Original Article

Comparison of Normal Saline, Ringer's Lactate, and Sodium Bicarbonate for Prevention of Contrast-induced Nephropathy in Patients with Coronary Angiography: A Randomized Double-blind Clinical Trial

Abstract

Contrast-induced nephropathy (CIN) is one the most important renal complications following contrast injection in percutaneous coronary intervention. We compared the protective effect of normal saline (NLS), Ringer's lactate (RL), and sodium bicarbonate (Bi). In this study, patients with coronary angiography indication were divided into three groups by simple randomization method: NLS, RL, and Bi solution groups. Creatinine (Cr) alterations, glomerular filtration rate, and urine pH were evaluated prior and after the procedure. Data were analyzed with SPSS and *P* value less than 0.05 was taken as significant. In this study, 300 patients [150 men (50%), mean age 59.1 ± 10.6 years] were studied. The CIN incidence overall was 10% (30 patients): 8.3% (8 patients) in NLS; 16.5% (17 patients) in RL; and 5% (5 patients) in Bi group. It was significantly different among three groups ($P = 0.018$), and CIN incidence was significantly lower in Bi vs. RL group ($P = 0.012$). Baseline Cr clearance was higher in patients who developed CIN (78.4 ± 26.0 vs. 69.8 ± 21.6 mL/dL, $P = 0.044$). Urine pH after trial in CIN group was lower than the patients without CIN (5.5 ± 1.4 vs. 6.3 ± 1.8 mL/dL, $P = 0.024$). Higher urine pH and its change during study were seen in Bi group ($P < 0.05$). Cr at the initiation of study and the use of RL vs. Bi may be prognostic factors in CIN progression ($P < 0.002$). Sodium barcarbonate as fluid had more protective effect than NSL or RL on prevention of CIN in patients undergoing coronary angiography. The risk factors for CIN in our study were higher baseline serum Cr and use of RL as hydration fluid.

Keywords: *Contrast-induced nephropathy, coronary angiography, Ringer's lactate, sodium bicarbonate*

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Introduction

Contrast-induced nephropathy (CIN) is one of the major causes of prolonged hospitalization in patients who have received iodine contrast medium, resulting in excessive cost, mortality, and morbidity.[1-4] CIN is a kind of reversible acute kidney injury (AKI) that is defined as an increase in serum creatinine (Cr) by ≥0.3 mg/dL within 48 h or ≥1.5 times baseline, which is presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/h for 6 h.[5] Traditionally, CIN is defined as an AKI that takes place 24–72 h after iodine radiographic contrast medium injection and is characterized by serum Cr rise by 0.5 or more; or its increase by 25% or more from its baseline.[2] However, in recent studies, any amount of Cr rise is considered important for diagnosis for CIN with exclusion of other causes of AKI.[2,5]

Incidence of CIN as a whole in general population is 0.6%–2.3%, but it is notably higher among different disease subgroups.[2] The accurate mechanism of contrast nephrotoxicity is not fully understood due to its multifactorial characteristics. Perhaps a combination of reduced medullary blood flow which leads to tissue hypoxia and a direct tubular injury due to toxic effects of contrast medium plays major roles in disease pathophysiology.[2]

Various strategies have been adapted for preventing CIN as vasoconstriction reduction, reestablishment of sufficient blood flow in renal capillaries, decreasing hypoxia in renal medulla, and anti-oxidant effect of some drugs.[6,7]

Despite heterogeneity in the results of different studies, European Renal Best Practice suggests that volume expansion

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with solutions such isotonic sodium chloride or sodium bicarbonate (Bi) is more beneficial rather than no volume expansion.[8] The rationale of administration of Bi or prescription of acetazolamide is that urine and medulla acidification is reduced with increased Bi excretion.

Since oxygen free radicals are produced in acidic environment and their production is withheld or their effects are neutralized in alkaline settings, urine alkalization can be considered as a preventive method for CIN.[9-14] One can propose that administration of Ringer's lactate (RL) as a hydration solution to the patients can be beneficial. Since this solution contains less chloride that normal saline (NLS), it draws on less hyperchloremic acidosis. In addition, other studies have shown that restriction of chloride-rich solutions, although decreasing the risk of acidosis and renal failure, may give rise to incidence of metabolic alkalosis.[12] Considering the fact that not many studies have focused on hydration with RL in prevention of CIN, this study was aimed to evaluate the effect of this solution in urine alkalization and also suggesting the more effective solution prevention of CIN.

