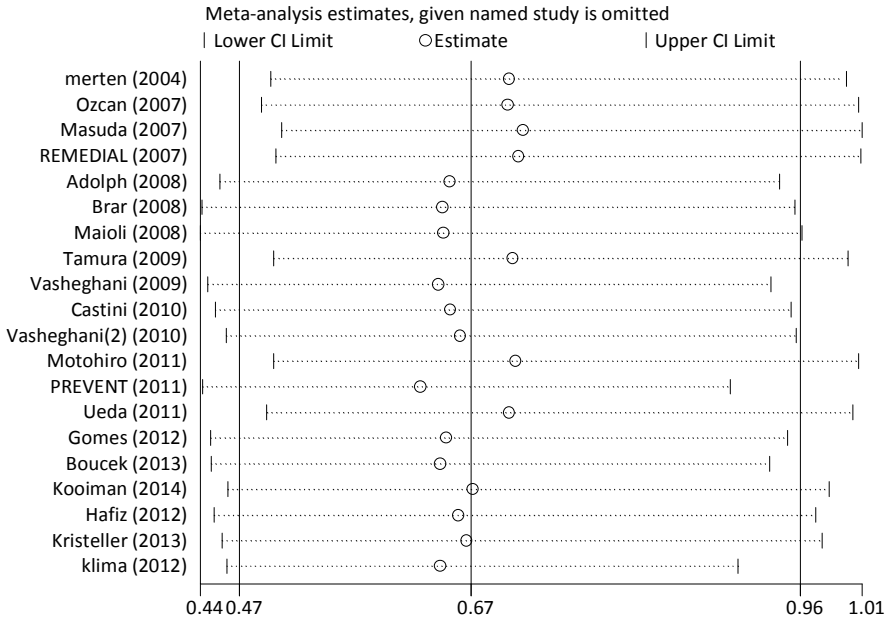
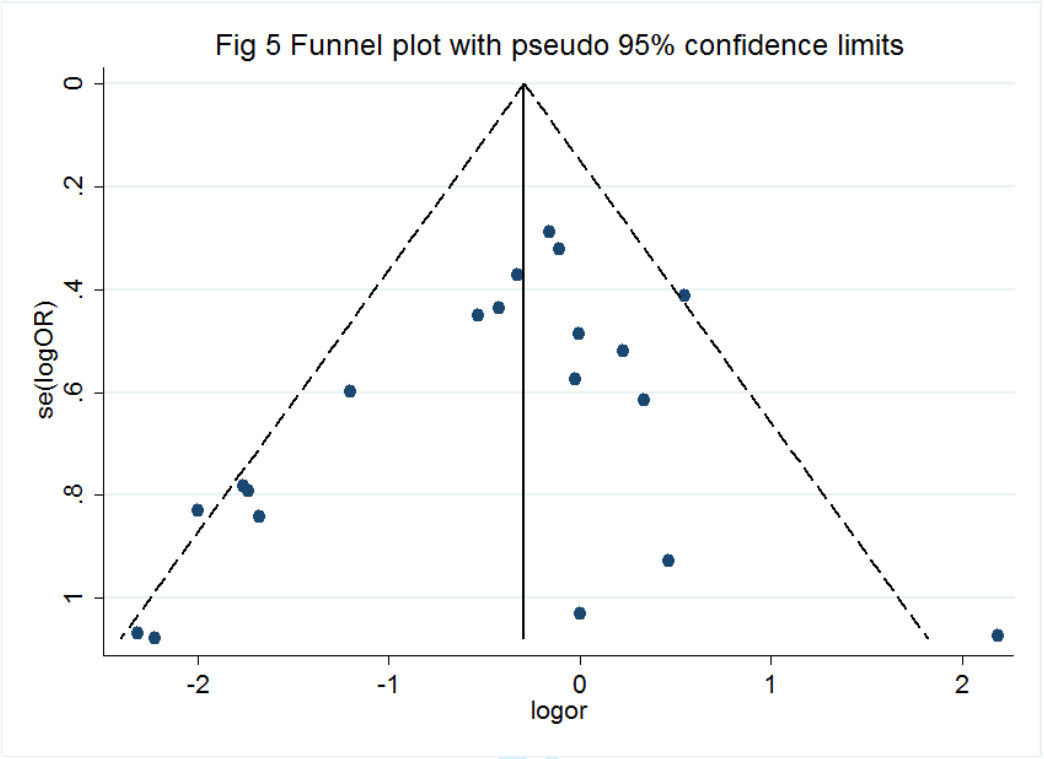


Fig 4 The influence of an individual study on the overall estimates



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig2/3a/3b
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8Figure2/3a/3b
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8Figure2/3a/3b
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8Figure 4/Table3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The efficacy of sodium bicarbonate preventing contrast-induced nephropathy in patients with preexisting renal insufficiency: a meta-analysis

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Key words：Sodium bicarbonate; Saline; Contrast-induced nephropathy; Renal insufficiency; Meta-analysis

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Running head: The efficacy of sodium bicarbonate in preventing CIN

ABSTRACT

Objective: The primary objective of this meta-analysis was to explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy (CIN) and assess if it could reduce the risks of dialysis and mortality, thus improving the clinical prognosis of patients with CIN.

Design: Meta-analysis

Participants: A comprehensive literature search of PubMed, Medline and Cochrane Library was conducted through August 2014.The effect estimate was expressed as pooled odds ratio(OR) with 95% confidence interval(CI),using the random-effects model.

Results: A total of 20 clinical trials consisting of 4,280 patients were absorbed into this study. Pre-procedural hydration with sodium bicarbonate was associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency(OR 0.67; 95%CI 0.47-0.96; P=0.027).However, moderate heterogeneity was noted among the included trials(I^2=48%;P=0.008).Therefore, we performed subgroup analyses and indicated a more pronounced effect of sodium bicarbonate in studies using low-osmolar contrast agents(OR 0.59; 95%CI: 0.37-0.93,P=0.024) compared with those using iso-osmolar ones(OR 0.76; 95%CI: 0.43-1.34,P=0.351). Similarly,a lower odds of CIN with sodium bicarbonate occurred in studies including exclusively patients undergoing emergency procedures (OR 0.16; 95%CI: 0.05-0.51, P=0.002)compared with those undergoing elective ones (OR 0.76;95%CI:0.54-1.06, P=0.105). Furthermore, sodium bicarbonate played a more active role in patients given bolus injection before procedures (OR 0.15; 95%CI: 0.04-0.54, P=0.004) compared with continuous infusion(OR 0.75; 95%CI:0.53-1.05,P=0.091). Sodium bicarbonate plus N-acetylcysteine (NAC) (OR 0.17; 95%CI:0.04-0.79,P=0.024) outweighed sodium bicarbonate alone (OR 0.71;95%CI:0.48-1.03,P=0.071).The effect of sodium bicarbonate was considered greater in papers published before 2008(OR

0.19;95%CI:0.09-0.41,P<0.0001) than after 2008(OR 0.85; 95%CI: 0.62-1.16, P=0.302). However, no significant difference was found in the mortality (OR 0.69;95%CI:0.36-1.32,P=0.263)and need for dialysis(OR 1.08;95%CI:0.52-2.25,P=0.841).

Conclusions: Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency. However, it failures to lower the risks of dialysis and mortality and thus cannot improve the clinical prognosis of patients with CIN.

Article summary

Article focus:

- To explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy.
- To assess if sodium bicarbonate could reduce the risks of dialysis and mortality, thus improving the clinical prognosis of patients with CIN.

Key messages:

- Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency.
- Infusion of sodium bicarbonate failures to lower the risks of dialysis and mortality.

Strengths and limitations of this study

- In this updated meta-analysis, we demonstrate that pre-procedural hydration with sodium bicarbonate is associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency.
- In this study, we find that sodium bicarbonate failures to lower the risks of dialysis and mortality and thus cannot improve the clinical prognosis of patients with CIN.
- New Jadad Scale after revision was used to assess the quality of articles.
- No publication bias.
- However,moderate heterogeneity was noted among the included trials.

Keywords: Sodium bicarbonate; Saline; Contrast-induced nephropathy; Renal insufficiency; Meta-analysis

Introduction

Contrast-induced nephropathy is the third leading cause of in-hospital acute kidney injury[1-3], which is a serious complication of angiographic procedures resulting from the administration of contrast media. Although the definition of CIN is various, CIN is usually defined as an increase in serum creatinine level of 25% or an increase of 0.5mg/dl (or 44μmol/L) from baseline within 48-72h of contrast exposure. It results in increased morbidity, prolonged hospital stay, and increased healthcare expenditure and is associated with a higher mortality[4].

The incidence of CIN in the general population is low, but increases exponentially in patients with high-risk factors, such as preexisting renal insufficiency, diabetes mellitus[5]. In a recent study, 21.7% of preexisting chronic renal insufficiency group and 6.3% of no preexisting chronic renal insufficiency group developed CIN[6]. Thus, baseline renal insufficiency was a significant predisposing factor of CIN.

To prevent CIN, sodium bicarbonate-based hydration has been proposed as one of the feasible therapies. According to recent studies, some of them suggested that for prevention of CIN, sodium bicarbonate elicited more protective effect compared with sodium chloride, but others did not [7-17]. Although most previous meta analyses were on the side of sodium bicarbonate with possible publication bias, none of them focused on the patients with preexisting renal insufficiency. Therefore, we performed this meta-analysis to test the efficacy of sodium bicarbonate in preventing of contrast-induced nephropathy among patients with renal insufficiency undergoing various procedures that need contrast agents. What's more, differences in need for dialysis and post-procedural death between two arms were also compared in this study.

Methods

Data Sources and Searches

We searched PubMed, Medline, Cochrane Library from 2004 through to 1 August

2014. Medical subject headings and keyword searches included the terms “contrast induced nephropathy”, “sodium bicarbonate”, “sodium chloride”, “saline”, “acute kidney injury”, “renal failure”. Reference lists of selected articles were reviewed for other potentially relevant citations. In addition, top 50 citations for each identified relevant study were searched by using the “related articles” function of PubMed.

Study Selection

Firstly, two investigators(B.Z and L.L) independently reviewed the titles and abstracts of all studies searched to identify all potentially relevant ones. Secondly, the online publications obtained from preliminary selection were reviewed in full text by the same two investigators to assess if studies met the following inclusion criteria: comparison of sodium bicarbonate versus sodium chloride or saline, RCT, age≧18 years, clinical end point assessment included CIN, patients with preexisting renal insufficiency: defined as a serum creatinine concentration of >1.1 mg/dl or estimated glomerular filtration rate(eGFR)<60ml/min[18]or creatinine clearance rate<60ml/min [9]. Reviewers were not blinded to study authors or outcomes. Final inclusion of studies was based on the agreement of both reviewers.

Data Extraction and Quality Assessment

Two reviewers(B.Z and WB.C) extracted relevant information from the literatures including baseline clinical characteristics(mean age, the percentage of males, risk factors other than renal insufficiency, baseline Scr, eGFR, procedures, interventions, type and volume of contrast media , hydration regimen, definition of CIN)(Tab1) and data on primary(the incidence of CIN) and secondary outcomes, such as need for dialysis, mortality. CIN was defined variously in studies, but most of them described it as a absolute or relative increase in the level of serum creatinine. Three studies defined CIN as a rise in serum creatinine by 25% or more within 2-5d of contrast exposure [12,19,20]. Thirteen studies regarded an increase of 0.5mg/dl or 25% in Scr within 2-4d of contrast. Two studies considered a elevated Scr of 0.5mg/dl after the

procedures[9, 15]. However, two other trials presented were different from all above, a decrease in eGFR of 25% within 4d and an absolute increase in Scr of at least 0.3mg/dl or 50% or Urine output<0.5ml·kg^{-1}·h^{-1}(>6h) within 5d were selected to define CIN, respectively[8,17]. We assessed the quality of articles using New Jadad Scale after revision(Tab 2).

