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ORIGINAL ARTICLE

Comparing Trimetazidine with Allopurinol in Prevention of Contrast Induced Nephropathy After Coronary Angiography

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Abstract

Objectives: **Contrast-induced nephropathy is considered a serious complication following coronary angiography increasing morbidity and mortality. Various drugs have been assessed to reduce the incidence of contrast-induced nephropathy. In this study, we compared trimetazidine and allopurinol as a pharmacological measure to reduce the incidence of contrast-induced nephropathy.**

Methods: **One hundred and twenty patients undergoing coronary angiography with baseline creatinine clearance more than 30 ml/minute were divided into three groups, 40 patients each. Group 1 received standard parenteral intravenous hydration in the form of isotonic saline at a rate of 1 ml/kg body weight per hour started 12 hours before angiography and up to 12 hours after the procedure. Group 2 received trimetazidine 35 mg twice per day for 72 hours starting 48 hours before the procedure in addition to intravenous hydration. Group 3 received allopurinol 300 mg once daily for 72 hours starting 48 hours before the procedure in addition to intravenous hydration. Serum creatinine and creatinine clearance were measured before and 72 hours after the procedure in addition to the volume of contrast media used.**

Results: **Trimetazidine and allopurinol failed to reduce contrast-induced nephropathy significantly. Among patients with contrast-induced nephropathy volume of contrast media was significantly higher.**

Conclusion: **Adding trimetazidine or allopurinol in addition to regular intravenous hydration with isotonic saline without targeting selectively high-risk patients did not reduce contrast-induced nephropathy following coronary angiography**

Keywords: Contrast-induced nephropathy, Interventional cardiology, Contrast volume, Acute kidney injury

1. Introduction

Contrast-induced nephropathy (CIN) is considered a serious complication following coronary angiography increasing morbidity, hospital stay and mortality. It may be defined as an absolute increase in serum creatinine (Scr) by at least 0.5 mg/dl, or a relative increase in Scr or creatinine clearance (CrCl) by at least 25% compared to the baseline level 24–72 h after exposure to contrast media that cannot be attributed to other causes reaching a peak rise in Scr after 3–5 days after exposure to contrast media and returning back to baseline within 10–14 days [1,2]. Till now, what is clearly beneficial in CIN is adequate hydration before and after coronary angiography [3] and to use low osmolar contrast media instead of high osmolar contrast media, especially in the presence of pre-existing kidney disease [4]. However, further measures are trialed, aiming to reduce more morbidity and mortality. One of the targets of anti-oxidants trialed in the prevention of CIN is to reduce the release of oxygen free radicals which are promoting CIN [5].

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Trimetazidine is a cellular anti-ischemic agent that inhibits the excessive release of oxygen-free radicals, shifts energy metabolism from fatty acid oxidation to glucose oxidation preserving adenosine triphosphate stores, diminishes intracellular acidosis, limits the peroxidation of membrane lipids and inhibits the infiltration of neutrophils after ischemia-reperfusion [6]. Allopurinol is xanthine oxidase inhibitor, which may decrease the fall in the glomerular filtration rate (GFR) following exposure to contrast media by inhibiting oxygen free radical release, adenine nucleotide degradation, and limiting vasodilator reaction to intra-renal adenosine [7].

Abbreviation list

ACS	acute coronary syndrome
CABG	coronary artery bypass graft
CIN	contrast induced nephropathy
CrCl	creatinine clearance
GFR	glomerular filtration rate
IV	intravenous
LV	left ventricle
PCI	percutaneous coronary intervention
Scr	serum creatinine