Materials and Methods

Study population

This study was performed from July 2015 until February 2016 as a prospective, single-center trial in the angiography unit of Shahid Faghihi hospital affiliated to Shiraz University of Medical Sciences. In this randomized, double-blind study, 300 patients >18 years old who had signed the consent sheet and were scheduled for angiography or angioplasty were studied. Patients with severe heart failure, pulmonary edema, hemodynamic instability or acid base disturbance, and those under dialysis or under medications affecting renal function were excluded.

Study protocol

Patients were divided into three equal groups by simple randomization. The first group received 0.9% saline as 3 mL/kg 1 h previous to angiography and 1 mL/kg till 6 h post operation. The second and third groups received RL solution and isotonic Bi solution, respectively, with the doses mentioned above. The composition of isotonic Bi solution was 850 cc dextrose water 5% in addition to 150 mEq $NaHco_3$. Neither the medical staff nor the patients were aware of the nature of the injected solutions and patients were selected using secret codes and simple random selection by a nurse who was not involved in the study. There were 47 (15.7%) patients with diabetes, out of whom 8 (17.0%) suffered from CIN. Patients who had increased non-fasting blood sugar >250 were managed by regular insulin. All three groups received 1200 mg oral *N*-acetyl cysteine tablets twice a day starting from a day before angiography till the day of contrast medium injection (48 h in total). Moreover, administration of metformin and diuretics was ceased 48 h before the procedure. Patients who had complications during or after angiography were excluded from the study. Laboratory data including serum blood urea nitrogen, Cr, Na, K, and urine pH were collected before and after angiography and their results were compared. Rise in serum Cr level more than 0.3 mg/dL or reduction in glomerular filtration rate (GFR) (calculated by MDRD equation) by 25% or more was considered as CIN. Nature of dye was Ultravist which was the same all through the study period and in all patients.

Ethical consideration

The study was done in accordance with the Declaration of Helsinki and approved by the local ethics committee of Shiraz University of Medical Sciences. At the initiation of the study, patients were informed completely about the process of study, treatment side effect, and benefits. Then a written consent was taken.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences software version 18.0 (SPSS Inc., Chicago, IL, USA). Qualitative data are expressed as number and percentage, which were analyzed by Chi-square test. Quantitative data were presented as mean and standard deviation and analyzed by Student's *t*-test, analysis of variance test, and least significant difference test as a *post hoc* test in case the results were significant, and by paired *T*-test for comparison of characteristics in each group prior and after performing angiography. Multiple logistic regression with enter method was used to estimate the odds ratio (OR) of significant risk factors. All the variables of our study were analyzed by univariate test, and then we considered significant variables for interring variables into multivariate model. A *P* value of less than 0.05 was considered as statistically significant.

Results

In this study, 300 patients including 150 men (50%) with a mean age of 59.1 ± 10.6 years were studied. Patients were divided into three groups: NLS group with 96 cases, RL group with 103 patients, and Bi group with 101 participants. Table 1 describes some of the demographic and clinical data of our patients; there was no significant difference in baseline data of three groups at the beginning of the study. The overall incidence of CIN in our study was 10% (30 patients) [8.3% (8 patients) in NLS, 16.5% (17 patients) in RL, and 5% (5 patients) in Bi group, $P = 0.018$]. Pairwise comparison showed that difference of CIN incidence was only significant among Bi and RL groups ($P = 0.012$).

Table 2 compares the characteristics between who developed CIN and those who did not. There was not significant difference in baseline GFR (78.4 ± 26.0 with CIN vs.

Table 1: Clinical and laboratory findings are compared among all cases and three groups' patient before contrast media administration

