

The role of Trimetazidine in prevention of contrast induced nephropathy in diabetic patients with renal insufficiency undergoing cardiac intervention

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ABSTRACT

This study aims to assess the possible protective role of Trimetazidine in the prevention of contrast induced nephropathy in patients with renal impairment undergoing coronary angiography or percutaneous coronary intervention. This was a randomized single-blind clinical trial study. A total of 100 consecutive diabetic patients with symptomatic ischemic heart disease and chronic kidney disease (CKD) were subjected to an elective percutaneous coronary intervention, at ALSADR teaching hospital /Al-Najaf Center for Cardiac surgery and Tran Catheter Therapy, Najaf, Iraq, in period between May and December 2018. The Patients were divided into two groups: **Group I**-Control Group (n=45) these patients with chronic kidney disease and critical coronary stenosis and they were needed to be subjected to coronary intervention. **Group II**- Treatment Group (n=44) also these patients with chronic kidney disease and critical coronary stenosis and they were need to be subjected to coronary intervention and treated with 35 mg tablet /twice daily of Trimetazidine for the period of three days.

Trimetazidine significantly reduce the elevation in serum level of monocyte chemo tactic protein1, expression of Toll-like receptor 2 and the urine levels of kidney injury molecule-1, F2-isoprostanes (p<0.05) while insignificantly reduce the elevation in serum level of creatinine . (p > 0.05). Our study concluded that Trimetazidine reduce the acute kidney injury response and systemic inflammatory response induced by contrast administration after coronary intervention.

Keywords: Trimetazidine ,Contrast induced nephropathy, Percutaneous coronary intervention, Creatinine, Monocyte chemo tactic protein1, Kidney injury molecule-1, F2-isoprostanes, Toll-like receptor 2.

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INTRODUCTION

In recent years, the number of percutaneous coronary intervention (PCI) is growing rapidly due to the new techniques and clinical interventions in cardiology science [1-2]. Contrast-induced nephropathy (CIN), are still possible outcomes after administration of contrast media (CM) during coronary intervention procedures, so unfortunately ,this approach results in problems related to renal function [3]. The focus of contrast media is directed toward assessing the sensitivity and accuracy of radiological examination, in addition to evaluating structures that are hard to see in classical radiological examination [4]. Iodinated CM can be categorized into three types based on osmolality; these are high osmolar contrast media (HOCM), low osmolar contrast media (LOCM), and isoosmolar contrast media (IOCM). Unfortunately, many cases of renal toxicity and adverse drug reactions (ADR) have been linked to HOCM [5]. When renal impairment develops after 1-3 days of intravascular injection of radiographic CM and no other clinical cause is apparent, the researchers can then diagnose the patient with CIN. It often begins during the first day after administering contrast media, intensifies during the following 3-5 days, and returns to normal within the next 10-14 days [6]. Most early studies as well as current study focus on the relative ($\geq 25\%$) or absolute

(≥ 0.5 mg/dl = $44 \mu\text{mol/l}$) increase in serum creatinine (SCr) is taken as a reference to define CIN following the intravascular injection of CM [7]. Serum level of creatinine (SCr) is not reliable indicator to determine kidney function in CIN, because it is not a real-time biomarker [8]. The Modification of Diet in Renal Disease equation (MDRD) is used to measure the estimated glomerular filtration rate (eGFR) (in ml/min/1.73 m²), beside depending on pre-procedure measurements of serum creatinine level as baseline [9]. The main mechanism of CIN can involve the following:

1. Vascular endothelial cells and renal tubules are vulnerable to injury by direct cytotoxicity of CM in the renal medulla, which causes vasoconstriction due to low level of nitric oxide (NO) and higher production of reactive oxygen species (ROS) [10].
2. Contractions of the renal vessel can be a direct result of contrast agent, which also can cause hypoxia and renal medullar ischemia.
3. Factors of CIN can cause renal hypoperfusion in conjunction with reduction in blood circulation [11-12].

Contrast induced nephropathy incidence increases in patients with chronic kidney disease (CKD) due to increased cellular exposure and reduced adaptive capacity, as fewer nephrons will only be available to filter the same amount of CM [13-14].