Data Synthesis and Analysis

The data from included studies were combined and expressed as pooled OR with 95%CI. All analyses were performed on an "intention-to-treat" basis. Initially, fixed -effects model (Mantel-Haenzel method) was used in this meta-analysis. We evaluated the heterogeneity across studies with the Q and I^2 statistics. If P value<0.1, statistically significant heterogeneity was considered. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0-30%,31-50% and greater than 50% representing mild, moderate and substantial heterogeneity, respectively. The outcome of fixed-effects model analysis demonstrated a statistical heterogeneity, so we selected random-effects model (Dersimonian and Laird method).

Considering of the clinical and statistical heterogeneity across studies, subgroup analyses were performed to assess the effect of sodium bicarbonate in various conditions, such as low-osmolar vs.iso-osmolar contrast agent, emergency vs.elective procedures, article published before vs. after 2008, and continuous vs.bolus infusion of sodium bicarbonate (Tab 3). An influence analysis was carried out to evaluate how robust the pooled estimator is after removal of individual studies(Fig 4). An individual study is suspected of excessive influence if the point estimate of its omitted analysis lies outside the 95%CI of the summary analysis.Publication bias was assessed using Begg' funnel plot and Egger' regression asymmetry test(Fig 5). All statistical analyses were conducted using STATA software, version 12.0(Stata Corp LP,College Station, Texas).

Results

A total of 837 articles were reviewed and 20 studies met the inclusion criteria were absorbed into this study finally(Fig 1).

A detailed description of the baseline characteristics of the included studies is given in Tab 1. Patients in most studies underwent coronary angiography or Interventional procedures. There were also seven studies depicted peripheral procedures, angioplasty, cardiopulmonary bypass and CT[8,18,19,21-24]. The sodium bicarbonate hydration regimen in thirteen studies was described as same as Merten et al: the infusion of sodium bicarbonate at rate of $3ml \cdot kg^{-1} \cdot h^{-1}$ for 1h before and $1ml \cdot kg^{-1} \cdot h^{-1}$ for 6h after the procedure.

Primary Outcome

CIN occurred in a total of 158 patients in the 2,130 patients of the sodium bicarbonate arm compared with that of 217 patients in the 2,150 patients who received saline, a lower overall incidence of CIN was found in the sodium bicarbonate group(Fig 2). The pooled OR was 0.67 (95%CI:0.47-0.96; P=0.027) also in favor of sodium bicarbonate(Fig 2).

However, moderate heterogeneity across studies was observed(I^2=48%,P=0.008) (Fig 2).

Therefore, subgroup analyses were constructed and suggested a more pronounced effect of sodium bicarbonate in studies using low-osmolar contrast media(OR 0.59; 95%CI: 0.37-0.93,P=0.024) (Tab 3). Similarly, subgroup analysis by the setting suggested lower odds of CIN with sodium bicarbonate in studies with patients undergoing emergency procedures (OR 0.16; 95%CI 0.05-0.51, P=0.002) (Tab 3). Before 2008, the effect of sodium bicarbonate was considered greater in articles reported(OR 0.19;95%CI:0.09-0.41,P<0.0001)(Tab 3). Furthermore, subgroup analysis according to the manner of sodium bicarbonate administration showed better effect in patients given bolus injection (OR 0.15; 95%CI 0.04-0.54, P=0.004) (Tab 3).Sodium

bicarbonate in combination with NAC showed a more salient efficacy in preventing CIN(OR 0.17;95%CI:0.04-0.79,P=0.024)(Tab 3).

Influence analysis showed no individual study had excessive influence on the overall estimate odds ratios and 95%CI(Fig 4).

Begg' funnel plot and Egger' test(P=0.396) implied no significant publication bias in this study(Fig 5).

Secondary Endpoints

Need for dialysis

The need for dialysis was described in a total of 17 studies(n=3,633). In eight of these studies, there was no dialysis event in both groups[11,12,15,16,18,19,22,24]. Overall, 14 out of 1,809 patients who treated with sodium bicarbonate underwent dialysis compared with 13 out of 1,824 patients treated with saline. No statistical significant difference was observed (OR 1.08; 95%CI 0.52-2.25, P=0.841) (Fig 3a), nonetheless, the OR for the requirement of dialysis suggested that maybe sodium bicarbonate was no better than saline in terms of reducing the dialysis events.

Mortality

Post-procedural death was described in a total of 12 studies(n=2,559), in six studies, there was no death in either group[11,13,14,16,23,24]. There were altogether 15 deaths in the 1,279 patients treated with sodium bicarbonate and 22 in the 1,280 patients treated with saline. Although there was no significant difference between the two arms (OR 0.69; 95%CI 0.36-1.32, P=0.263) (Fig 3b), a trend toward lower mortality risk occurred in sodium bicarbonate arm compared with saline arm.

Discussion

Although CIN is generally regarded as a transient decline in renal function after contrast procedures, it cannot be regarded as a benign complication[25,26]. It accounts for 12% of all cases of acute renal failure[27]. In a observational study, 0.8% of included patients undergoing coronary angiography or Interventional procedures

started dialysis and 13% of them needed a permanent one[28]. Furthermore, the development of CIN is associated with a longer hospital stay, an increased morbidity and mortality, in addition to a higher financial cost. Consequently, we can never be blind to the hazard of CIN.

Various risk factors may contribute to CIN, which are divided into two groups: patient- and procedure-related[29]. Preexisting renal insufficiency and diabetes mellitus are the two main patient- related risk factors. That is one reason why we focus on the patients with a history of renal insufficiency. Renal insufficiency was usually defined as a decrease in eGFR and since the eGFR has to be reduced by 50% before a rise in serum creatinine occurs, an elevated serum creatinine level was used as the cut-off point for the definition for renal insufficiency[21]. In a retrospective review of 938 patients with stable renal insufficiency, the overall incidence of CIN was 6.1%, and the incidence was 4.4%, 10.5%, 10.0% for patients whose eGFR was 45-60, 30-45, and ≤30ml/min, respectively[30]. Hence special care should be taken in patients with renal insufficiency.

In order to prevent CIN, sodium bicarbonate has been proposed by various mechanisms[31,32]. Namely, how does it work remains unknown. Some potential mechanisms are that alkalinizing the tubular urine with sodium bicarbonate may attenuate free radical formation and peroxide injury[28].Oxygen free radicals and peroxide usually generate in acidic conditions, infusion of sodium bicarbonate could increase the PH of local renal tissue to neutral or slightly alkaline, thereby reducing the production of free radicals and peroxide. Merten et al[19] first introduced the administration of sodium bicarbonate in a concentration of 154mmol/L to prevent CIN. In this study, hydration regimens of 13 trials [9-17,19-21,33] were performed similarly to “Merten protocol”. Although most previous systematic reviews and relevant meta-analyses demonstrated that sodium bicarbonate infusion could decrease the incidence of CIN[25,26,34-42], secondary clinical endpoints as diverse

as renal replacement therapy and mortality were not ameliorated. Furthermore, a retrospective cohort study of 7,977 patients at Mayo Clinic got a surprising result: sodium bicarbonate was associated with an increased incidence of CIN[43]. By contrast with a majority of RCTs using creatinine elevations within 48-72h after contrast exposure to define CIN, From et al extended the definition time of CIN to a week based on the fact that creatinine may peak 3 to 7d after contrast. However, this issue remains to be discussed. Because in our study, all the patients with a history of renal insufficiency, the peak of serum creatinine may advance.

In this meta-analysis, underlying sources of moderate heterogeneity should be taken into account, because the study subjects, study settings and type of contrast media were varied. In this case, subgroup analyses were conducted and the results revealed significant differences between emergency and elective procedures, the protective role of sodium bicarbonate played better in the former than latter. In a meta-analysis[42] of the effect of sodium bicarbonate for the prevention of CIN, subgroup analyses also showed a more pronounced efficacy of sodium bicarbonate in 3 trials[18,33,44] included patients undergoing emergency procedures compared with those undergoing elective procedures. But the exact mechanism by which sodium bicarbonate results in a decrease incidence of CIN is still a mystery. Maybe it's related to manner of administration and dosage. Similarly, sodium bicarbonate was more beneficial in patients who received low-osmolar contrast agents[45,46]. However, because of the significantly smaller case number of included patients who received iso-osmolar contrast media (n=1,189) compared with those received low-osmolar ones(n=2,823), the major reason responsible for the more salient effect of sodium bicarbonate is difficult to elucidate.

Although the utilization of N-acetylcysteine(NAC) has been known to reduce the incidence of CIN and the value of it has been the focus of many studies, the definitive effect of NAC is not yet established. Not a few trials and meta-analyses indicated the

combination of sodium bicarbonate and NAC is superior to either regimen in preventing of CIN. Also, three studies[20,44,47] included patients who received NAC in both groups after the infusion of sodium bicarbonate or saline and the results were in favor of sodium bicarbonate. The BINARIO[48]study indicated that hydration with sodium bicarbonate in addition to high-dose NAC in the setting of urgent PCI for STEMI was associated with a net clinical benefit. However, Yang et al[27]and Thayssen et al [49]concluded that use of NAC caused no significant reduction in the incidence of CIN. In our study, because of only one trial[20]using NAC included in the sub-analyses, the effect of which may be overestimated (OR 0.17;95%CI 0.04-0.79, P=0.024). Accordingly, more large-scale and well-designed randomized clinical trials are warranted to determine whether sodium bicarbonate plus NAC is more useful in preventing CIN than either alone.

Many studies have now shown that patients with CIN have a greater risk for the renal replacement therapy and death. In fact, almost all the dialysis and death events occurred in patients with CIN who have high-risk factors. So we could not rely on sodium bicarbonate alone to improve the bad situations caused by CIN together with basic diseases, such as renal insufficiency, diabetes mellitus. Maybe that is one vital reason why we did not find a significant difference in both requirement of dialysis and mortality. However, the lack of power of included RCTs could also be attributed to. In this meta-analysis, not all studies described renal replacement therapy and mortality and sample sizes were relatively small. So this issue needs further research.

Conclusions

Our meta-analysis demonstrates the administration of sodium bicarbonate is superior to the administration of saline in the prevention of CIN in patients with preexisting renal insufficiency undergoing procedures requiring contrast media. However, the use of sodium bicarbonate did not result in clear benefit in regard to reductions in requirement of dialysis and mortality. Therefore, more large sample

trials are required to detect the efficacy of sodium bicarbonate in preventing CIN and improving the clinical prognosis of patients with CIN.

Footnotes

Contributors: B.Z, L.L and WB.C searched the studies. B.Z wrote the manuscript.

L.L ,WB.C, CH.L and SX.Z reviewed, analyzed and helped writing the manuscript.

All authors contributed to the conception and design of this study.

