International Journal of Cardiology 201 (2015) 237–242

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Comparison of combination therapy of high-dose oral N-acetylcysteine and intravenous sodium bicarbonate hydration with individual therapies in the reduction of Contrast-induced Nephropathy during Cardiac Catheterisation and Percutaneous Coronary Intervention (CONTRAST): A multi-centre, randomised, controlled trial☆

Eric Chong [a,b,1], Kian-Keong Poh [a,c,*,1], Qingshu Lu [d], James Jun-Jie Zhang [e], Ning Tan [f], Xu Min Hou [g], Hean-Yee Ong [h], Aizai Azan [i], Shao-Liang Chen [e], Ji-Yan Chen [f], Rosli Mohd Ali [i], Wei-Yi Fang [g], Titus Wai Leong Lau [j], Huay-Cheem Tan [a,c,*]

[a] Department of Cardiology, National University Heart Centre, National University Health System, Singapore
[b] Department of Medicine, Jurong Health, Singapore
[c] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[d] Singapore Clinical Research Institute, Singapore
[e] Cardiology Department, Nanjing First Hospital, Nanjing Medical University, Nanjing, China
[f] Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
[g] Shanghai Chest Hospital, Shanghai, China
[h] Department of Cardiology, Khoo Teck Puat Hospital, Singapore
[i] National Heart Institute, Kuala Lumpur, Malaysia
[j] Divison of Nephrology, Department of Medicine, National University Health System, Singapore

ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form 30 June 2015
Accepted 31 July 2015
Available online 5 August 2015

Keywords:
Contrast-induced nephropathy
Cardiac catheterisation
Percutaneous coronary intervention
N-acetylcysteine
Sodium bicarbonate
Combination therapy

ABSTRACT

Introduction: N-acetylcysteine (NAC) and sodium bicarbonate (SOB) therapies may prevent contrast-induced nephropathy (CIN). However, the efficacy of using combination over individual therapies was not established, and there was no large randomised study comparing abbreviated SOB therapy with conventional sustained saline pre-hydration with oral NAC.

Methods: In a multi-centre, open-label, randomised, controlled trial (NCT00497328), we prospectively enrolled 548 patients with at least moderate renal impairment undergoing cardiac catheterisation with or without percutaneous coronary intervention. Patients were randomly assigned to 3 groups: 1) NAC: 154 mEq/L sustained sodium chloride regime (1 mL/kg/h 12 h before, during and 6 h after the procedure) with oral NAC at 1.2 g bid for 3 days (n = 185); 2) SOB: 154 mEq/L abbreviated SOB regime at 3 mL/kg/h 1 h before the procedure, and 1 mL/kg/h during and 6 h after the procedure (n = 182); and 3) COM: combination of abbreviated SOB regime and oral NAC (n = 181). The primary end point was incidence of CIN. The secondary end points were rise in serum creatinine, hospitalisation duration, haemodialysis, morbidity and mortality within 30 days.

Results: The 3 groups had similar baseline characteristics: age 68 ± 10 years, 76% male, 48% diabetic and baseline glomerular filtration rate (GFR) 47.7 ± 13.0 mL/min. There were 41 (8.8%) patients with GFR < 30. The CIN incidences were NAC 6.5%, SOB 12.8% and COM 10.6%. The COM regimen was not superior to either the NAC (relative risk (RR) = 1.61, 95% confidence interval (CI): 0.76 to 3.45, p = 0.225) or SOB (RR = 0.83, 95% CI: 0.44 to 1.56, p = 0.593) regimens. The CIN incidence was lower in the NAC group than the SOB group (adjusted odds ratio (OR) = 0.40, 95% CI: 0.17 to 0.92; p = 0.032). Multivariate analysis showed contrast volume (OR = 1.99, 95% CI: 1.33 to 2.96, p < 0.001 per 100 mL), female (OR = 2.47, 95% CI: 1.22 to 5.00, p = 0.012) and diabetes

Abbreviations: AE, adverse event; CABG, coronary artery bypass graft surgery; CI, confidence interval; CIN, contrast medium-induced nephrotoxicity; eGFR, estimated glomerular filtration rate; ITT, intention to treat; NAC, N-acetylcysteine; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; SAE, serious adverse event; SOB, isotonic sodium bicarbonate.

☆ **Relationship with Industry**: None, in relation to this article.