Both diabetes and iodinated radio contrast agents are responsible for many renal physiologic changes, including intensification of medullar hypoxia, changes in GFR, renal hemodynamic, enhanced tubular transport activity and oxygen expenditure, and ROS production. Diabetes magnifies the effect of these changes and devastates the protective mechanisms that the body usually uses to maintain oxygenation levels in the medulla and eliminate oxidative stress, leading eventually to CIN [15]. Reducing the incidence of CIN can be achieved by decreasing the osmolality of the CM. Unfortunately, the relationship between CM osmolality and viscosity is reversed; which means the higher the viscosity, the lower the osmolality [16-17]. To prevent contrast nephropathy, hydration and maintenance of circulating volume are undoubtedly still good options [18]. Intravenous fluids can decrease the concentration and viscosity of contrast media in the tubular lumen and reduce the toxic effect of contrast agents in epithelial cells of renal tubules [19]. Actually, glomerular filtration rate (GFR) can be reduced significantly before any remarkable changes are seen in serum creatinine levels. Unfortunately, a noticeable delay in diagnosing acute kidney injury (AKI) can be result, especially with a contrast administration as well as the probability of chronic kidney injury (CKI) increases because the creatinine value may not return to previous level [20]. The vulnerability of serum creatinine (SCr) concentration to such factors makes it unworthy and temporally insufficient biomarker to diagnose CI-AKI. [21]. A transmembrane glycoprotein, called Kidney injury molecule-1(KIM-1), is found in the membrane of renal proximal tubule epithelial cell. The expression of this substance is minimal in the normal renal tissue and the expression occurs only in case of hypoxia or ischemia inside the renal tissue [22]. Within 1-2 days after the onset of the kidney injury, the level of urinary KIM-1 reaches a remarkable peak [23] but it can distinguish also within 12-24 hours after renal damage [24]. Actually, reactive oxygen species (ROS) metabolites such as malondialdehyde (MDA) or F2 isoprostane can be increased after injecting CM [25]. Indeed, diagnosing oxidative injury resulted from diseases in humans can be achieved by using a strong biomarker such as F2-isoprostanes (F2-IsoP) [26].The level of F2 isoprostane in urine was significantly raised in patients subjected to coronary angiography (CAG) [27] and three time increase in chronic renal failure patients [28]. The vascular endothelium and medullar epithelial cells in the kidney are susceptible to great damage by cytotoxic effects of the contrast medium. This of course will lead to activation of inflammation and accumulating of oxygen-free radicals. MCP-1 is the ligand for chemokine C-C ligand-2 (CCR-2), which is found only in monocyte that accumulate in the bone marrow [29]. The major MCP-1 producing cells in the kidney are smooth muscle cells, mesangial cells, tubular cells, and podocytes [30]. The main functions of MCP-1 can be summarized as follows: Firstly, MCP-1 brings the monocyte and precursors to the blood after recruiting them initially from the bone marrow. Circulating MCP-1 is more likely to regulate the first recruitment process and multiple inflammatory conditions

might accelerate this step as well. Secondly, a chemokine gradient is formed after the MCP-1 is stored in the local glycocalyx at sites of inflammation. The circulating monocyte begins to accumulate into the inflamed tissue after being recruited by the MCP-1. Thirdly, the differentiation and inflammatory cytokines in the monocyte or macrophages are finally induced by the locally produced MCP-1. Through mobilization, localization, recruitment, and differentiation, MCP-1 organizes the inflammatory response and becomes active through the all three levels mentioned above [31]. TLR2 is a important member of TLRs, because of its ability to induce major inflammatory response [32]. Renal damage at the epithelial level and ischemia-related cytokines are possibly the result of increased expression of TLR 2 during AKI. In the other hand, the levels of cytokine are reduced when the expression of TLR 2 is minimal, leading to improvement of the renal injury [33]. Trimetazidine can serve as a metabolic agent that causes shifting in the cardiac energy metabolism from beta-oxidation of free fatty acid (FFA) to glucose oxidation, which is more efficient step. In patients with AMI and diabetes mellitus (DM), TMZ can protect the cells from oxygen free radicals (OFRs), which has significant harmful effects in cells [34]. Indeed, the pathogenesis of CIN is involving ischemic injury and oxygen-free radical release and in renal tubular epithelial cells, TMZ can actually reduce cell lysis and contrast agent toxicity. It also can decrease the oxygen-free radicals releasing [35]. Clinical applications for TMZ in many other medical conditions, including sepsis, diabetic cardiomyopathy, and CIN [36]. Trimetazidine is a good drug choice to protect against histopathological changes in CIN, according to an animal study [37].

METHODS

MATERIALS

Everolimus eluting coronary stent system (Xience/Ireland), Sirolimus eluting coronary stent system (Orsiro/Switzerland), Zotarolimus eluting coronary stent system (Resolute/USA), Lidocaine HCL 2% (India), Iopromide (Ultravist-370), Heparine vial (LEO/Denmark), Trimetazidine Dihydrochloride Tablet 35 mg (VASTAREL /France), Human Kits of urea, creatinine, and sugar (Fujifilm /Japan), Human Kits of PT (BIOLABO /France), PTT (BIOMAGHREB/Tunisia), and INR (Human/Germany), Human Neutrophils Gelatinase Associated Lipocalinis (NGAL-ELISA) Kit , Human High Mobility Group Protein 1 (HMGB1-ELISA) Kit, Human V-Rel Reticuloendotheliosis Viral Oncogene Homolog A (NFκB-ELISA) KIT ,were produced by (Cloud-Cone /UK),Toll like receptor 2-Ab (eBioscience/ America) and Erythrocyte lysing reagent A&B for flow cytometry (Unique Lyse/Japan).