2. Materials and methods

Our non-randomized controlled clinical trial was conducted at Ain Shams University hospital starting in February 2018 till July 2018. The study design was approved by the ethical committee of the Cardiology department, faculty of medicine, Ain Shams University and was in accordance with the declaration of Helsinki updated in 2008. All patients gave informed written consent.We aimed in this study to compare as a head to head comparison between 2 of the potentially beneficial pharmacological measures sharing the same main assumed mechanism in CIN prevention which is reduction of free oxygen radicals.The study included 120 patients undergoing coronary angiography with baseline CrCl more than 30 ml/min either due to chronic stable angina or acute coronary syndrome (ACS). Convenience sampling was applied initially in recruitment of patients with chronic stable angina who accepted to be admitted 48 h before elective coronary angiography to receive adequate hydration plus or minus the studied medications. Among patients with ACS we excluded patients who needed urgent intervention as primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction or urgent invasive strategy for non ST-segment elevation myocardial infarction. Patients with severe congestive heart failure, anemia or patients receiving nephrotoxic drugs were excluded from the study in addition to patients with allergy to trimetazidine or allopurinol. After applying inclusion and exclusion criteria we randomized recruited patients using simple randomization to either of the study groups. They were divided into three groups 40 patients each.Group 1 received standard intravenous (IV) hydration in the form of isotonic saline at a rate of 1 ml/kg bodyweight per hour starting 12 h before angiography and up to 12 h after the procedure representing the control group. Patients with left ventricular (LV) systolic dysfunction received IV hydration with isotonic saline at a rate of 0.5 ml/kg body weight per hour. Group 2 received trimetazidine 35 mg twice per day for 72 h, starting 48 h before the procedure in addition to IV hydration as in group 1. Group 3 received allopurinol 300 mg once daily for 72 h, starting 48 h before the procedure in addition to IV hydration as in group 1. Scr and CrCl were measured before the procedure and 72 h after exposure to contrast media. CrCl was estimated using Cockroft–Gault equation ((140- age in years) x (weight in kg))/((72 × Scr in mg/dl) x (0.85 in females)) [8]. Contrast media used were low osmolar, and volume of contrast media used during the procedure was measured. CIN was defined as an absolute increase in Scr by at least 0.5 mg/dl, or a relative increase in Scr or CrCl by at least 25% compared to the baseline level 24–72 h after exposure to contrast media [1,2]. LV ejection fraction by modified Simpson's method was measured to all patients before coronary angiography.

3. Statistical analysis

Data were collected, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Data were presented as numbers and percentages for the qualitative data, mean and standard deviations for the quantitative data with parametric distribution. Chi-square test was used to compare between two groups with qualitative data. Independent t-test was used to compare between two groups with quantitative data and parametric distribution. One Way ANOVA was used to compare between more than two groups with quantitative data and parametric distribution.-Confidence interval was 95% and accepted margin

of error was 5%. So, the p-value was considered significant <0.05.

4. Results

This study included 120 patients equally divided into three groups. Group 1 received IV isotonic saline hydration, group 2 received trimetazidine in addition to IV isotonic saline hydration and group 3 received allopurinol in addition to IV isotonic saline hydration. There was no significant difference between the three groups in baseline characteristics with a mean age (58.63 ± 9.63 versus (versus) 61.10 ± 11.16 versus 59.43 ± 8.89 years, p = 0.526). There was no significant difference also in risk factors of coronary artery disease and existing cardiovascular disease including smoking (70% versus 55% versus 47.5%, p = 0.117) hypertension (57.5% versus 62.5% versus 70%, p = 0.506), diabetes mellitus (67.5% versus 47.5% versus 55%, p = 0.190), previous percutaneous coronary intervention (PCI) (12.5% versus 15% versus 22.5%, p = 0.458), previous coronary artery bypass graft (CABG) (7.5% versus 2.5% versus 5%, p = 0.591), cerebrovascular stroke (12.5% versus 17.5% versus 7.5%, p = 0.401) and peripheral arterial disease (7.5% versus 10% versus 12.5% p = 0.757).There was no significant difference in mean LV ejection fraction between the three groups (47.85 ± 8.75 versus 49.50 ± 10.25 versus 47.03 ± 9.93%, p = 0.508).There was no significant difference in baseline Scr and CrCl in the 3 groups with baseline Scr (1.36 ± 0.32 versus 1.33 ± 0.36 versus 1.24 ± 0.25 mg/dl, p = 0.214) and CrCl (65.23 ± 16.14 versus 67.45 ± 13.95 versus 72.15 ± 11.48, p = 0.082). 72 h after exposure to contrast media Scr and CrCl were measured again, and there was no significant difference between the 3 groups too with Scr (1.66 ± 0.66 versus1.65 ± 0.67 versus1.58 ± 0.80, p = 0.849) and CrCl (55.65 ± 16.39 versus57.80 ± 17.89 versus 62.58 ± 15.50, p = 0.167). CIN was slightly lower in patients who received allopurinol occurring in 9 patients (22.5%) than patients who received trimetazidine in which CIN occurred in 10 patients (25%) and control group of patients in which CIN occurred in 11 patients (27.5%) despite the larger volume of contrast in allopurinol group (215.63 ± 67.19 ml) versus (186.63 ± 72.39 ml) in trimetazidine group and (184.75 ± 53.68 ml) in control group however these minor differences were not statistically significant (p = 0.875, p = 0.062). Among the whole study group CIN occurred in 30 patients (25%) with higher volume of contrast media in this group (235.67 ± 66.63 versus 182.33 ± 60.34 ml, p = 0.000) Table (1).