Characteristics	Total (*n*=300)	Study groups			*P*
		Normal saline (*n*=96)	Ringer (*n*=103)	Bicarbonate (*n*=101)	
Age, years (mean±SD)	59.1±10.6	58.9±10.1	58.8±10.5	59.5±11.3	0.877
Male/female, *n* (%)	150/150	49/47	52/51	49/52	0.932
Weight, kg (mean±SD)	64.5±10.7	66.4±12.6	64.7±11.3	62.6±7.3	0.060
Ejection fraction, *n* (%)	50.2±9.4	48.5±11.4	50.9±9.1	51.2±7.4	0.091
Contrast volume, mL (mean±SD)	79.0±61.7	72.1±57.3	85±60.2	78.6±55.4	0.080
Diabetes mellitus, *n* (%)	47 (15.7)	18 (18.8)	17 (16.5)	12 (11.9)	0.398
GFR, mL/min (mean±SD)	70.7±22.2	73.8±23.0	71.1±22.8	67.4±21.0	0.123
Blood pressure, mm Hg (mean±SD)					
Systolic blood pressure	136.3±24.6	129.6±32.2	140.4±28.8	138.2±25.0	0.863
Diastolic blood pressure	91.2±11.3	92.0±10.5	91.8±12.6	95.7±13.0	
Hemoglobin, g/dL (mean±SD)	11.6±3.8	12.3±2.1	11.8±2.2	12.1±3.5	0.263
Mean arterial pressure, g/dL (mean±SD)	105.4±18.6	104.9±15.2	107.0±19.8	105.5±21.4	0.368
Medication, *n* (%)					
ASA	286 (95.2)	91 (94.8)	95 (92.2)	100 (99.0)	0.123
Atorvastatin	240 (80.0)	86 (89.6)	92 (89.3)	62 (61.4)	
Nitrates	226 (75.5)	88 (91.7)	83 (80.6)	55 (54.5)	
B-blocker	151 (50.3)	51 (53.1)	62 (60.2)	38 (37.6)	
Calcium channel blocker	100 (33.3)	32 (33.3)	18 (17.5)	50 (49.5)	
Angiotensin receptor blockers	122 (40.6)	48 (50.0)	35 (34.0)	39 (38.1)	
Angiotensin-converting enzyme inhibitors	32 (10.5)	14 (14.6)	8 (7.8)	10 (9.9)	
Others	16 (5.4)	6 (6.3)	4 (3.9)	6 (5.9)	
Indication for CAG, *n* (%)					
STEMI (late)	100 (33.4)	36 (36.5)	32 (31.1)	32 (31.7)	0.093
Non-STEMI (late)	28 (9.2)	7 (7.4)	11 (11.6)	10 (9.9)	
Stable angina	144 (48.1)	45 (46.9)	51 (49.5)	48 (47.5)	
Cardiac dysfunction	13 (4.2)	5 (5.2)	4 (3.8)	4 (4.0)	
Others	15 (5.1)	3 (3.1)	5 (4.9)	7 (6.9)	
Angiography findings, *n* (%)					
Three-vessel disease	99 (33.2)	42 (43.7)	31 (30.1)	26 (25.8)	0.586
Two-vessel disease	58 (19.1)	17 (17.7)	22 (21.3)	19 (18.8)	
Single-vessel disease	63 (21.0)	17 (17.7)	18 (17.5)	28 (27.7)	
Non-significant CAD	56 (18.5)	15 (15.6)	20 (19.4)	21 (20.8)	
Normal	24 (8.2)	5 (5.3)	12 (11.7)	7 (6.9)	

SD: Standard deviation, GFR: Glomerular filtration rate, ASA: Acetylsalicylic acid, CAG: Coronary angiography, STEMI: ST-Elevation Myocardial Infarction, CAD: Coronary Artery Disease

Table 2: Demographic and clinical characteristics of patients with and without contrast nephropathy

Variables	Contrast nephropathy (*n*=3)	No contrast nephropathy (*n*=270)	*P*
Age, years (mean±SD)	61.7±9.5	58.8±10.7	0.163
Male/female (*n*, %)	12/18	138/132	0.336
Ejection fraction (*n*, %)	50.0±10.7	50.2±9.3	0.895
Contrast volume, mL (mean±SD)	83.3±71.5	79.4±70.5	0.329
Diabetes mellitus (*n*, %)	8 (26.7)	39 (14.4)	0.108
GFR <60 mL/min/1.73 m^2 (*n*, %)	7 (23.3)	93 (34.4)	0.307
Creatinine clearance (mL/min)			
Before trial	78.4±26.0	69.8±21.6	0.044*
Urine pH (mean±SD)			
Before trial	5.1±1.3	4.9±1.1	0.212
After trial	5.5±1.4	6.3±1.8	0.024*
Δ urine pH	0.4±1.5	1.4±1.8	<0.001*

SD: Standard deviation, GFR: Glomerular filtration rate, Δ urine pH: After minus before administration of contrast values. *Significant differences between pre- and post-contrast administration

69.8 ± 21.6 without CIN, P = 0.154). Although baseline urine pH had no significant difference at baseline (5.1 ± 1.3 in CIN vs. 4.9 ± 1.1 in without CIN, P = 0.212), urine pH after trial in CIN group was lower than in who did not develop CIN (5.5 ± 1.4 vs. 6.3 ± 1.8, P = 0.024). In addition, delta of urine pH was higher in those who did not develop CIN (1.4 ± 1.8 vs. 0.4 ± 1.5, P < 0.001).