Patient's collection and study design

This was a randomized single-blind clinical trial study. A total of 100 consecutive diabetic patients with symptomatic ischemic heart disease and chronic kidney disease (CKD) planned for an elective percutaneous coronary intervention, at ALSADR teaching hospital AI-Najaf Center for Cardiac

surgery and Tran Catheter Therapy in period between May and December 2018 were enrolled in this study. Their age ranged between 40-80 years old. Patients were diagnosed with CKD based on estimated GFR according to: Cockcroft-Gault equation and Modification of Diet in Renal Disease study equation (MDRD) [38]. Eleven patients were excluded from this study due to early discharge from the center before 24 hours after CAG or PCI while 89 of the remaining 100 patients were included in this study. Patients were excluded from the study if one of the following criteria are present:

1. Acute renal failure or end-stage renal disease requiring dialysis.
2. Congestive heart failure.
3. Acute myocardial infarction requiring primary or rescue coronary intervention.
4. Cardiogenic shock.
5. Intake of nephrotoxicity agents from 24 hours before to 24 hours post injection of contrast media such as: NSAID (naproxen , Ibuprofen), antibiotics aminoglycoside , cisplatin , cyclosporine , amphotericin B and any drug to prevent CIN such as N- acetyl cysteine.
6. Patients with a known allergy to Trimetazidine
7. Hypersensitivity to iodine containing CM
8. Pregnancy.

Before 24 hour of surgical procedure ,each patient, was admitted to AL-Najaf Center followed by this information and analysis: Electrocardiography (ECG), Blood pressure, Heart rate, Blood oxygen saturation level (SpO₂), Complete blood count, Blood urea, Serum creatinine, Total cholesterol, Fasting blood sugar, Coagulation testing: International normalized ratio (INR), Prothrombin time (PT), Activated partial thromboplastin time (APTT) and Viral screening test: Anti hepatitis C virus antibody (Anti HCV Ab), Hepatitis B surface antigen (HBsAg), Human immunodeficiency virus (HIV). All enrolled patients administrated standard protocol of intravenous pre procedural hydration with 0.9% normal saline at 1 ml/kg/h twelve hour before and after surgical procedure [39]. The Patients were divided into two groups: Group I- Control Group (n=45) these patients with chronic kidney disease and critical coronary stenosis and they were needed to be subjected to coronary intervention. Group II- Treatment Group (n=44) also these patients with chronic kidney disease and critical coronary stenosis and they were need to be subjected to coronary intervention and treated with 35 mg tablet /twice daily of Trimetazidine (VASTAREL) modified release tablet at a period of three days, starting 48 hours before surgical procedure and for 24 hours post the procedure [40]. All randomized patients that included in this study were subjected to detailed questionnaire and were signed written informed consent as well as the study protocol was approved by the University of Kufa college of Medicine ethics committees.

Surgical procedure

The contrast agent Iopromide (Ultravist 370) was used for all patients included in this study. A sheath was placed into the femoral artery after local anesthesia lidocaine was used

followed by insertion of coronary angiography and angioplasty catheters. The protocol of all patients subjected to the surgical procedure must be pre treated with aspirin tablet (100 mg/day) or clopidogrel tablet (75mg/day) seven days before the surgical procedure or 600-mg loading dose was administrated in special condition at least twelve hour before surgical procedure. After intravenous bolus injection of 10,000 unit dose of heparin or less was used the surgical procedure was started immediately.

Collection of blood samples

A two blood samples were taken from each patient included in this study. 5ml blood take via peripheral vein and 3 ml urine specimens of patients take at time of admission before the surgical procedure (S1) and then 24 hours post surgical procedure (S2). The blood samples were separated into two tubes, 2ml was put in a sterile tube containing ethylene diamine tetra acetate (EDTA) as anticoagulant and mixed carefully then it was used for expression of Toll-like receptor 2 (TLR 2) in peripheral blood monocyte by flowcytometry analysis, while the residual blood 3ml was allowed to clot in a clot activator gel tube (25-30) min. in room temperature at 37°C then it was centrifuged at 3000 rpm. After 5 minutes, the supernatant was removed by pipette then small quantity of it was used for assay SCr and the other was put it in Eppendorf tube. Finally , the samples were stored in deep freezing at 80 C° after collecting it for the determination of: serum monocyte chemo tactic protein1 (MCP-1), while 3ml urine was be centrifuged at 3000 ×g for 5 minute that was be used for the assay of: urinary kidney injury molecule-1 (KIM-1), urinary F2-isoprostanes by Enzyme -linked immunosorbent assay (ELISA) technique.

Statistical analysis

Data of the 89 patients in both studied group were analyzed by using the statistical package for social sciences (SPSS) software for Windows version 25. Descriptive statistics of the variables expressed as mean, standard deviation, standard error, frequencies and percentages according to the variable type. Chi square test used to compare frequencies of a variable across the studied group, Fisher's exact test used as an alternative when chi-square was inapplicable. Student's t test used to compare any two means between groups, pre and post treatment and the mean difference. When the variable/parameter did not follow the normal statistical distribution throughout the study population, Mann-Whitney test was used. The comparison of mean values of each parameter before and after treatment within each group was assessed using Paired t test and when the variable did not follow the statistical normal distribution, non-parametric Wilcoxon test was applied. For all studied parameters when compared between groups, an effect size was calculated. If: ≤ 0.2 (small effect), 0.3 – 0.7 (Medium effect), 0.8 or more (large effect). Level of significance was set at 0.05 or less indicated a significant difference. Finally, results and findings were presented in tables and figures with an explanatory paragraph for each using the Microsoft Office Word and Excel software version 2013.