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Table and figure legends:

Table 1: The baseline characteristics of included studies

Table 2: Quality assessment of included studies

Table 3:Subgroup analyses: to assess the effect of sodium bicarbonate in various conditions

Figure 1: Selecting flow chart showing the number of excluded trials and the reasons, As well as the number of included trials

Figure 2: The forest plot of odds ratios of contrast induced nephropathy

Figure 3a: Need for dialysis

Figure 3b: Mortality

Figure 4: The influence of an individual study on the overall estimates

Figure 5: Funnel plot with pseudo 95% confidence limits

Tab 1 The baseline characteristics of included studies

Study	Cases	Age(years)		Male(%)	DM	HT	Baseline Scr(mg/dl)		eGFR(ml/min/1.73m²)	
		Bicarbonate	Saline		%	%	Bicarbonate	Saline	Bicarbonate	Saline
Merten	119	66.7*	69.2*	73/76	50/46	NA	1.89*	1.71*	41.0*	45.0*
Ozcan	176	68.0*	70.0*	76/75	42/48	75/81	1.36*	1.40*	NA	NA
Masuda	59	75.0±8.0	76.0±11.0	63/59	27/35	NA	1.31±0.52	1.32±0.65	40.2±15.4	38.7±15.4
REMEDIAL	219	70.0±9.0	71.0±9.0	88/81	49/55	92/87	2.04*	1.95*	32.0±7.0	71.0±9.0
Adolph	145	70.1±8.4	72.7±6.6	75/81	37/28	83/91	1.54±0.51	1.57±0.36	NA	NA
Brar	323	71.0*	71.0*	62/65	43/46	NA	1.49#	1.49#	47.7#	48.3#
Maioli	502	74.0*	74.0*	57/61	25/23	59/57	1.21±0.30	1.20±0.30	NA	NA
Tamura	144	72.3±9.9	73.3±7.7	92/83	60/57	85/83	1.36±0.18	1.38±0.19	40.0±7.5	38.2±0.2
Vasheghani	265	62.9±10.0	63.8±9.0	84/82	22/21	30/41	1.63±0.32	1.66±0.50	46.4±12.0	45.4±12.0
Castini	103	70.0±8.3	72.7±8.2	85/84	35/20	71/78	1.59±0.38	1.49±0.30	46.9±12.8	49.9±10.3
Vasheghani(2)	72	61.4#	62.7#	78/81	33/38	66/71	1.77#	1.71#	42.7#	44.2#
Motohiro	155	71.0±9.0	74.0±7.0	76/64	56/63	86/83	1.54±0.43	1.55±0.44	45.7±12.9	42.8±13.8
PREVENT	382	65.8*	67.5*	71/71	100/100	77/80	1.50*	1.50*	46.0*	46.0*
Ueda	59	77.0±9.0	75.0±10.0	77/79	10/10	NA	1.32±0.46	1.51±0.59	42.4±11.5	38.7±12.6
Klima	176	78.0*	75.0*	66/62	39/34	90/81	1.60*	1.60*	43.1#	43.0#
Gomes	301	64.1±12.0	64.5±12.0	15/75	29/30	77/74	1.50±0.40	1.49±0.50	50.5±13.0	51.9±13
Hafiz	320	74.0*	73.0*	57/57	49/45	95/94	1.65*	1.60*	41.5*	40.5*
Kristeller	92	72.0±11.0	73.0±11.0	64/52	52/38	89/92	NA	NA	48.9#	49.4#
Boucek	120	63.0#	67.0#	75/75	NA	NA	1.92#	1.81#	43.6#	44.6#
Kooiman	548	71.6#	72.5#	60/61	27/27	NA	NA	NA	49.9#	50.9#

Note: DM=diabetes mellitus HT=hypertension eGFR=estimated glomerular filtration rate NA= not applicable

*median value #mean value

Tab 1 Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective diagnostic /interventional procedures	SB vs SC	NA	NA	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥25% within 2d
		Iopamidol,nonionic,Low-osmolar			
Elective CAG/PCI	SB vs SC	100*	100*	1ml·kg^{-1}·h^{-1} for 6h before and after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Ioxaglate,ionic,Low-osmolar			
Emergency CAG/PCI	SB vs SC	112±89	120±61	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Iopamidol,nonionic,Low-osmolar			
Elective CAG/ PCI /peripheral procedure	SB+NAC vs NS+NAC	169±92	179±9	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑≥25% within 2d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG/PCI	SB vs SC	141±50	138±52	2ml·kg^{-1}·h^{-1} for 2h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG	SB vs SC	126*	137*	3ml·kg^{-1}·h^{-1} for 1h before and 1.5ml·kg^{-1}·h^{-1} for 4h after the procedure of SB or SC	eGFR↓>25% within 4d
		Ioxilan,nonionic,Iso- osmolar			
Elective CAG/PCI	SB vs IS	160*	170*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h after:IS	Scr↑≥0.5mg/dl within 5d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG/PCI	Bolus SB+SC vs SC	82±40	88±45	Single-bolus SB 20ml for 5min before and SC 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure; 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure of SC	Scr↑>0.5mg/dl or 25% within 3d
		Iohexol,nonionic,Low-osmolar			
Elective CAG	SB+Is vs IS	115±41	113.2±36	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after in both groups	Scr↑≥0.5mg/dl or 25% within 2d
		Iohexl,nonionic,Low-osmolar			
Elective CAG/PCI	SB vs SC	179±125	196±128	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and after:SC	Scr↑≥25% within 5d
		Iodixanol,nonionic,Low-osmolar			

Note： CAG=coronary angiography PCI=percutaneous coronary intervention SB=sodium bicarbonate SC= sodium chloride IS=isotonic saline NAC=N-acetylcysteine NS=normal saline Scr=serum creatinine

Tab 1 Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective CAG	SB+half SC vs half SC	112#	123# Iohexol,nonionic, Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of 75ml SB to1L of 0.45%SC; 1075ml 0.45%SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB+SC vs SC	140±50	130±40 Iopamidol, nonionic, Low-osmolar	1ml·kg^{-1}·h^{-1} SC 12h before and 1ml·kg^{-1}·h^{-1} SB from 3h pre-to 6h post-procedure, then 1ml·kg^{-1}·h^{-1} SC for 12h; 1ml·kg^{-1}·h^{-1} SC 12h pre- and 12h post- procedure	Scr↑≥0.5mg/dl or>25% within 2d
Elective CAG/ angioplasty/ endovascular intervention	SB vs SC	113*	120* Iodixanol,nonionic , Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h:SC	Scr↑≥0.5mg/dl or>25% within 2d
Emergency CAG/ PCI	SB vs SC	116±63	104±57 Iopamidol/Iohexol, Low-osmolar	Bolus 0.5mg/ml SB before and SC 1ml·kg^{-1}·h^{-1} for 6h during and after in both groups	Scr↑≥0.5mg/dl or >25% within 2d
Elective CAG/ PCI/ PTA/CT/ PAG	SB vs SC	100*	100* Iopromide/iohexol.etc. Iso/Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 24h:SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB vs NS	124±65	125±87 Hexabrix/Loxaglate, Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or NS	Scr↑≥0.5mg/dl within 2d
Elective CAG/ PAG/ intervention	SB±NAC vs NS±NAC	110*	100* Iodixanol/Iopamidol/Ioversol, nonionic,Low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑>0.5mg/dl or 25% within 2d
Elective CPB	SB vs IS	74#	83# NA	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or IS	Scr↑≥0.3mg/dl or 50% or Urine output <0.5ml·kg^{-1}·h^{-1} (>6h) within 5d
Elective CAG/ Lower-limb angiography and /or angioplasty	SB vs NS	115#	104# Iodinated,nonionic , low-osmolar	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CECT	SB vs IS	105.7#	104.7# Iomeprol/Iobitridol/ Iodixanol,Low-osmolar	250ml SB for 1h before; 1000ml IS before and 1000ml IS after	Scr↑＞0.5mg/dl or 25% within 4d

Note: PTA=percutaneous transluminal angioplasty PAG=peripheral angiography CPB=cardiopulmonary bypass CECT=contrast-enhanced computerized tomography

Tab 2 Quality assessment of included studies

Included trials	Trial described as randomized (1=yes, 0=no)	Randomized method described & appropriate (1=yes, 0=no)	Allocation concealment described† (1=yes, 0=no)	Allocation concealment described & appropriate (1=yes, 0=no)	Trial described as double blind (1=yes, 0=no)	Double blind method described & appropriate (1=yes,0=no)	Withdrawals & Dropouts described (1=yes,0=no)	Jadad score *
Merten	1	1	0	0	0	0	1	4
Ozcan	1	0	0	0	0	0	1	2
Masuda	1	1	0	0	0	0	1	4
REMEDIAL	1	1	0	0	1	0	1	5
Adolph	1	1	0	0	1	0	1	5
Brar	1	1	1	1	0	0	1	5
Maioli	1	1	1	1	0	0	0	4
Tamura	1	1	0	0	0	0	1	4
Vasheghani	1	1	0	0	1	0	0	4
Castini	1	1	0	0	0	0	0	3
Vasheghani(2)	1	1	0	0	1	0	0	4
Motohiro	1	1	0	0	0	0	1	4
PREVENT	1	1	0	0	0	0	1	4
Ueda	1	1	0	0	0	0	0	3
Klima	1	0	1	1	0	0	0	3
Gomes	1	0	1	1	0	0	0	3
Hafiz	1	1	0	0	0	0	1	4
Kristeller	1	1	1	1	1	0	0	5
Boucek	1	1	1	1	1	0	1	6
Kooiman	1	1	0	0	0	0	1	4

Note: †One point can be obtained from Jadad Score if randomization method of the trial is described &appropriate

*Calculation for quality assessment of included trials:low,1-3;high,4-7

Tab 3 Subgroup analyses: to assess the effect of sodium bicarbonate in various conditions

Subgroups	Trials/patients	OR(95%CI)	Test for overall effect	Heterogeneity
Type of contrast				
Low-osmolar	14/2823	0.59[0.37,0.93]	Z=2.26(P=0.024)	X^2=26.61,df=13(P=0.014),I^2=51%
Iso-osmolar	4/1189	0.76[0.43,1.34]	Z=0.93(P=0.351)	X^2=4.67, df=3(P=0.198),I^2=36%
Setting				
Elective	18/4162	0.76[0.54,1.06]	Z=1.62(P=0.105)	X^2=29.54,df=17(P=0.030),I^2=43%
Emergency	2/118	0.16[0.05,0.51]	Z=3.11(P=0.002)	X^2=0.07,df=1(P=0.784),I^2=0%
Using NAC or not				
Use	1/219	0.17[0.04,0.79]	Z=2.26(P=0.024)	Not applicable
Non-use	18/3741	0.71[0.48,1.03]	Z=1.80(P=0.071)	X^2=33.13,df=17(P=0.011),I^2=49%
Publication year				
Before 2008	4/573	0.19[0.09,0.41]	Z=4.26(P=0.000)	X^2=1.06,df=10(P=0.788),I^2=0%
After 2008	16/3707	0.85[0.62,1.16]	Z=1.03(P=0.302)	X^2=22.13,df=15(P=0.105),I^2=32%
Manner of administration				
Continuous	18/4077	0.75[0.53,1.05]	Z=1.69(P=0.091)	X^2=30.21,df=17(P=0.025),I^2=44%
Bolus	2/203	0.15[0.04,0.54]	Z=2.90(P=0.004)	X^2=0.23,df=1(P=0.632),I^2=0%