* Corresponding authors at: Department of Cardiology, National University Heart Centre, Singapore, Yong Loo Lin School of Medicine, National University of Singapore, NUHS Tower Block, Level 9, 1E Kent Ridge Road, Singapore 119228, Singapore.
E-mail addresses: kian_keong_poh@nuhs.edu.sg (K.-K. Poh), huay_cheem_tan@nuhs.edu.sg (H.-C. Tan).

[1] The first 2 authors contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.ijcard.2015.07.108
0167-5273/

(OR = 2.03, 95% CI: 1.03 to 3.99, p = 0.041) were independent risk predictors. There were no differences in the secondary outcomes among the 3 groups.
Conclusion: The combination regimen was not superior to individual regimens in preventing CIN in patients with baseline renal impairment. There was a trend suggesting that the 12-hour sustained sodium chloride pre-hydration regimen was more protective than the 1-hour abbreviated SOB regimen.

1. Introduction

Contrast-induced nephropathy (CIN) occurs when renal function deteriorates within 48 h of contrast administration in the absence of other causes [1]. It is commonly defined as a ≥25% increase of baseline serum creatinine (Cr) or a ≥44 μmol/L (0.5 mg/dL) increase in serum Cr concentration [2]. CIN can be self-limited, with serum Cr levels peaking at 48 h and returning to baseline within 7 to 10 days. However, renal dysfunction can be permanent, leading to dialysis and mortality [3–5], The risk is significantly higher in patients with baseline renal impairment [6]. CIN is a known complication after percutaneous coronary intervention (PCI) [7–9]. Mortality can rise from 4% when serum Cr increases by 50 μmol/L, to as much as 64% when serum Cr increases by more than 250 μmol/L [10,11].

Intravenous (IV) pre-hydration with 0.9% sodium chloride (normal saline) is the cornerstone for CIN prevention [12]. But the optimal preventive regimen in high-risk patients with baseline renal impairment is unknown. Several prophylactic regimens have been investigated in clinical trials [13], including high-dose N-acetylcysteine (NAC) and isotonic sodium bicarbonate (SOB) infusion [14–17]. The efficacy of combining both regimens has not been evaluated in a large Asian study. Our study was designed primarily to evaluate the benefit of using a combination of NAC and SOB compared to individual therapies. It was also designed to assess the superiority of SOB regimen over a sodium chloride/NAC regimen in a large multi-centre trial.

2. Methods

2.1. Eligibility criteria

The study complied with the Declaration of Helsinki, gaining approval from a locally appointed ethics committee for the research protocol and obtaining informed consent from all patients. The CONTRAST trial was registered on ClinicalTrials.gov (NCT00497328). Eligible patients included adults >21 years of age with a glomerular filtration rate (GFR) of 15–60 mL/min/1.73 m^2 – calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula – who were scheduled to undergo elective cardiac catheterisation with or without PCI and were able to receive pre-hydration for 12 h. Exclusion criteria included end-stage renal failure with GFR of <15 mL/min/1.73 m^2, acute renal failure with a >44 μmol/L increase in serum Cr levels in the previous 24 h, pre-existing dialysis, pulmonary oedema or moderate to severe congestive heart failure (New York Heart Association III–IV), inability to withstand the fluid load and presence of haemodynamic compromise, uncontrolled hypertension (untreated systolic blood pressure >160 mm Hg, or diastolic blood pressure >100 mm Hg) and emergency cardiac catheterisation (that is, the patient presenting with ST segment elevation myocardial infarction undergoing primary PCI). Additional exclusion criteria included exposure to contrast in the previous two days; allergies to contrast or NAC; administration of sodium bicarbonate or NAC within 48 h of cardiac catheterisation; clinical conditions requiring continuous fluid therapy such as severe sepsis; or the use of potentially renal-toxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycoside, cyclosporin and cisplatin within 48 h of cardiac catheterisation and throughout the study duration.

2.2. Study design

This was an open-label, randomised, controlled, multi-centre trial. All eligible patients were randomly assigned in a 1:1:1 ratio to receive high-dose oral NAC with a sustained IV sodium chloride infusion (NAC group), abbreviated IV sodium bicarbonate infusion (SOB group) or both oral NAC and abbreviated IV SOB infusion (COM group). Investigators and research coordinators at each site allocated participants through block randomisation, stratified by site, using a web-randomisation system or back-up randomisation envelopes. Prior to patient enrolment, a randomisation list was uploaded to the web-randomisation system at the Singapore Clinical Research Institute, which was an independent research centre not involved in patient enrolment and assessment. An independent research coordinator prepared the randomisation envelopes. Both randomisation protocols were generated using a validated SAS® (SAS Institute Inc., North Carolina, USA) program. Eligible patients participated in the study for 30 days.