No statistically significant differences had been reported between both groups with regards to: Demographic characteristics (Table 1), type of affected vessels and medications (Table 2), types and number of stents (Table 3) and clinical and laboratory parameters (Table 4), in all comparisons (P. value > 0.05).

Results

Table .1 Baseline characteristics in both studied groups

Variable		Control group (n = 45)		Treatment group (n = 44)		P. value
		No.	%	No.	%	
Age (year)	< 60	11	24.4	12	27.3	0.936 [†] (N.S)
	60 - 69	21	46.7	19	43.2	
	≥ 70	13	28.9	13	29.5	
	Mean (SD)	64.9 (7.7)	-	64.4(8.1)	-	0.764 [#] (N.S)
Gender	Male	28	62.2	23	52.3	0.343 [†] (N.S)
	Female	17	37.8	21	47.7	
Smoking	Yes	22	48.9	19	43.2	0.743 [†] (N.S)
	No	23	51.1	25	56.8	
Hyper tension	Yes	43	95.6	43	97.7	0.570 ^{**} (N.S)
	No	2	4.4	1	2.3	
Diabetes Mellitus	Yes	45	100.0	44	100.0	-
	No	0	0.0	0	0.0	

SD: standard deviation , [†]Chi-square test , ^{**}Fisher's exact test , [#] independent student t test Data presented as Mean ± SD , N.S Not significant , P-value < 0.05

Table .2 Distribution of affected vessels and medications of patients in both studied groups

Variable		Group				P. value*
		Control (n = 45)		Treatment (n = 44)		
		No.	%	No.	%	
Vessel	LAD	31	68.9%	33	75.0%	0.521 [†] (N.S)
	RCA	11	24.4%	13	29.5%	0.588 [†] (N.S)
	RCX	13	28.9%	9	20.5%	0.356 [†] (N.S)
	Femerol	45	100.0%	44	100.0%	-
Medic-ation	Statin	45	100.0%	44	100.0%	-
	Aspirin	45	100.0%	44	100.0%	-
	Clopidogrel	45	100.0%	44	100.0%	-
	B-blocker	29	64.4%	26	59.1%	0.603 [†] (N.S)
	CCB	9	20.0%	11	25.0%	0.572 [†] (N.S)
	Nitrate	13	28.9%	16	36.4%	0.452 [†] (N.S)
	Oral hypogyny.	40	88.9%	42	95.5%	0.434 ^{**} (N.S)
Insulin	5	11.1%	2	4.5%		

*Chi-square test , ^{**}Fisher's exact test , N.S Not significant , P-value < 0.05

Table .3 Types and number of Stents in both studied groups

Variable		Group				P. value*
		Control (n = 45)		Treatment (n = 44)		
		No.	%	No.	%	
Type of Stent	Resolute	33	73.3	32	72.7	0.686(N.S)
	Xience	7	15.6	9	20.5	

	Orsiro	5	11.1	3	6.8	
Number of stents	One	29	64.4	30	68.2	0.752(N.S)
	Two	12	26.7	12	27.3	
	Three	3	6.7	2	4.5	
	Four	1	2.2	0	0.0	
*Fisher's exact test , N.S Not significant , P-value < 0.05						

Table .4 Comparison of clinical and laboratory parameters in both studied groups

Parameter	Group				P. value *
	Control (n = 45)		Treatment (n = 44)		
	Mean	SD	Mean	SD	
Systolic blood pressure	146.2	29.4	145.4	33.2	0.903 (N.S)
Diastolic blood pressure	91.7	22.3	88.6	14.4	0.433 (N.S)
Hear rate	79.0	18.0	80.0	12.8	0.763 (N.S)
SPO2	96.9	1.8	96.8	1.9	0.812 (N.S)
Fasting blood sugar	165.4	71.9	166.5	79.4	0.944 (N.S)
Total Cholesterol	202.71	14.3	197.0	17.6	0.096 (N.S)
Blood Urea	58.4	12.5	57.7	16.9	0.815 (N.S)
INR	1.2	0.2	1.2	0.2	0.148 (N.S)
PT	14.2	1.7	14.9	1.6	0.065 (N.S)
APTT	31.0	2.6	31.6	4.9	0.530 (N.S)
Platelet	247.8	65.0	250.8	92.2	0.862 (N.S)
WBC	9.2	2.2	8.9	1.6	0.478 (N.S)
Hemoglobin	11.9	1.4	12.1	2.4	0.590 (N.S)
Contrast volume (ml)	138.6	38.3	132.4	44.1	0.483 (N.S)
Heparin (unit)	8244.4	1170.7	8113.6	1602.6	0.661 (N.S)
* t- test , SD: standard deviation , N.S Not significant , P-value < 0.05					

Effect of contrast media and Trimetazidine on levels of SCr. and estimated GFR

In the present study, the mean serum creatinine was significantly increased at 24 hrs after contrast administration in both control and treatment groups (P. value < 0.001 & =0.034, respectively). When compared between two studied groups, pre contrast administration, there was insignificant difference in level of serum creatinine between two groups.