Table 3 presents comparisons of laboratory data before and after contrast administration among our patients. It revealed significant Cr level reduction (1.0 ± 0.2 vs. 0.9 ± 0.2, P = 0.007) and increase in eGFR (67.4 ± 21.0 vs. 72.2 ± 22.5, P = 0.003) in Bi group. The K level after trial was significantly different among three groups (P = 0.012); *post hoc* analysis showed significance level among RL and NLS (P < 0.001) as well as RL and Bi (P = 0.033). The K level was significantly decreased after injection of Bi solutions (4.4 ± 0.5 before trial vs. 4.2 ± 0.4, P = 0.030). The urine pH level after trial was significantly increased in all study population (4.9 ± 1.2 vs. 6.2 ± 1.8, P < 0.001) and also in each group (4.9 ± 1.3 vs. 5.4 ± 1.3 in NLS, 4.8 ± 1.0 vs. 5.7 ± 1.3 in RL, and 4.9 ± 1.1 vs. 7.5 ± 1.9 in Bi; P < 0.001). Additionally, after trail urine pH was significantly different among three groups (P < 0.001); *post hoc* analysis revealed that this significance was only between Bi and NLS (P < 0.001) and between RL and Bi (P < 0.001). Calculation of urine pH difference prior and after trial was significantly different in three groups (P < 0.001); the greatest delta urine pH was in Bi group; hence, higher urine pH and higher urine delta pH after administration were seen in Bi group. Delta GFR pre and post hydration was statistically significant only in Bi group and showed greater increase in GFR after hydration with this solution (P = 0.043).

The results of regression analysis revealed use of RL versus Bi solution (OR: 5.9, confidence interval: 1.8–14.2, P = 0.004) as effective factor in prevention of CIN. At the end of this study, no patient needed renal replacement therapy and mortality was not seen in any group.

Discussion

CIN is one of the major complications of contrast injection, so its prevention methods have always been considered.[15,16]

Table 3: Comparisons of biochemical data and urinary pH pre- and post-contrast media administration among all cases and the three groups of patients

Variable, mean±SD	Total (n=300)	Study groups			P
		Normal saline (n=96)	Ringer (n=103)	Bicarbonate (n=101)	
Cr clearance (mL/min)					
Before trial	70.7±22.2	73.8±23.0	71.1±22.8	67.4±21.0	0.123
After trial	72.3±23.3	75.4±25.0	69.6±22.4	72.2±22.5	0.218
P	0.089	0.318	0.347	0.003*	-
BUN (mL/dL)					
Before trial	16.5±6.6	16.5±7.7	16.3±4.8	16.7±7.1	0.922
After trial	16.9±8.3	16.7±10.7	17.7±7.6	16.4±6.2	0.537
P	0.281	0.801	0.052	0.644	
Serum Cr (mL/dL)					
Before trial	1.0±0.3	1.0±0.4	1.0±0.2	1.0±0.2	0.951
After trial	1.0±0.3	1.0±0.4	1.0±0.3	0.9±0.2	0.157
P	0.406	0.486	0.217	0.007*	-
Serum Na (meq/L)					
Before trial	139.7±3.1	139.2±3.7	139.7±2.9	140.0±2.7	0.397
After trial	138.9±3.3	138.6±3.6	138.7±2.9	139.3±3.4	0.382
P	0.074	0.727	0.373	0.006*	-
Serum K (meq/L)					
Before trial	4.3±0.5	4.3±0.5	4.3±0.4	4.4±0.5	0.660
After trial	4.2±0.5	4.2±0.5	4.3±0.5	4.2±0.4	0.012**,≠
P	0.103	0.793	0.815	0.030*	-
Urine pH					
Before trial	4.9±1.2	4.9±1.3	4.8±1.0	4.9±1.1	0.335
After trial	6.2±1.8	5.4±1.3	5.7±1.3	7.5±1.9	<0.001**,##
P	<0.001*	<0.001*	<0.001*	<0.001*	-
Δ urine pH	1.3±1.7	0.46±1.2	0.92±1.3	2.5±2.1	<0.001**,###