2.3. Treatment groups

The patients received one of three regimens, as per their randomisation and were not allowed to switch to other arms of treatment. Outpatients were allowed to be administered NAC before cardiac catheterisation in the NAC and COM arms. However, all intravenous fluid therapy had to be administered strictly for inpatients. All patients were monitored regularly for pulmonary congestion and haemodynamic compromise after cardiac catheterisation or PCI, hourly for 6 h, and 4-hourly thereafter for 24 h. The contrast agents used were non-ionic low-osmolality types (iohexol, iopamidol, ioversol and iopromide).

Patients in the NAC group received a sustained IV infusion of 154 mEq/L sodium chloride (0.9% normal saline) at a rate of 1 mL/kg/h from 12 h before cardiac catheterisation or PCI. The infusion was continued for 6 h after the procedure. Patients in the NAC group received 1.2 g oral NAC (2 tablets of 600 mg NAC dissolved in approximately 250 mL of water) twice a day for 3 consecutive days, starting from the day before cardiac catheterisation (to a total of 6 doses). For patients weighing more than 110 kg, the infusion was limited to a 110 kg patient dose.

Patients in the SOB group received abbreviated loading IV infusion of 154 mEq/L sodium bicarbonate in 5% dextrose solution at a rate of 3 mL/kg/h for 1 h before cardiac catheterisation or PCI, and 1 mL/kg/h during and until 6 h after the procedure. For patients weighing more than 110 kg, the infusion was limited to a 110 kg patient dose.

Patients in the COM group received 1.2 g oral NAC and an abbreviated IV infusion of 154 mEq/L sodium bicarbonate at the same dose and rate as the SOB group. The patients were not infused with 0.9% normal saline. The sodium bicarbonate solution had the same osmolality as the saline solution, and was infused for 12 h prior to the procedure to avoid over-alkalinisation. Our study followed the same protocol in the study by Merten et al. and the REMEDIAL trials, where abbreviated sodium bicarbonate was infused 1 h before the procedure [17,18].

2.4. Clinical end points

The primary outcome was CIN, which was defined as ≥25% increase of serum Cr concentration or a ≥44 μmol/L (0.5 mg/dL) increase in serum Cr within 48 h of cardiac catheterisation or PCI [2]. Secondary outcomes included haemodialysis, 30-day mortality, maximum change in serum Cr and GFR within 30 days, peak serum Cr level and length of hospital stay. Serum Cr was assessed at screening, on Day 1 (optional procedure day), Day 2, Day 3 and Day 30 (end-of-study visit). The serum Cr from days 2 and 3 was used to calculate the change from baseline to determine CIN. If the serum Cr level from days 2 or 3 increased >25% above baseline, the patient would be monitored daily for up to a week or longer – at the discretion of the investigator – until serum Cr improved or CIN resolved.

2.5. Statistical analysis

The CIN incidence was calculated, with the denominator being the number of patients who were assessed for serum Cr level on Day 2 and/or Day 3. Pair-wise comparisons of CIN incidence were performed between the COM and NAC groups, and between the COM and SOB groups, using Fisher's exact test, together with 95% confidence intervals (CIs) to determine the difference between CIN incidence and relative risk (RR) of CIN. The significance level was not adjusted, as the primary objective was to show the combination therapy's superiority to both NAC and SOB. Multiple logistic regressions were carried out to adjust the treatment effect estimate (namely, odds ratio (OR) of CIN) for potential prognostic factors at baseline, including the volume of contrast received by individual patients. Pair-wise comparisons of continuous secondary outcomes were performed using the Mann–Whitney *U* test, as they did not satisfy the normality test.

The length of hospital stay from the procedure day to the discharge day attributable to cardiac catheterisation (with or without PCI) was compared using the log-rank test. For patients who died in hospital or underwent coronary artery bypass graft surgery (CABG), the date of death or the date of CABG would be considered as the censored time of hospitalisation.

All statistical analyses were made on an intention-to-treat (ITT) basis and performed using SAS® 9.3 (SAS Institute Inc., North Carolina, USA).

Based on our own data and other data from the literature, it was assumed that the CIN incidence would be approximately 12.5% in the NAC group, 12.5% in the SOB group and 4% in the COM group [1–3,5,7,8]. A group sample size of 220 patients was required to detect a significant difference, with a power of 90% and two-tailed test size of 5% between the COM