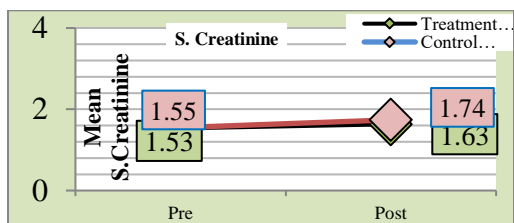


Figure1: Graphical comparison of the mean Sr. creatinine (mg/dl) value in both studied groups (P-value < 0.05)

The mean difference and percentage change in treatment group was smaller than that in control group , however, the differences between both groups did not reach the statistical significance, (P. value =0.068), nonetheless the effect size was (0.28) indicated a small effect attributed to treatment with Trimetazidine in protection of further elevation in serum creatinine . All these changes are summarized in figures (1-2).

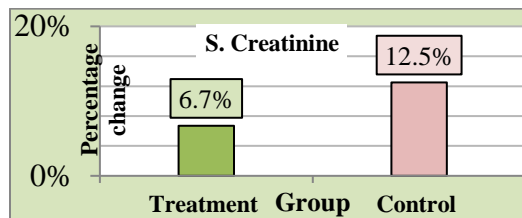


Figure 2: Bar chart comparing the percentage change in Sr. creatinine (mg/dl) level in both studied groups (P-value < 0.05).

The mean serum estimated GFR was significantly decreased at 24 hrs after contrast administration in both control & treatment groups, (P. value < 0.001).When compared between

two studied groups, pre contrast administration, there was insignificant difference in level of serum estimated GFR between two groups. The mean difference and percentage

change in treatment group was smaller than that in control group, however, the differences between both groups did not reach the statistical significance, (P. value =0.084), nonetheless the effect size was (0.10) indicated a small effect attributed to

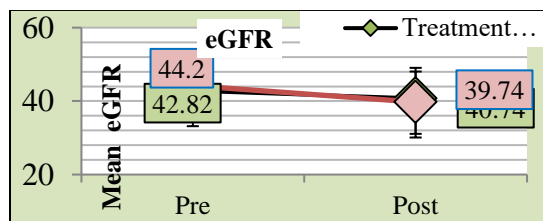


Figure 3: Graphical comparison of mean values and changes of eGFR (ml/min/1.73m²) in both studied groups (P-value < 0.05)

treatment with Trimetazidine in protection of further reduction in serum estimated GFR. All these changes are summarized in figures (3-4).

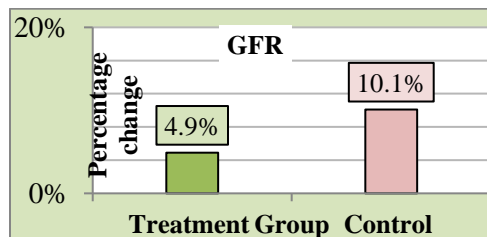


Figure 4: Bar chart comparing the percentages changes in eGFR (ml/min/1.73 m²) in both studied groups (P-value < 0.05)

Effect of contrast media and Trimetazidine on levels of KIM-1& F2-isoprostanes

In the present study, the mean urinary KIM-1& F2-isoprostanes levels were significantly increased at 24 hrs after contrast administration in both control & treatment groups (P. value < 0.001). When compared between two studied groups, pre contrast administration, there were insignificant difference in levels of urine KIM-1 & F2 -isoprostane between two groups. The mean differences and percentages changes in treatment group were smaller than that in control group however, the elevation in KIM- 1& F2-isoprostanes in control

group were significantly larger, (almost three folds), than that in treatment group, (P. value =0.025 & =0.001, respectively), moreover, the effect size in KIM-1 was (0.53) indicated a medium effect with protective effect of Trimetazidine to prohibit further elevation in urinary KIM- 1, while the effect size in F2-isoprostanes was (0.91) indicated a large effect with protective effect of Trimetazidine to prohibit further elevation in urinary F2 isoprostane. All these changes are shown in figures(5-8).