5. Discussion

Till now, the mainstay in CIN prevention is adequate IV hydration using isotonic saline with some benefit from high dose statin before coronary angiography, especially in statin naïve patients. However, other preventive measures till now have no sufficient evidence in the prevention of CIN [9]. Different studies in literature focused on the effect of trimetazidine or allopurinol in the prevention of CIN. However, many of these studies presented contradictory results. In addition most of these studies (especially studies with potential benefit of these drugs) targeted selectively relatively high risk group as patients with pre-

Table 1. Difference in basic characteristics, CIN and contrast media volume between the study groups.

	Group 1 Control	Group 2 Trimetazidine	Group 3 Allopurinol	P-value
	Number = 40	Number = 40	Number = 40	
Age (years)	58.63 ± 9.63	61.10 ± 11.16	59.43 ± 8.89	0.526
Gender (Males)	29 (72.5%)	30 (75.0%)	29 (72.5%)	0.958
Smoking	28 (70.0%)	22 (55.0%)	19 (47.5%)	0.117
Hypertension	23 (57.5%)	25 (62.5%)	28 (70.0%)	0.506
Diabetes mellitus	27 (67.5%)	19 (47.5%)	22 (55.0%)	0.190
Previous PCI	5 (12.5%)	6 (15%)	9 (22.5%)	0.458
Previous CABG	3 (7.5%)	1 (2.5%)	2 (5%)	0.591
Cerebrovascular Stroke	5 (12.5%)	7 (17.5%)	3 (7.5%)	0.401
Peripheral arterial Disease	3 (7.5%)	4 (10%)	5 (12.5%)	0.757
LV ejection Fraction	47.85 ± 8.75	49.50 ± 10.25	47.03 ± 9.93	0.508
Scr before angiography	1.36 ± 0.32	1.33 ± 0.36	1.24 ± 0.25	0.214
Scr 72 h after Angiography	1.66 ± 0.66	1.65 ± 0.67	1.58 ± 0.80	0.849
CrCl before angiography	65.23 ± 16.14	67.45 ± 13.95	72.15 ± 11.48	0.082
CrCl 72 h after Angiography	55.65 ± 16.39	57.80 ± 17.89	62.58 ± 15.50	0.167
Contrast volume	186.63 ± 72.39	184.75 ± 53.68	215.63 ± 67.19	0.062
CIN	11 (27.5%)	10 (25.0%)	9 (22.5%)	0.875