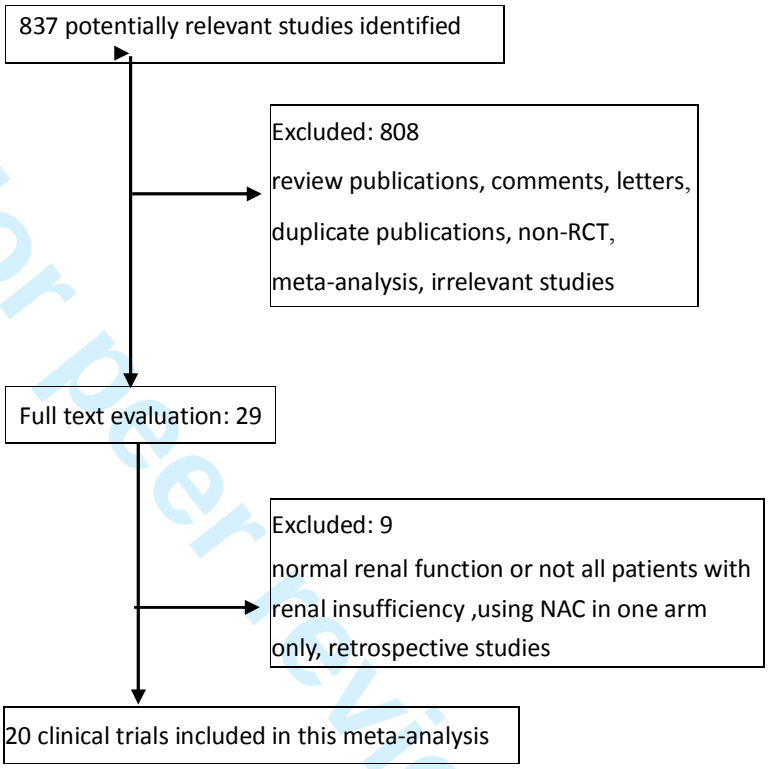


Fig 1 Selecting flow chart showing the number of excluded trials and the reasons, as well as the number of included trials

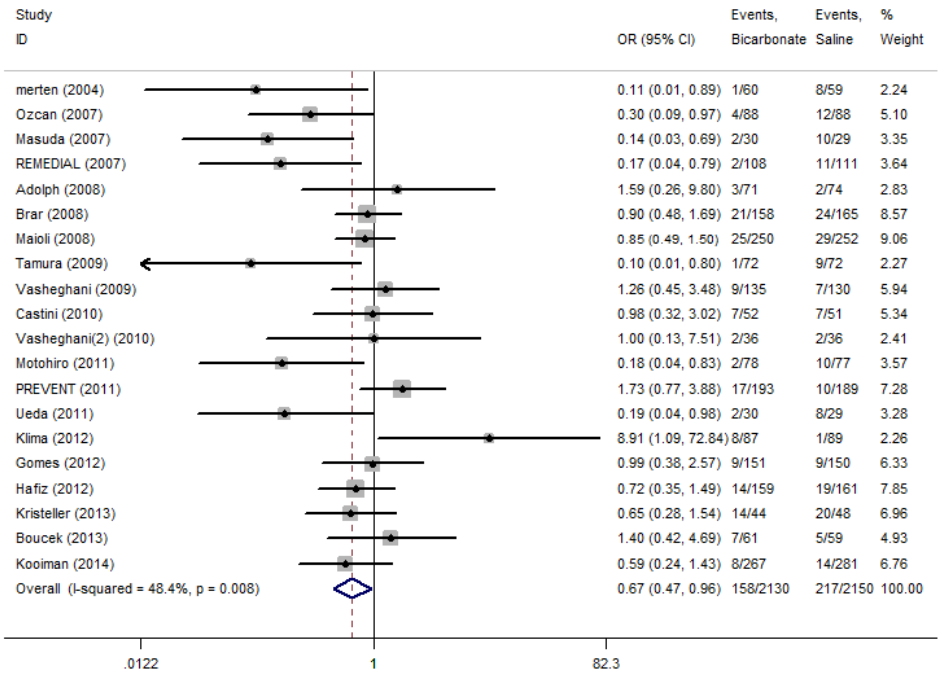


Fig 2 The Forest plot of odds ratios of contrast-induced nephropathy

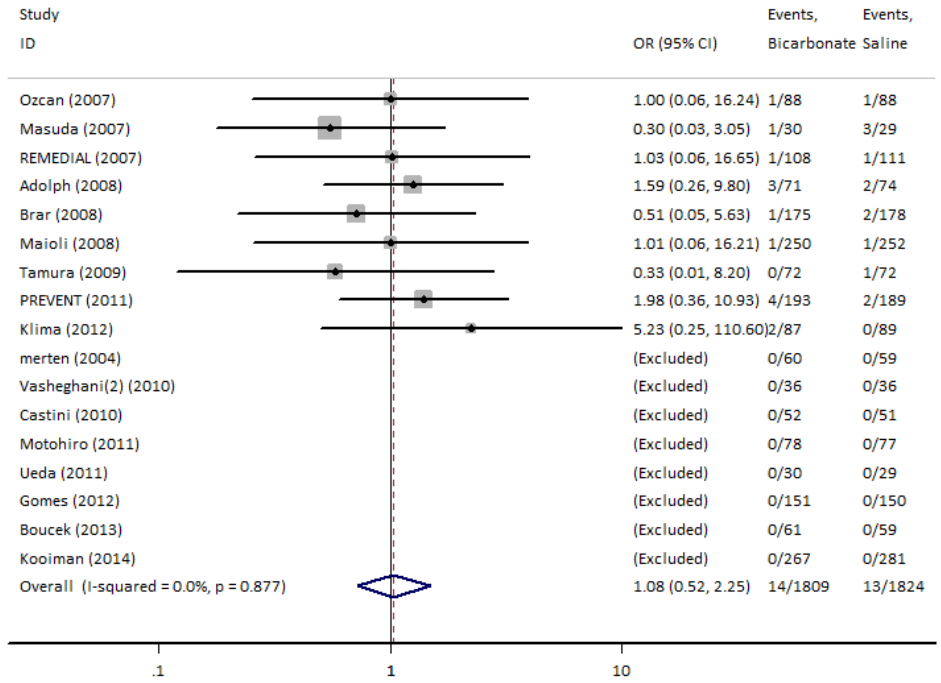


Fig 3a Need for dialysis

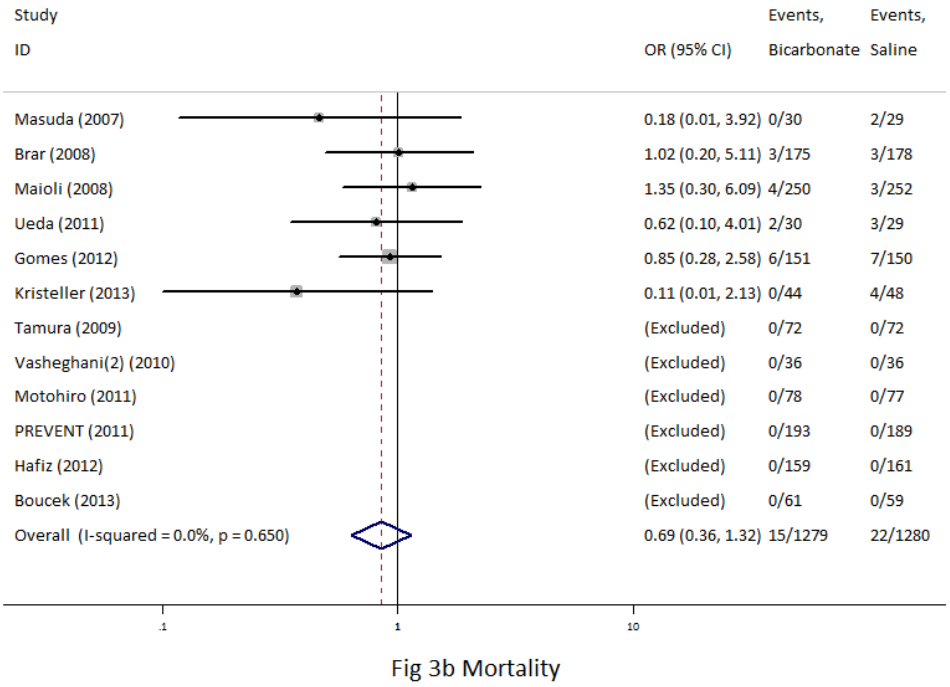


Fig 3b Mortality

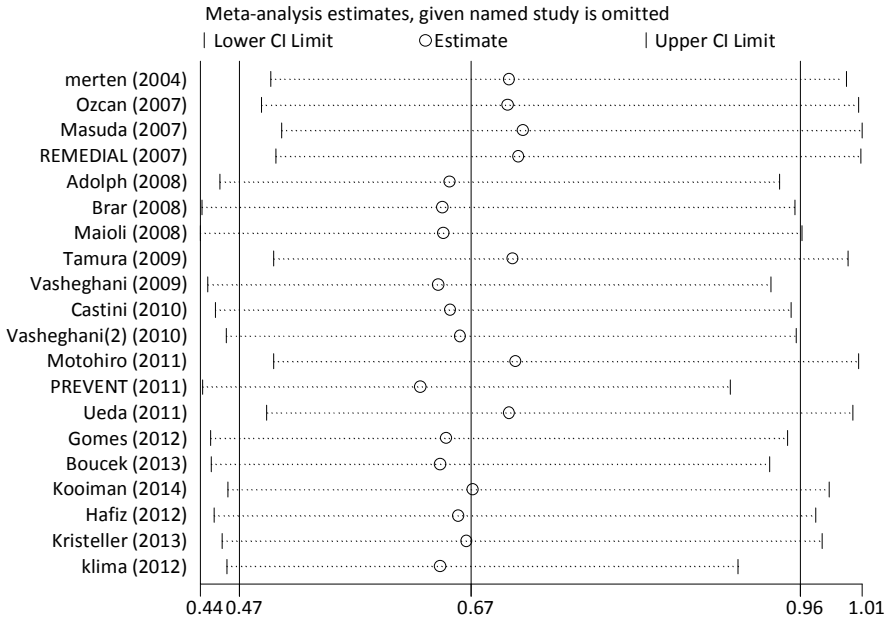
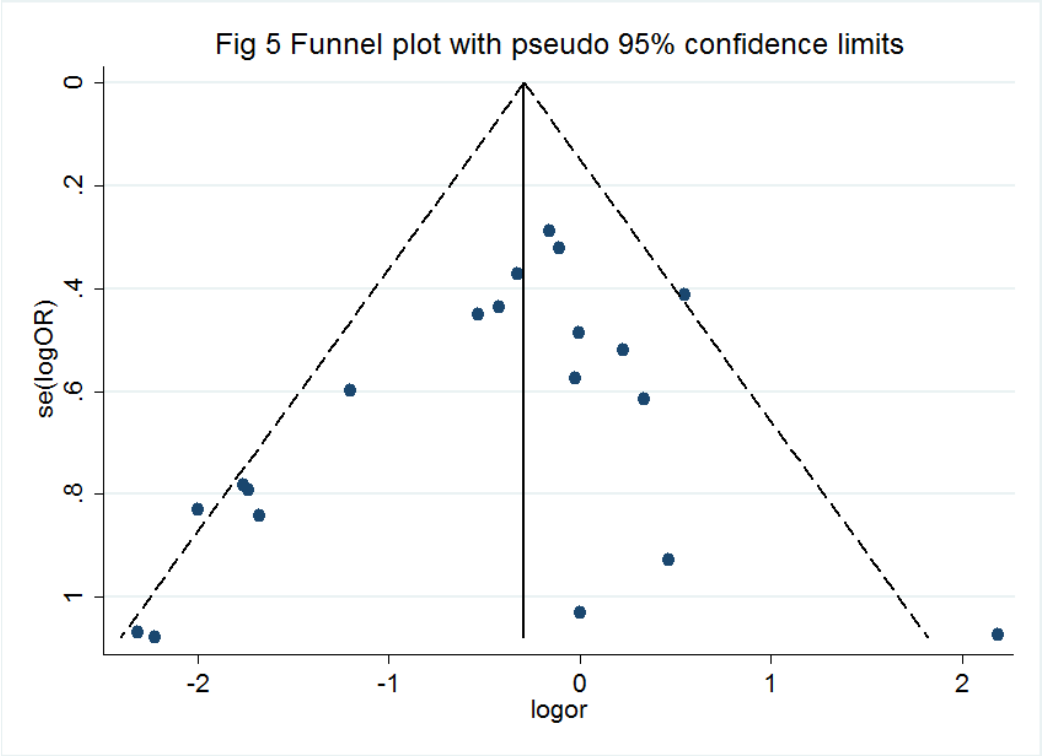


Fig 4 The influence of an individual study on the overall estimates.