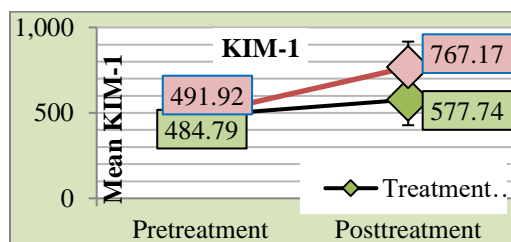


Figure 5: Graphical comparison of mean values and changes of urinary KIM-1 (pg/ml) in both studied groups (P-value < 0.05)

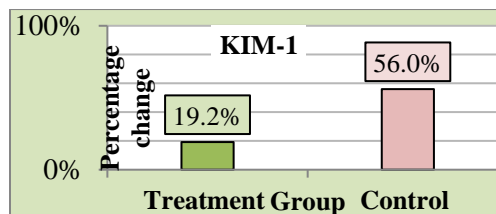


Figure 6: Bar chart comparing the percentages changes in urinary KIM-1 (pg/ml) level in both studied groups (P-value < 0.05).

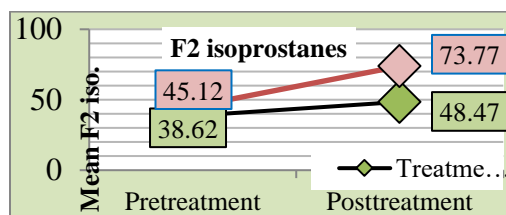


Figure 7: Graphical comparison of mean values and changes of urinary F2 isoprostane (pg/ml) in both studied groups (P-value < 0.05)

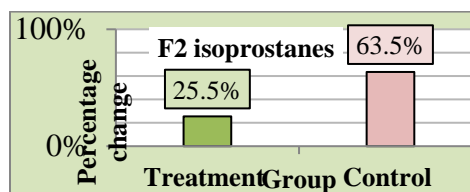


Figure 8: Bar chart comparing the percentages changes in urinary F2 isoprostane (pg/ml) level in both studied groups (P-value < 0.05)

Effect of contrast media and Trimetazidine on level of MCP-1

In the present study, the mean serum MCP-1 level was significantly increased at 24 hrs after contrast administration

in control and treatment groups, (P. value < 0.001). When compared between two studied groups, pre contrast administration, there was insignificant difference in level of serum MCP-1between two groups. The mean difference and

percentage change in treatment group was smaller than that in control group, however, the difference between both groups was statistically significant, (P. value < 0.001) , with a moderate effect size of (0.66) , indicated the protective effect

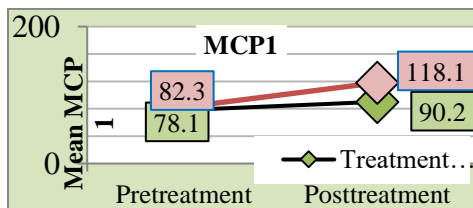


Figure 9: Graphical comparison of mean values and changes of serum MCP1 (pg/ml) in both studied groups (P-value < 0.05)

of Trimetazidine in protection of further elevation in serum MCP-1. All these changes in serum MCP-1 level are shown in (Figures 9&10).

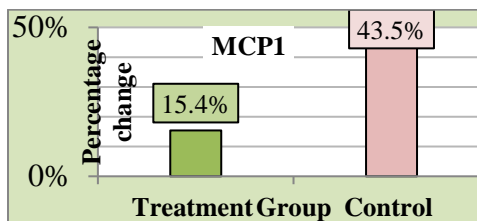


Figure 10: Bar chart comparing the percentages changes in serum MCP-1 (pg/ml) in both studied groups (P-value < 0.05).

Effect of contrast media and Trimetazidine on level of TLR 2

In the present study, the mean TLR2 expression was significantly increased at 24 hrs after contrast administration in control and treatment groups, (P. value < 0.001).When compared between two studied groups, pre contrast administration, there was insignificant difference in expression

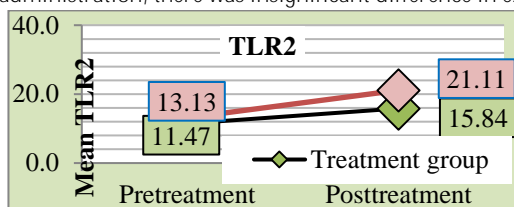


Figure 11: Graphical comparison of mean values and changes of mean TLR2 expression (% in peripheral monocyte) in both studied groups (P-value < 0.05).

of TLR2 between two groups. The mean difference and percentage change in treatment group was smaller than that in control group , however, the difference between both groups was statistically significant, (P. value = 0.036) , with a moderate effect size of (0.41) , indicated the protective effect of Trimetazidine to prohibit further elevation in TLR2 expression. All these changes are shown in figures (11-14).

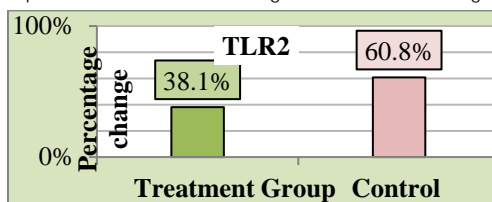


Figure 12: Bar chart comparing the percentages changes in TLR2 expression (% in peripheral monocyte) in both studied groups (P-value < 0.05).