existing kidney disease. But in our study we aimed to assess if either of both drugs may show additional preventive effect beside adequate hydration. Both trimetazidine and allopurinol may have a role in CIN prevention through their reduction of free oxygen radicals.In this study they did not reduce the incidence of CIN significantly with a minor difference in favor of allopurinol despite slightly higher contrast volume depending on Scr and CrCl measured 72 h after contrast exposure. In addition, the incidence of CIN was relatively high and this may be related to the inclusion of patients with ACS undergoing non-urgent coronary intervention. Meta-analysis by Ye et al. included 6 studies targeting effect of trimetazidine in the prevention of CIN with total 377 patients in trimetazidine group and 387 patients in the control group receiving only IV isotonic saline hydration reported that Scr was significantly lower in trimetazidine group than control group 24 h and 48 h after contrast exposure, however, this difference was not significant on measuring Scr 72 h after contrast exposure [10]. This denotes the possibility of reaching a peak elevation of Scr before 72 h. Moreover, Onbasili et al. in their study, showed significantly reduced incidence of CIN on measuring Scr 48 h after contrast exposure in patients with pre-existing chronic kidney disease who received trimetazidine before contrast exposure [11].However, a study of Lian et al. failed to show a reduction in CIN in patients who received trimetazidine group (529 patients) versus the control group (1625 patients) taking into consideration that they used trimetazidine 20 mg three times per day starting 24 h before angiography [12]. Ibrahim et al. in their study, added trimetazidine 35 mg twice daily 72 h before coronary angiography to isotonic saline hydration versus isotonic saline hydration only in patients with CrCl less than 90 ml/min undergoing elective coronary angiography and it showed a reduced incidence of CIN in trimetazidine group [13]. These data suggest that trimetazidine may be beneficial in reducing CIN if given in the dose of 35 mg twice 48 h especially in patients with chronic kidney disease undergoing elective angiography. On the other hand, Ma et al. showed in a meta-analysis of 8 studies (1141patients) significant reduction in CIN in patients who received allopurinol before exposure to contrast media [14]. Ghelich Khan et al. study did not show a significant reduction in CIN in allopurinol groups (102 patients) versus the control group (108 patients) with 600 mg of allopurinol being given 24 h before elective PCI [15]. Moreover, Iranirad et al. on their study (140 patients) reported that in patients with at least 2 risk factors for CIN undergoing coronary angiography, allopurinol failed to show significant reduction in CIN [16]. The increased amount of contrast media was associated with an increased incidence of CIN and it is strongly recommended to minimize the volume of contrast media used [9].In comparison to other studies we did not show a significant reduction in CIN on measuring Scr and CrCl 72 h following contast exposure after using trimetazidine or allopurinol 48 h before angiography in addition to adequate hydration, but this study may point to the importance of measuring Scr and CrCl 48 h not 72 h after contrast exposure to avoid missing of CrCl decline and Scr rise and also may show that adequate hydration in patients not in high risk for development of CIN may be satisfactory as the benefit of pharmacological measures in addition to adequate hydration was seen in high risk patients as in the presence of pre-existing kidney disease [10,13].Although contrast induced nephropathy occurred in 30 patients in our study (25%) all of them were managed conservatively by nephrologists and renal replacement therapy was not needed. Our explanation for this point is that most of the included patients in our study did not have pre-existing renal disease. Based on biochemical definitions of CIN, slight decline in renal functions after contrast exposure in patients without pre-existing kidney disease mostly will be managed conservatively. On the other hand the presence of pre-existing kidney disease not only increases incidence of CIN but also it will increase the need for renal replacement therapy for acute renal failure, morbidity and mortality [17].

6. Conclusion

Adding trimetazidine or allopurinol in addition to regular IV hydration with isotonic salinedid not reduce incidence of CIN depending on measuring Scr and CrCl 72 h following coronary angiography, especially without targeting high-risk patients for CIN as patients with chronic kidney disease. Increased contrast volume is associated with an increased incidence of CIN.

Study limitation

This study was a single-center non-randomized clinical trial that depended on measuring Scr and

CrCl 72 h after coronary angiography only instead of serial daily measurementsso peak increase in Scr and decrease in CrCl may be missed in some patients if occurred earlier than 72 h.

Author contribution

Conception and design of Study, Acquisition of data: Haitham Galal, Mahmoud Shehta. Literature review: Haitham Galal, Mahmoud Shehta, Sameh Attia, Islam Bastawy. Analysis and interpretation of data, Funding for the research: Mahmoud Shehta. Analysis and interpretation of data; Research investigation and analysis; Data collection; Research coordination and management: Mahmoud Shehta, Islam Bastawy. Research investigation and analysis: Mahmoud Shehta, Sameh Attia, Islam Bastawy. Drafting of manuscript; Data preparation and presentation: Islam Bastawy. Revising and editing the manuscript critically for important intellectual contents; Supervision of the research: Haitham Galal, Sameh Attia, Islam Bastawy.

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Data availability statement

Anonymized data not published in the article will be shared by request from any qualified investigator. The corresponding author takes full responsibility for the data, the analyses, and interpretation, and the conduct of the research, has full access to all of the data, and has the right to publish any and all data separate and apart from any sponsor.

Conflict of interest

None declared.

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