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The efficacy of sodium bicarbonate preventing contrast-induced nephropathy in patients with preexisting renal insufficiency: a meta-analysis

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Abstract

Objective: The aim of this meta-analysis was to explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy (CIN) and assess if it could reduce the risks of dialysis and mortality to improve the clinical prognosis of patients with CIN.

Methods: We searched PubMed, Medline and the Cochrane Library from January 1, 2004 to August 1, 2014. The effect estimate was expressed as pooled odds ratio (OR) with 95% confidence interval (CI), using the fixed effects model or random effects model.

Results: 20 randomized controlled trials (RCT) (n=4, 280) were identified. Hydration with sodium bicarbonate was associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency (OR 0.67; 95%CI: 0.47-0.96; *P*=0. 027). However, moderate heterogeneity was noted across trials (I^2=48%; *P*=0. 008). Therefore, we performed subgroup analyses and indicated a better effect of sodium bicarbonate in studies using low-osmolar contrast agents (OR 0.59; 95%CI: 0.37-0.93, *P*=0. 024) compared with those using iso-smaller ones (OR 0.76; 95%CI: 0.43-1.34, *P*=0. 351). A lower odds of CIN with sodium bicarbonate occurred in studies including exclusively patients undergoing emergency procedures (OR 0.16; 95%CI: 0.05-0.51, *P*=0. 002) compared with those undergoing elective ones (OR 0.76; 95%CI: 0.54-1.06, *P*=0. 105). Sodium bicarbonate played a more beneficial role in patients given a bolus injection before procedures (OR 0.15; 95%CI: 0.04-0.54, *P*= 0. 004) compared with continuous infusion (OR 0.75; 95%CI: 0.53-1.05, *P*=0. 091).

Sodium bicarbonate plus N-acetylcysteine (NAC) (OR 0.17; 95%CI: 0.04-0.79, *P*= 0.024) outweighed sodium bicarbonate alone (OR 0.71; 95%CI: 0.48-1.03, *P*=0. 071). The effect of sodium bicarbonate was considered greater in papers published pre-2008 (OR 0.19; 95%CI: 0.09-0.41, *P*=0. 000) than post-2008 (OR 0.85; 95%CI: 0.62-1.16, *P*=0. 302). However, no significant differences were found in the mortality (OR 0.69; 95%CI: 0.36-1.32, *P*=0. 263) and the requirement for dialysis (OR 1.08; 95%CI: 0.52-2.25, *P*=0. 841).

Conclusions: Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency. However, it failures to lower the risks of dialysis and mortality and therefore cannot improve the clinical prognosis of patients with CIN.

Article summary

Article focus:

• To explore the efficacy of sodium bicarbonate in preventing contrast-induced nephropathy.

• To assess if sodium bicarbonate could reduce the risks of dialysis and mortality to improve the clinical prognosis of patients with CIN.

Key messages:

• Sodium bicarbonate is effective in preventing CIN among patients with preexisting renal insufficiency.

• Infusion of sodium bicarbonate failures to lower the risks of dialysis and mortality.

Strengths and limitations of this study

• In this updated meta-analysis, we demonstrated that pre-procedural hydration with

sodium bicarbonate was associated with a significant decrease in the incidence of CIN among patients with preexisting renal insufficiency.

• In this study, we found that sodium bicarbonate couldn't lower the risks of dialysis and mortality to improve the clinical prognosis of patients with CIN.

• New Jadad Scale after the revision was used to assess the quality of articles.

• No publication bias.

• However, moderate heterogeneity was noted among the included trials.

Keywords: Sodium bicarbonate; Saline; Contrast-induced nephropathy; Renal insufficiency; Meta-analysis

Introduction

Contrast-induced nephropathy is the third leading cause of in-hospital acute kidney injury [1-3], which is a serious complication of angiographic procedures resulting from the administration of contrast media. Although the definition of CIN is various, CIN is usually defined as an increase in serum creatinine (Scr) level of 25% or an increase of 0.5 mg/dl (or 44 μmol/L) from baseline within 48-72 hours of contrast exposure. It results in increased morbidity, prolonged hospital stay, and increased healthcare expenditure and is associated with a higher mortality [4].

The incidence of CIN in the general population is low, but increases exponentially in patients with high-risk factors, such as preexisting renal insufficiency, diabetes mellitus [5]. In a recent study, 21.7% of preexisting chronic renal insufficiency group and 6.3% of no preexisting chronic renal insufficiency group developed CIN [6]. Thus, baseline renal insufficiency may be a significant predisposing factor of CIN.

To prevent CIN, sodium bicarbonate-based hydration has been proposed as one of the feasible therapies. According to recent studies, some of them suggested sodium bicarbonate elicited more protective effect compared with sodium chloride for the prevention of CIN, but others did not [7-17]. Although most previous meta analyses were on the side of sodium bicarbonate with possible publication bias, none of them focused on the patients with preexisting renal insufficiency. Therefore, we performed this meta-analysis to determine the efficacy of sodium bicarbonate in preventing of contrast-induced nephropathy among patients with renal insufficiency undergoing procedures needing contrast agents. What's more, differences in the requirement for dialysis and post-procedural death between two groups were compared in this study as well.

Methods

Data sources and searches

We searched PubMed, Medline, and the Cochrane Library from January 1, 2004 to August 1, 2014 without language limitations. Medical subject headings and keyword searches included the terms "contrast induced nephropathy", "sodium bicarbonate", "sodium chloride", "saline", "acute kidney injury", "renal failure". Reference lists of selected articles were reviewed for other potentially relevant citations. In addition, top 50 citations for each identified relevant study were searched by using the "related articles" function of PubMed.

Study selection

First, two investigators (B.Z and L.L) independently reviewed the titles and abstracts

of all studies to identify all potentially ones. Second, the online publications obtained from preliminary selection were reviewed in full text to assess if studies met the following inclusion criteria:

1) Participants: adult patients (≥18 years) with preexisting renal insufficiency, defined as a serum creatinine concentration of >1.1 mg/dl or estimated glomerular filtration rate (eGFR)<60 ml/min [18] or creatinine clearance rate<60 ml/min [9].

2) Comparison: sodium bicarbonate (and/or N-acetylcysteine) versus saline (and/or N-acetylcysteine).

3) Outcome: the primary outcome of this study is the incidence of CIN, the secondary outcomes include the requirement for dialysis and the mortality.

4) Type of study: only RCT.

Reviewers were not blinded to study authors or outcomes. Final inclusion of studies was based on the agreement of both reviewers.

Exclusion criteria: insufficient data to extract, using N-acetylcysteine in only one arm.

Data extraction and quality assessment

Two independent reviewers (B.Z and WB. C) extracted relevant information from the literatures including baseline clinical characteristics (mean age, the percentage of males, risk factors other than renal insufficiency, baseline Scr, eGFR, procedures, interventions, type and volume of contrast media, hydration regimen, definition of CIN) (Table 1), data on primary (the incidence of CIN) and secondary outcomes (i.e., the requirement for dialysis and the mortality). CIN was defined variously in studies, but most of them described it as an absolute or relative increase in the level of serum

creatinine. 3 studies defined CIN as a rise in serum creatinine by 25% or more within 2-5 days of contrast exposure [12,19,20]. 13 studies regarded an increase of 0.5 mg/dl or 25% in Scr within 2-4 days of contrast as CIN. 2 studies considered an elevated Scr of 0.5 mg/dl after the procedures [9,15]. However, the remaining 2 trials were different from all above, a decrease in eGFR of 25% within 4 days and an absolute increase in Scr of at least 0.3 mg/dl or 50% or Urine output <0.5 $ml \cdot kg^{-1} \cdot h^{-1}$ (>6 h) within 5 days were used to define CIN, respectively [8,17]. We assessed the quality of articles using the New Jadad Scale after the revision (Table 2).

Data synthesis and analysis

Data from included studies were combined and expressed as pooled OR with 95%CI. All analyses were performed on an "intention-to-treat" basis. Initially, fixed -effects model (Mantel-Haenzel method) was used in this meta-analysis. We evaluated the heterogeneity across studies with the Cochrane's Q test and I^2 statistics. If the *P* value <0.10, statistically significant heterogeneity was considered. The I^2 statistic was used to quantify the magnitude of heterogeneity, with values of 0-30%, 31-50% and greater than 50% representing mild, moderate and substantial heterogeneity, respectively. The outcome of fixed-effects model analysis demonstrated a statistical heterogeneity, so we selected the random-effects model (Dersimonian and Laird method).

Considering of the clinical and statistical heterogeneity across studies, subgroup analyses using random effects model were performed to assess the effect of sodium bicarbonate in various conditions, such as low-osmolar vs. iso-osmolar contrast agent, emergency vs. elective procedures, the articles published pre- vs. post-2008, and

continuous vs. bolus infusion of sodium bicarbonate (Table 3). An influence analysis was carried out to evaluate how robust the pooled estimator was after the removal of an individual study at a time (Figure 4). An individual study is suspected of excessive influence if the point estimate of its omitted analysis lies outside the 95%CI of the summary analysis. Publication bias was assessed using Begg' funnel plot and Egger' regression asymmetry test (Figure 5). All statistical analyses were performed using STATA software, version 12.0 (Stata Corp LP, College Station, Texas).

Results

A total of 837 articles were reviewed and 20 studies reached the inclusion criteria were absorbed into this study finally (Figure 1).

A detailed description of the baseline characteristics of the included studies was given in Table 1. Patients in most studies underwent coronary angiography or interventional procedures. There were also 7 studies examined peripheral procedures, angioplasty, cardiopulmonary bypass and computed tomography (CT) [8,18,19,21-24]. The sodium bicarbonate hydration regimen in 13 studies was described as same as Merten et al, the infusion of sodium bicarbonate was at a rate of 3 $ml \cdot kg^{-1} \cdot h^{-1}$ for 1 h before and 1 $ml \cdot kg^{-1} \cdot h^{-1}$ for 6 h after the procedure.

Primary outcome

CIN occurred in a total of 158 patients out of 2,130 patients received sodium bicarbonate compared with that of 217 patients from 2,150 patients received saline, a lower overall incidence of CIN was found in the sodium bicarbonate group (Figure 2). The pooled OR was 0.67 (95%CI: 0.47-0.96; P=0.027) also in favor of sodium

bicarbonate (Figure 2).

However, moderate heterogeneity (I^2=48%, P=0. 008) across studies was found (Figure 2).