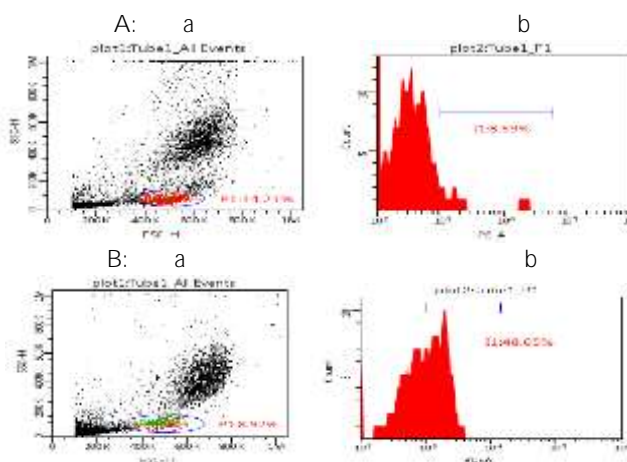


Figure 13: Expression of TLR2 in peripheral blood monocyte in control group. A: before contrast administration (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte), B: 24 hour after contrast administration (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte) obtained by flow cytometry with MR flow software.

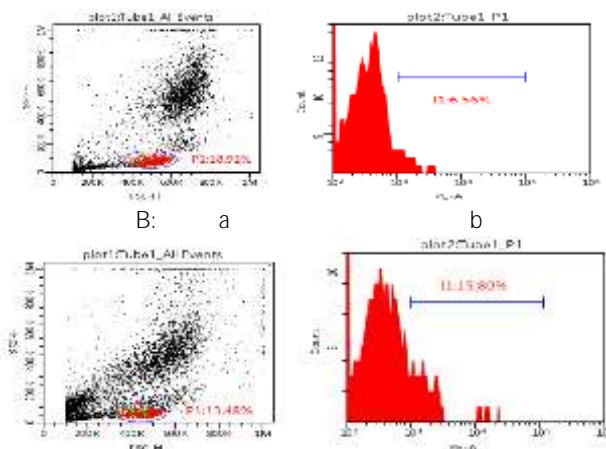
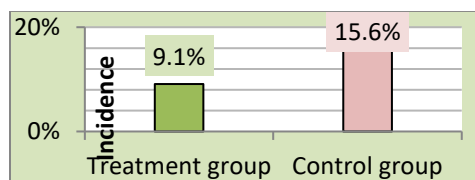


Figure 14: Expression of TLR 2 in peripheral blood monocyte in treatment group. A: before contrast administration (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte), B: 24 hour after contrast administration (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte) obtained by flow cytometry with MR flow software.

Incidence of contrast induced nephropathy

Further analysis, revealed that lower incidence of contrast induced nephropathy, in treatment group than control group.



However, the difference in incidence of CIN did not reach the statistical significance, (P. value > 0.05), figure (15).

Figure 15: Bar-chart for the comparison of incidence rate of Contrast induced Nephropathy in both studied groups (P-value < 0.05).

DISCUSSION

A large number of contrast agents are used in complex coronary lesions and in coronary interventions in general; but acute renal impairment is a potential consequence when using CM in clinical CAG and PCI treatment, especially in cases of previous kidney failure [41].

Effect of contrast media and Trimetazidine on levels of SCr and estimated GFR

In the present study, the mean serum creatinine was significantly increased at 24 hrs after contrast administration while the mean serum estimated GFR was significantly decreased at 24 hrs after contrast administration in both studied groups. The mean differences and percentages changes in treatment group were smaller than that in control group, however, the differences between both groups did not reach the statistical significance, (P. value = 0.068 & 0.084 respectively). After the administration of contrast medium, an increase in creatinine values is often observed within 72 hours. Thus, the creatinine values are not considered useful for early diagnosis of CIN [42-43] noticed SCr level was measured after 24 hours of CAG procedure and it was insignificant at that time. After comparing the baseline level of SCr with a control group, (44) observed a remarkable increase in the baseline level of SCr within 1-2 days after coronary angiography. The present study led to results similar to the some observed results of the mentioned studies, which found significant increase in the SCr level at 24 hrs after cardiac intervention. Trimetazidine (TMZ) can improve myocardial ischemia and

elevate glucose oxidation in myocytes. In addition, TMZ work as an antioxidant that can prevent ischemia reperfusion injury. To prevent transient renal dysfunction due to radio contrast media, [45] suggested that the administration of oral TMZ as a dose 20 mg three times daily with saline is an efficient method. The chance of developing CIN in patients undergoing CAG can be decreased by adding Trimetazidine to normal saline + N-Acetyl Cysteine, as pointed out by [46]. Giving patients with mild to moderate basal renal insufficiency an oral 35mg dose of trimetazidine twice daily with standard saline hydration was seemingly enough to decrease the incidence of CIN after the administration of CM during cardiac intervention procedures as mentioned by study of [47]. The basic finding of the current study are agree with the above mentioned observation that TMZ reduce the incidence of CIN after cardiac intervention despite this reducing did not reach the statistical significance, (P. value > 0.05).