SD: Standard deviation, Cr: Creatinine, BUN: Blood urea nitrogen, Na: Sodium, K: Potassium, Δ urine PH, after minus before administration of contrast values. *Significant differences between pre- and post-contrast administration. **Significant differences between three group values, *post hoc* test (LSD test). ≠Significant differences between post-contrast administration of K in NLS and RL groups (P<0.001) and RL and Bi (P=0.033). ##Significant differences between post-contrast administration of urine pH RL and Bi (P<0.001) and NLS and Bi (P<0.001). ###Significant in all groups (P<0.001)

Several studies have been conducted to prevent CIN.[17-23] Our study showed that the overall incidence of CIN was 10%, which was slightly higher than similar studies.[2] This could be due to the fact that we set the criteria of CIN definition as 0.3 or more increase in Cr level, whereas most studies have set these criteria as 0.5. The largest number of patients had CIN in RL group and the smallest one was in Bi group. Numerous studies have reported the effectiveness of Bi in prevention of CIN.[17,24,25] The suggested mechanism is that alkalization of renal tubular fluid may decrease the damages caused by free radicals.[17,26] Other researches have stated that administration of NLS may increase the risk of AKI incidence by mechanism of inducing acidosis and have suggested RL as an alternative in prevention of AKI.[27,28] Yunos *et al.* evaluated the effect of 0.9% saline and balanced crystalloid in 1644 patients in intensive care unit (ICU) and concluded that 0.9% saline causes more AKI compared with crystalloid solutions.[27] There was a very high proportion of CIN with RL. We know that one of the major theories in pathogenesis of contrast nephropathy is medullary hypoxia; otherwise lactate is involved in maintaining the acid–base equilibrium under aerobic conditions. Studies by Hussmann *et al.* and Khajavi *et al.* clearly demonstrate that RL is toxic in severe hemorrhagic shock.[29,30] In an analogy performed by Chowdhury *et al.* between 0.9% saline and RL on 12 patients, 0.9% saline caused 13% reduction in renal and cortical blood flow compared with other solutions.[31] In contrast, some studies report that 0.9% saline although causing acidosis in patients does not have significant adverse effects.[32] The other two studies compared the effects of different solutions used after kidney transplantation and showed that NLS although causing hyperchloremic acidosis is no different from RL in outcome.[33,34]

In SPLIT randomized clinical trial in 2278 ICU-admitted patients, buffered crystalloid compared with NLS did not reduce the risk of AKI.[35]

Waters *et al.* in a study performed on patients undergoing aortic reconstructive therapy showed that excessive administration of NLS versus RL, despite saline-induced hyperchloremic acidosis, made no difference in complications, ICU stay, and hospital stay.[36] Since few studies have focused on the effects of RL in prevention of CIN, we decided to evaluate the effect of this solution on prevention of CIN, which showed inferiority for RL in prevention of CIN. On the other hand, NLS showed more desirable results in prevention of CIN compared with RL; however, they were not statistically significant. We have reported previously that both Bi and AZ reduce the risk of CIN-related AKI;[17] also in this study we showed that Bi has more protective effect rather than NSL or RL on prevention of CIN. No significant difference in prevention of CIN was seen in comparison of RL versus NLS and NLS versus Bi. It seems likely that hydration with Bi is more effective in prevention of CIN and our study could not prove superiority of RL over the two other solutions.

In previous trials, urine alkalization has been proved to prevent CIN.[17,26] Our study confirmed it as well. All the solutions in this study significantly increased urine pH. Therefore, considering the fact that delta urine pH in Bi group was remarkably greater than the others, the incidence of CIN was the least in this group. It is likely that more alkalinized urine comes with less incidence of CIN.

Hypokalemia is one of the complications of Bi's injection.[15] This phenomenon took place in our Bi group but it was not clinically significant. In this setting, RL brings about less hypokalemia rather than other solutions.

Study limitations

The most important limitations of this study were small sample size and single-center study. Moreover, it would have been better to perform a comparison between serum pH alterations and serum Bi before and after hydration in each group.

Conclusion

Bicarbonate solution is more effective than RL in prevention of CIN in patients undergoing coronary angiography. There was no significant difference between Bi group and NLS group.

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Conflicts of interest

There are no conflicts of interest.

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