Therefore, subgroup analyses were constructed using random effects model and showed a more pronounced effect of sodium bicarbonate in studies using low-osmolar contrast media (OR 0.59; 95%CI: 0.37-0.93, P=0. 024) (Table 3). Similarly, subgroup analysis by settings suggested lower odds of CIN with sodium bicarbonate in studies with patients undergoing emergency procedures (OR 0.16; 95%CI 0.05-0.51, P=0. 002) (Table 3). The effect of sodium bicarbonate was considered greater in articles reported pre-2008 (OR 0.19; 95%CI:0.09-0.41, P<0.001) (Table 3). Subgroup analysis based on the manner of sodium bicarbonate administration indicated a better effect in patients given a bolus injection (OR 0.15; 95%CI: 0.04-0.54, P=0. 004) (Table 3). Sodium bicarbonate in combination with NAC demonstrated a more salient efficacy in preventing CIN (OR 0.17; 95%CI: 0.04-0.79, P=0. 024) (Table 3).

Influence analysis showed no individual study had an excessive influence on the overall estimate odds ratios and 95%CI (Figure 4).

Begg' funnel plot and Egger' test (P=0. 396) implied no significant publication bias in this study (Figure 5).

Secondary outcomes

The requirement for dialysis

The requirement for dialysis was described in a total of 17 studies (n=3, 633). In 8 of these studies, there was no dialysis event in both groups [11,12,15,16,18,19,22,24].

Overall, 14 out of 1,809 patients who treated with sodium bicarbonate compared with 13 out of 1, 824 patients treated with saline that underwent dialysis. No statistical significant difference was observed (OR 1.08; 95%CI: 0.52-2.25, *P*=0. 841) (Figure 3a). Nonetheless, the OR for the requirement of dialysis suggested that maybe sodium bicarbonate was no better than saline in reducing the dialysis events.

Mortality

Post-procedural death was described in a total of 12 studies (n=2, 559), of these, 6 studies reported no death in either group [11,13,14,16,23,24]. There were 15 deaths in the 1, 279 patients treated with sodium bicarbonate and 22 in the 1, 280 patients treated with saline. Although there was no significant difference between the two arms (OR 0.69; 95%CI: 0.36-1.32, *P*=0. 263) (Figure 3b), a trend toward lower mortality risk was found in sodium bicarbonate arm compared with saline arm.

Discussion

Although CIN is generally regarded as a transient decline in renal function after contrast procedures, it cannot be regarded as a benign complication [25,26]. It accounts for 12% of all cases of acute renal failure [27]. In an observational study, 0.8% of included patients undergoing coronary angiography or interventional procedures started dialysis and 13% of them needed a permanent one [28]. Furthermore, the development of CIN is associated with a longer hospital stay, an increased morbidity and mortality, in addition to a higher financial cost. Consequently, we can never be blind to the hazard of CIN.

Various risk factors may contribute to CIN, which are divided into two groups:

patient- and procedure-related [29]. Preexisting renal insufficiency and diabetes mellitus are the two main patient-related risk factors. That is one reason why we focus on the patients with a history of renal insufficiency. Renal insufficiency was usually defined as a decrease in eGFR and since the eGFR has to be reduced by 50% before a rise in serum creatinine occurs, an elevated serum creatinine level was used as the cutoff point for the definition for renal insufficiency [21]. In a retrospective review of 938 patients with stable renal insufficiency, the overall incidence of CIN was 6.1%, and the incidence was 4.4%, 10.5%, 10.0% for patients whose eGFR was 45-60, 30-45, and ≤30 ml/min, respectively [30]. Hence special care should be taken in patients with renal insufficiency.

In order to prevent CIN, sodium bicarbonate has been proposed by various mechanisms [31,32]. Namely, how does it work remains unknown. Some potential mechanisms speculated are that alkalinizing the tubular urine with sodium bicarbonate may attenuate free radical formation and peroxide injury [28]. Oxygen free radicals and peroxide usually generate in acidic conditions, infusion of sodium bicarbonate could increase the PH of local renal tissue to neutral or slightly alkaline, thereby reducing the production of free radicals and peroxide. Merten et al. [19] first introduced the administration of sodium bicarbonate in a concentration of 154 mmol/L to prevent CIN. In our study, hydration regimens of 13 trials [9-17,19-21,33] were performed similarly to “Merten protocol”. Although most previous systematic reviews and relevant meta-analyses demonstrated that sodium bicarbonate infusion could decrease the incidence of CIN [25, 26, 34-42], secondary clinical endpoints as

diverse as renal replacement therapy and mortality were not ameliorated. Furthermore, a retrospective cohort study of 7, 977 patients at Mayo Clinic drew a surprising conclusion: sodium bicarbonate was associated with an increased incidence of CIN [43]. By contrast with a majority of RCTs using creatinine elevations within 48-72 h after contrast exposure to define CIN, From et al. extended the definition time of CIN to a week based on the fact that creatinine may peak 3 to 7 days after contrast. However, this issue remains to be discussed. Since in our study, all patients had a history of renal insufficiency, the peak of serum creatinine may advance.

In this meta-analysis, the underlying sources of moderate heterogeneity should be taken into account, because the study subjects, study settings and type of contrast media were varied. In this case, subgroup analyses were conducted and the results revealed significant differences between emergency and elective procedures, the protective role of sodium bicarbonate played better in the former than the latter. In a meta-analysis [42] of the effect of sodium bicarbonate for the prevention of CIN, subgroup analyses also showed a more pronounced efficacy of sodium bicarbonate in 3 trials [18,33,44] included patients undergoing emergency procedures compared with those undergoing elective procedures. But the exact mechanism by which sodium bicarbonate results in a decrease incidence of CIN is still a mystery. Maybe it's related to the manner of administration and dosage. Similarly, sodium bicarbonate was more beneficial in patients who received low-osmolar contrast agents [45,46]. However, since the significantly fewer patients received iso-osmolar contrast media (n=1, 189) compared with those received low-osmolar ones (n=2,823), the major reason

responsible for the more salient effect of sodium bicarbonate was difficult to elucidate.

Although the utilization of N-acetylcysteine (NAC) has been known to reduce the incidence of CIN and whose value has been detected by many studies, the definitive effect of NAC is not yet established. A number of trials and meta-analyses indicated the combination of sodium bicarbonate and NAC is superior to either regimen in preventing of CIN. 3 studies [20,44,47] included patients who received NAC in both groups after the infusion of sodium bicarbonate or saline and the results were also in favor of sodium bicarbonate. The BINARIO study [48] indicated that hydration with sodium bicarbonate in addition to high-dose NAC in the setting of urgent PCI for STEMI was associated with a net clinical benefit. However, Yang et al. [27] and Thayssen et al. [49] concluded that use of NAC caused no significant reduction in the incidence of CIN. In our study, since only one trial [20] using NAC included in the sub-analysis, the effect of which may be overestimated (OR 0.17; 95%CI: 0.04-0.79, *P*=0. 024). Accordingly, more large-scale and well-designed RCTs are warranted to determine whether sodium bicarbonate plus NAC is more useful in preventing CIN than either alone.

Many studies have already shown patients with CIN have greater risks for the renal replacement therapy and death. In fact, almost all the dialysis and death events occurred in patients with high-risk factors for CIN. So we could not rely on sodium bicarbonate alone to improve the bad situations caused by CIN and underlying diseases, such as renal insufficiency, diabetes mellitus. Maybe that is one reason why

we did not find significant differences in both requirement of dialysis and mortality. However, insufficient power of included RCTs could be another reason. In this meta-analysis, not all studies described renal replacement therapy and mortality and sample sizes were relatively small. So this issue remains to be explored in the future.

Conclusions

Our meta-analysis demonstrates sodium bicarbonate is superior to saline for the prevention of CIN in patients with preexisting renal insufficiency undergoing procedures using contrast media. However, use of sodium bicarbonate did not result in obvious benefit in reducing the requirement for dialysis and the mortality. Therefore, larger trials are required to detect the efficacy of sodium bicarbonate in preventing CIN and improving the clinical prognosis of patients with CIN.

Footnotes

Contributors: B.Z, L.L and WB.C searched the studies. B.Z wrote the manuscript. L.L, WB.C, CH.L and SX.Z reviewed, analyzed and helped write the manuscript. All authors contributed to the conception and design of this study.

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Table 1. The baseline characteristics of included studies

Study	Cases	Age(years)		Male (%)	DM	HT	Baseline Scr(mg/dl)		eGFR(ml/min/1.73m²)	
		Bicarbonate	Saline		%	%	Bicarbonate	Saline	Bicarbonate	Saline
Merten	119	66.7*	69.2*	73/76	50/46	NA	1.89*	1.71*	41.0*	45.0*
Ozcan	176	68.0*	70.0*	76/75	42/48	75/81	1.36*	1.40*	NA	NA
Masuda	59	75.0±8.0	76.0±11.0	63/59	27/35	NA	1.31±0.52	1.32±0.65	40.2±15.4	38.7±15.4
REMEDIAL	219	70.0±9.0	71.0±9.0	88/81	49/55	92/87	2.04*	1.95*	32.0±7.0	71.0±9.0
Adolph	145	70.1±8.4	72.7±6.6	75/81	37/28	83/91	1.54±0.51	1.57±0.36	NA	NA
Brar	323	71.0*	71.0*	62/65	43/46	NA	1.49#	1.49#	47.7#	48.3#
Maioli	502	74.0*	74.0*	57/61	25/23	59/57	1.21±0.30	1.20±0.30	NA	NA
Tamura	144	72.3±9.9	73.3±7.7	92/83	60/57	85/83	1.36±0.18	1.38±0.19	40.0±7.5	38.2±0.2
Vasheghani	265	62.9±10.0	63.8±9.0	84/82	22/21	30/41	1.63±0.32	1.66±0.50	46.4±12.0	45.4±12.0
Castini	103	70.0±8.3	72.7±8.2	85/84	35/20	71/78	1.59±0.38	1.49±0.30	46.9±12.8	49.9±10.3
Vasheghani(2)	72	61.4#	62.7#	78/81	33/38	66/71	1.77#	1.71#	42.7#	44.2#
Motohiro	155	71.0±9.0	74.0±7.0	76/64	56/63	86/83	1.54±0.43	1.55±0.44	45.7±12.9	42.8±13.8
PREVENT	382	65.8*	67.5*	71/71	100/100	77/80	1.50*	1.50*	46.0*	46.0*
Ueda	59	77.0±9.0	75.0±10.0	77/79	10/10	NA	1.32±0.46	1.51±0.59	42.4±11.5	38.7±12.6
Klima	176	78.0*	75.0*	66/62	39/34	90/81	1.60*	1.60*	43.1#	43.0#
Gomes	301	64.1±12.0	64.5±12.0	15/75	29/30	77/74	1.50±0.40	1.49±0.50	50.5±13.0	51.9±13
Hafiz	320	74.0*	73.0*	57/57	49/45	95/94	1.65*	1.60*	41.5*	40.5*
Kristeller	92	72.0±11.0	73.0±11.0	64/52	52/38	89/92	NA	NA	48.9#	49.4#
Boucek	120	63.0#	67.0#	75/75	NA	NA	1.92#	1.81#	43.6#	44.6#
Kooiman	548	71.6#	72.5#	60/61	27/27	NA	NA	NA	49.9#	50.9#

Note: DM=diabetes mellitus HT=hypertension eGFR=estimated glomerular filtration rate NA= not applicable
*median value #mean value

Table 1. Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective diagnostic /interventional procedures	SB vs. SC	NA	NA	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥25% within 2d
		Iopamidol,nonionic,Low-osmolar			
Elective CAG/PCI	SB vs. SC	100*	100*	1ml·kg^{-1}·h^{-1} for 6h before and after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Ioxaglate,ionic,Low-osmolar			
Emergency CAG/PCI	SB vs. SC	112±89	120±61	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Iopamidol,nonionic,Low-osmolar			
Elective CAG/ PCI /peripheral procedure	SB+NAC vs. NS+NAC	169±92	179±9	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑≥25% within 2d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG/PCI	SB vs. SC	141±50	138±52	2ml·kg^{-1}·h^{-1} for 2h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑>0.5mg/dl or 25% within 2d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG	SB vs. SC	126*	137*	3ml·kg^{-1}·h^{-1} for 1h before and 1.5ml·kg^{-1}·h^{-1} for 4h after the procedure of SB or SC	eGFR↓>25% within 4d
		Ioxilan,nonionic,Iso- osmolar			
Elective CAG/PCI	SB vs. IS	160*	170*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h after:IS	Scr↑≥0.5mg/dl within 5d
		Iodixanol,nonionic,Iso- osmolar			
Elective CAG/PCI	Bolus SB+SC vs. SC	82±40	88±45	Single-bolus SB 20ml for 5min before and SC 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure; 1ml·kg^{-1}·h^{-1} for 12h pre- and post-procedure of SC	Scr↑>0.5mg/dl or 25% within 3d
		Iohexol,nonionic,Low-osmolar			
Elective CAG	SB+Is vs. IS	115±41	113.2±36	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after in both groups	Scr↑≥0.5mg/dl or 25% within 2d
		Iohexl,nonionic,Low-osmolar			
Elective CAG/PCI	SB vs. SC	179±125	196±128	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and after:SC	Scr↑≥25% within 5d
		Iodixanol,nonionic,Low-osmolar			

Note: CAG=coronary angiography PCI=percutaneous coronary intervention SB=sodium bicarbonate SC= sodium chloride IS=isotonic saline NAC=N-acetylcysteine NS=normal saline Scr=serum creatinine

Table 1. Continued

Procedure	Interventions	Contrast type and Volume(ml)		Hydration regimen	Definition of CIN
		Bicarbonate	Saline		
Elective CAG	SB+half SC vs. half SC	112# Iohexol,nonionic, Low-osmolar	123#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of 75ml SB to1L of 0.45%SC; 1075ml 0.45%SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB+SC vs. SC	140±50 Iopamidol, nonionic, Low-osmolar	130±40	1ml·kg^{-1}·h^{-1} SC 12h before and 1ml·kg^{-1}·h^{-1} SB from 3h pre-to 6h post-procedure, then 1ml·kg^{-1}·h^{-1} SC for 12h; 1ml·kg^{-1}·h^{-1} SC 12h pre- and 12h post- procedure	Scr↑≥0.5mg/dl or>25% within 2d
Elective CAG/ angioplasty/ endovascular intervention	SB vs SC	113* Iodixanol,nonionic , Low-osmolar	120*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h:SC	Scr↑≥0.5mg/dl or>25% within 2d
Emergency CAG/ PCI	SB vs SC	116±63 Iopamidol/Iohexol, Low-osmolar	104±57	Bolus 0.5mg/ml SB before and SC 1ml·kg^{-1}·h^{-1} for 6h during and after in both groups	Scr↑≥0.5mg/dl or >25% within 2d
Elective CAG/ PCI/ PTA/CT/ PAG	SB vs SC	100* Iopromide/iohexol.etc. Iso/Low-osmolar	100*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 24h:SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CAG/PCI	SB vs NS	124±65 Hexabrix/Loxaglate, Low-osmolar	125±87	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or NS	Scr↑≥0.5mg/dl within 2d
Elective CAG/ PAG/ intervention	SB±NAC vs NS±NAC	110* Iodixanol/Iopamidol/Ioversol, nonionic,Low-osmolar	100*	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after:SB; 1ml·kg^{-1}·h^{-1} for 12h before and 12h after:NS	Scr↑>0.5mg/dl or 25% within 2d
Elective CPB	SB vs IS	74# NA	83#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or IS	Scr↑≥0.3mg/dl or 50% or Urine output <0.5ml·kg^{-1}·h^{-1} (>6h) within 5d
Elective CAG/ Lower-limb angiography and /or angioplasty	SB vs NS	115# Iodinated,nonionic , low-osmolar	104#	3ml·kg^{-1}·h^{-1} for 1h before and 1ml·kg^{-1}·h^{-1} for 6h after the procedure of SB or SC	Scr↑≥0.5mg/dl or 25% within 2d
Elective CECT	SB vs IS	105.7# Iomeprol/Iobitridol/ Iodixanol,Low-osmolar	104.7#	250ml SB for 1h before; 1000ml IS before and 1000ml IS after	Scr↑＞0.5mg/dl or 25% within 4d

Note: PTA=percutaneous transluminal angioplasty PAG=peripheral angiography CPB=cardiopulmonary bypass CECT=contrast-enhanced computerized tomography

Table 2. Quality assessment of included studies

Included trials	Trial described as randomized (1=yes, 0=no)	Randomized method described & appropriate (1=yes, 0=no)	Allocation concealment described† (1=yes, 0=no)	Allocation concealment described & appropriate (1=yes, 0=no)	Trial described as double blind (1=yes, 0=no)	Double blind method described & appropriate (1=yes,0=no)	Withdrawals & Dropouts described (1=yes,0=no)	Jadad score *
Merten	1	1	0	0	0	0	1	4
Ozcan	1	0	0	0	0	0	1	2
Masuda	1	1	0	0	0	0	1	4
REMEDIAL	1	1	0	0	1	0	1	5
Adolph	1	1	0	0	1	0	1	5
Brar	1	1	1	1	0	0	1	5
Maioli	1	1	1	1	0	0	0	4
Tamura	1	1	0	0	0	0	1	4
Vasheghani	1	1	0	0	1	0	0	4
Castini	1	1	0	0	0	0	0	3
Vasheghani(2)	1	1	0	0	1	0	0	4
Motohiro	1	1	0	0	0	0	1	4
PREVENT	1	1	0	0	0	0	1	4
Ueda	1	1	0	0	0	0	0	3
Klima	1	0	1	1	0	0	0	3
Gomes	1	0	1	1	0	0	0	3
Hafiz	1	1	0	0	0	0	1	4
Kristeller	1	1	1	1	1	0	0	5
Boucek	1	1	1	1	1	0	1	6
Kooiman	1	1	0	0	0	0	1	4

Note: †One point can be obtained from Jadad Score if randomization method of the trial is described &appropriate

*Calculation for quality assessment of included trials: low, 1-3; high, 4-7

Table 3. Subgroup analyses used to assess the effect of sodium bicarbonate in various conditions

Subgroups	Trials/patients	OR(95%CI)	Test for overall effect	Heterogeneity
Type of contrast				
Low-osmolar	14/2823	0.59[0.37,0.93]	Z=2.26(*P*=0.024)	χ^2=26.61,df=13(*P*=0.014), I^2=51%
Iso-osmolar	4/1189	0.76[0.43,1.34]	Z=0.93(*P*=0.351)	χ^2=4.67, df=3(*P*=0.198), I^2=36%
Setting				
Elective	18/4162	0.76[0.54,1.06]	Z=1.62(*P*=0.105)	χ^2=29.54,df=17(*P*=0.030), I^2=43%
Emergency	2/118	0.16[0.05,0.51]	Z=3.11(*P*=0.002)	χ^2=0.07,df=1(*P*=0.784), I^2=0%
Using NAC or not				
Use	1/219	0.17[0.04,0.79]	Z=2.26(*P*=0.024)	Not applicable
Non-use	18/3741	0.71[0.48,1.03]	Z=1.80(*P*=0.071)	χ^2=33.13, df=17(*P*=0.011), I^2=49%
Publication year				
Before 2008	4/573	0.19[0.09,0.41]	Z=4.26(*P*=0.000)	χ^2=1.06, df=10(*P*=0.788), I^2=0%
After 2008	16/3707	0.85[0.62,1.16]	Z=1.03(*P*=0.302)	χ^2=22.13, df=15(*P*=0.105), I^2=32%
Manner of administration				
Continuous	18/4077	0.75[0.53,1.05]	Z=1.69(*P*=0.091)	χ^2=30.21, df=17(*P*=0.025), I^2=44%
Bolus	2/203	0.15[0.04,0.54]	Z=2.90(*P*=0.004)	χ^2=0.23, df=1(*P*=0.632), I^2=0%

Figure legends

Figure 1. Flow diagram of included studies

Figure 2. The forest plot of odds ratios of contrast-induced nephropathy

Figure 3a. The forest plot of odds ratios of the requirement for dialysis

Figure 3b. The forest plot of odds ratios of the mortality

Figure 4. The influence of an individual study on the overall estimates

Figure 5. Funnel plot with pseudo 95% confidence limits

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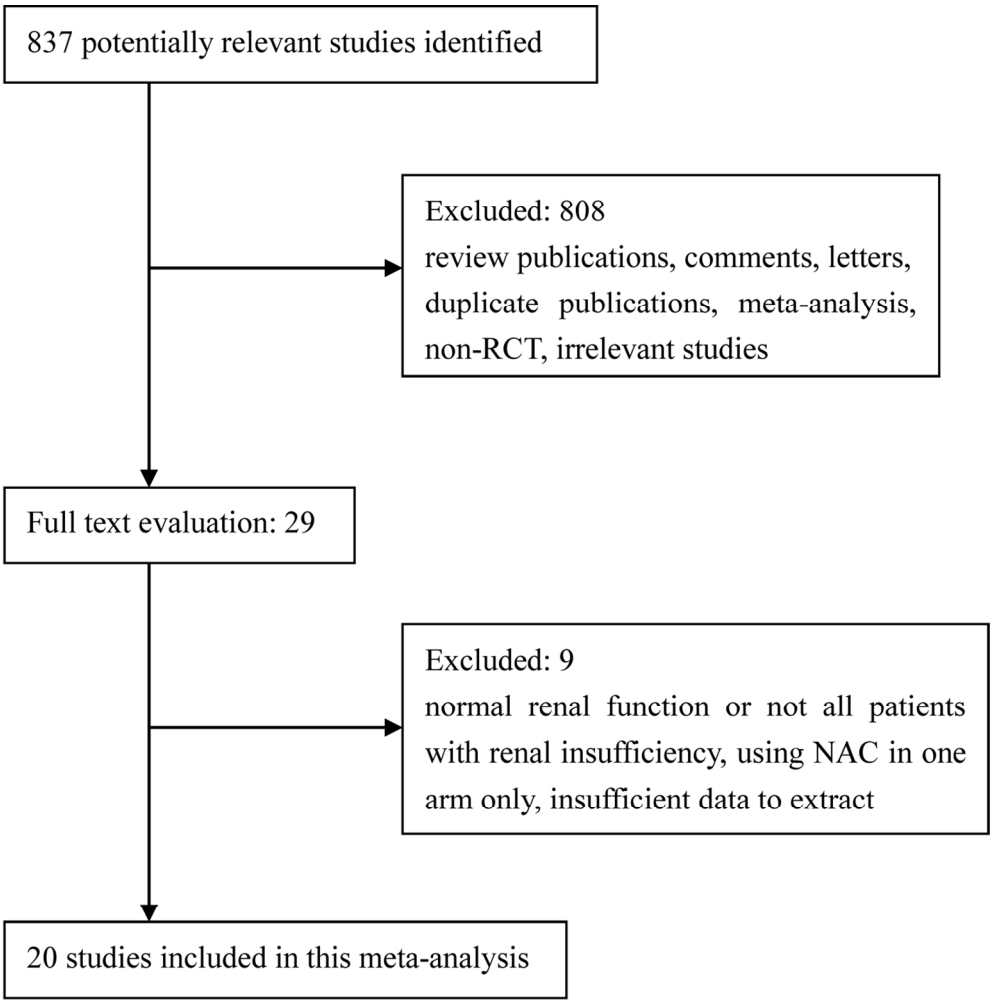
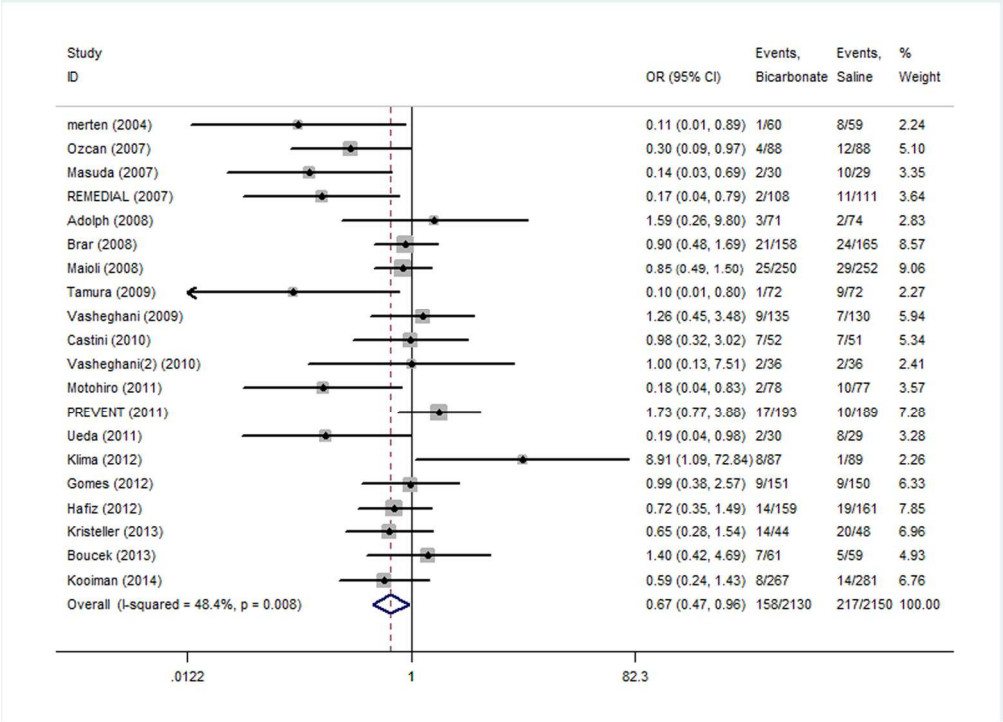
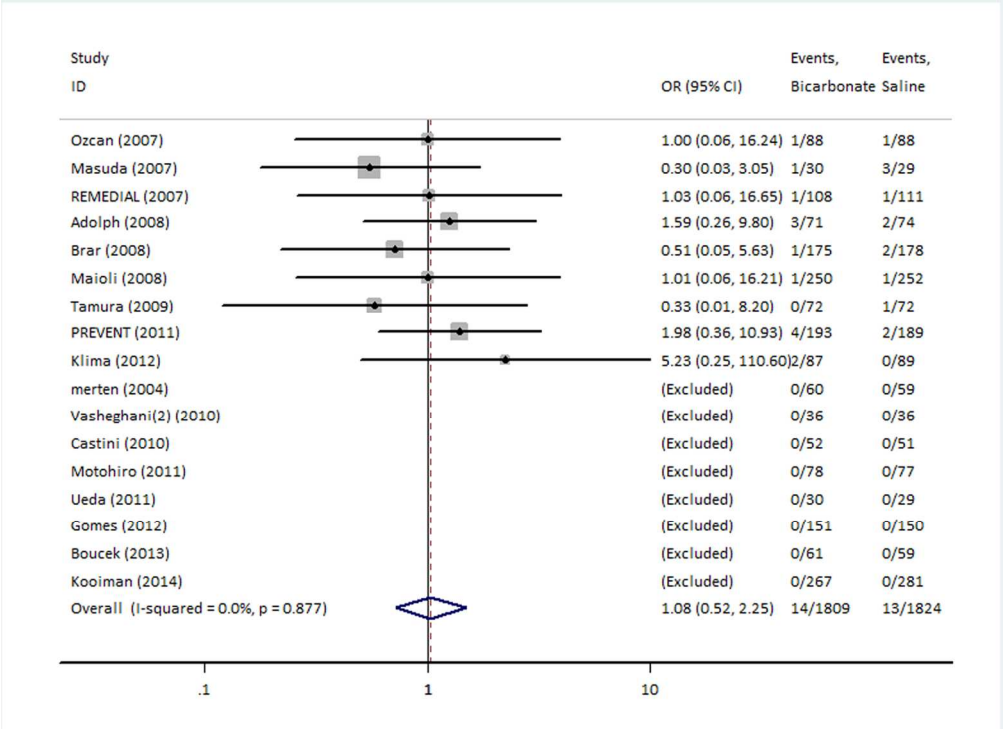


Flow diagram of included studies
119x119mm (300 x 300 DPI)



The forest plot of odds ratios of contrast-induced nephropathy
173x124mm (300 x 300 DPI)



The forest plot of odds ratios of the requirement for dialysis
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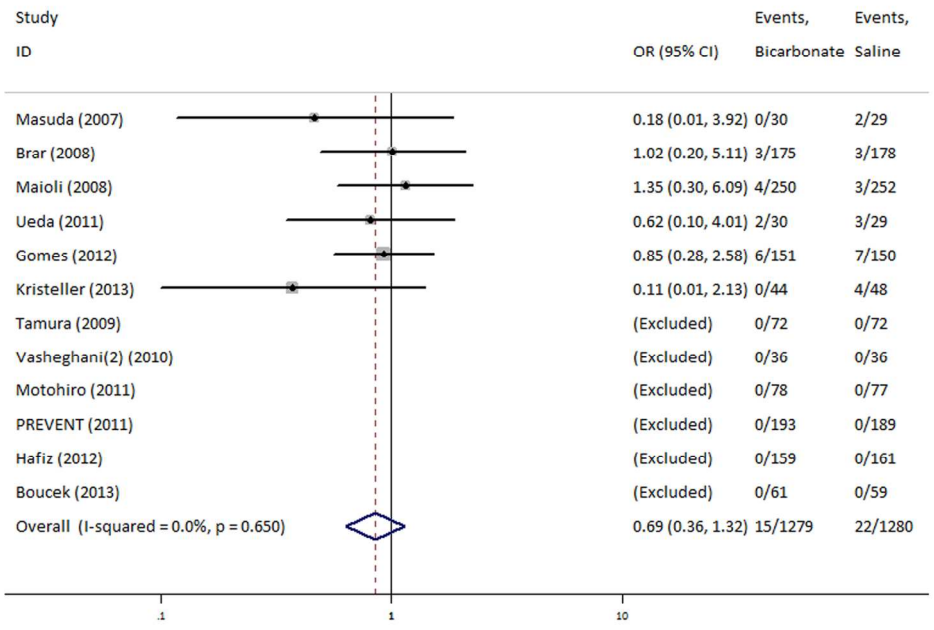
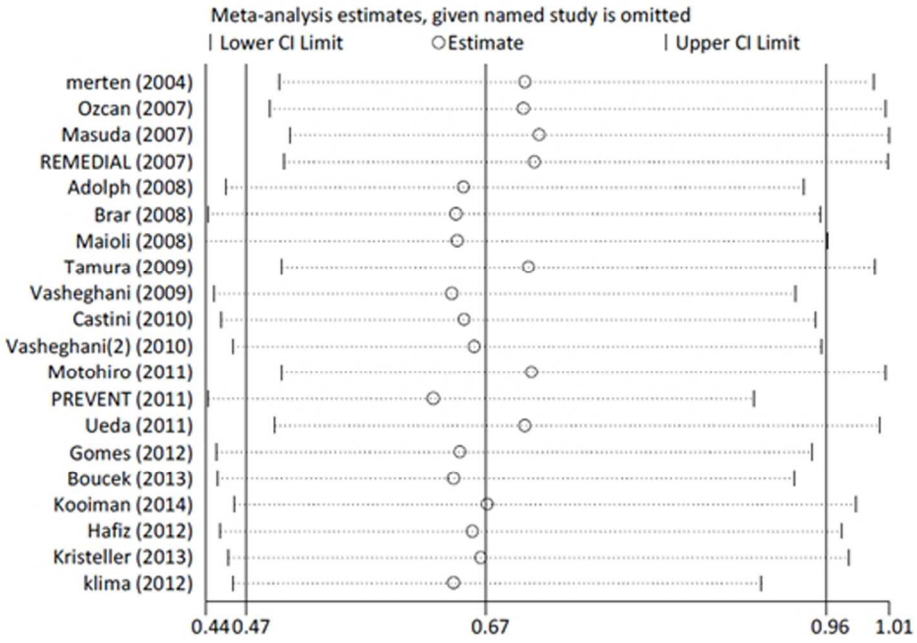
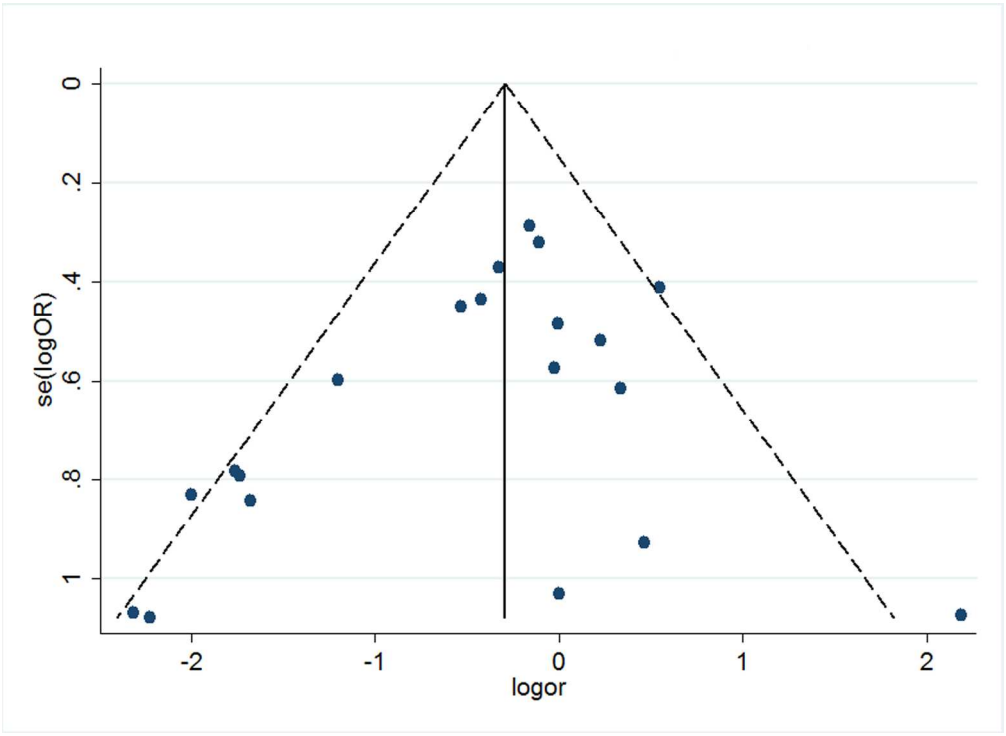


The forest plot of odds ratios of the mortality
173x121mm (300 x 300 DPI)



The influence of an individual study on the overall estimates
152x107mm (300 x 300 DPI)



Funnel plot with pseudo 95% confidence limits
173x126mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig2/3a/3b
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10Figure2 /3a/3b
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10Figure2 /3a/3b
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10Figure 4 /Table3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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