Effect of contrast media and Trimetazidine on level of KIM-1 & F2-isoprostanes

In the present study, the mean urinary KIM-1 & F2-isoprostanes levels were significantly increased at 24 hrs after contrast administration. The mean differences and percentages changes in treatment group were smaller than that in control group however, the difference between both groups were statistically significant, (P. value = 0.025 & = 0.001, respectively). KIM-1 is slightly expressed in the normal renal tissue, but if ischemia and hypoxia developed in the kidney, the KIM-1 expression increases remarkably, making it a good indicator to show the presence of renal injury. After measuring

the KIM-1 levels at 2, 6, 12, 24 and 48 hours following the procedure of PCI, documented a significant difference ($P < 0.05$) between the levels of these measurements and levels obtained before undergoing PCI in patients with CI-AKI. To accomplish earlier CIN diagnosis, [48] described a remarkable increase in urinary KIM-1 levels was observed in patients with CIN after 6 hours and 2 days of contrast agent administration. According to study of [49], urine KIM-1 levels reached their maximum levels at 12-24 hours after PCI procedure in patients with CIN, but they initially started to increase 6 hours after intervention and began to diminish at 48 hours after PCI procedure and the differences were significant when taken from statistical view ($P < 0.05$). However, when comparing our results to those of previous studies it must be pointed out that the finding of the present study agree with the above observation that KIM-1 level increase significantly after cardiac intervention. However, when reviewing other studies that focused on other conditions such as in study of [50] who observed the patients were undergoing cardiac catheterization with normal serum creatinine, their KIM-1 levels were statistically increase after 24 and 48 hours but the differences are not statistically significance. An increase in urinary KIM-1 by 1.6-fold at 6 hours and by 3.5-fold at 24 hours was observed by [23] in patients with AKI after administration of contrast media. Urinary KIM-1 levels gain enough sensitivity to help diagnose CIN and they increase at 6 hours in patients with normal kidney function, as mentioned by study of [51]. [52] Indicated a noticeable significant increase in urinary KIM-1 after 48 hours of PCI in patients with CIN and have serum creatinine level (Cr) less than 2.0 mg/dL. As far as we know, no previous research has investigated and available at yet about the effect of Trimetazidine on urinary KIM-1 level after CM administration in patients undergoing coronary intervention. F2-isoprostanes (F2-isoPs) have acquired important attention in different fields as an indicator of oxidative stress in vivo [53]. The reference [27] concluded that urinary isoprostane level increases by 28% when radio contrast is administrated, but the results were not significant in both groups. Measuring F2-isoprostane can actually reveal the high level of oxidative stress caused by the radio contrast agent administration, according to study detected by (28). In study of (43) observed the increase in urinary F2-isoprostane post 1 day of CAG. A similar pattern of results was obtained in these studies indicate that the elevation of F2-isoprostane post CM injection in patients subjected to cardiac intervention procedure in spite of different in other condition. To our knowledge, no study has yielded to show the effect of Trimetazidine on the elevation of urinary F2-isoprostanes level following contrast agent administration in cardiac intervention procedure.

Effect of contrast media and Trimetazidine on level of MCP-1

In the present study, the mean serum MCP-1 level was significantly increased at 24 hrs after contrast administration in both studied groups. The mean difference and percentage change in treatment group was smaller than that in control group, however, the difference between both groups was statistically significant, (P . value < 0.001). Several studies have

been proposed Monocyte chemoattractant protein 1 plays a crucial role as inflammatory cytokine during many inflammatory responses and process. It also participates in activation of monocyte/ macrophages and up regulation of the expression of monocyte /macrophage adhesion molecules [54]. To our knowledge, MCP-1 has not been studied at yet to know the effect of CM on it in patients undergoing CAG or PCI . In the study of other design ,the supernatant epithelial cells of human renal proximal tubule are having the higher release of MCP-1 significantly after 2 hours of exposure to contrast media according to study investigated by [55]. The results of current study lead to similar conclusion where the contrast agent administration leads to elevation of MCP-1 level. No data existing about the effect of Trimetazidine on MCP-1 level following CM administration and CAG or PCI implantation.

Effect of contrast media and Trimetazidine on level of Toll-like receptor 2 (TLR 2)

In the present study, the mean TLR2 expression was significantly increased at 24 hrs after contrast administration in both studied groups. The mean difference and percentage change in treatment group was smaller than that in control group, however, the difference between both groups was statistically significant, (P . value = 0.036). Inflammatory mediators, such as cytokines and heroines, can be generated after leukocytes accumulate inside the injured kidneys [56]. In spite of different in type of contrast media and other condition ,also (55), tried to assess the expression of TLR2 after exposing the epithelial cells of renal proximal tubule in humans to 2 hours of CM. The results confirmed the notion that CM can actually induce maximal expression of TLR2. There are no studies performed on the effect of CM on TLR2 expression following CAG and PCI implantation. However, the present study supports that contrast agent administration lead to elevation of TLR2 expression. In fact no previous studies to date has performed to explain the effect of Trimetazidine on the TLR2 following CM administration and CAG or PCI implantation and to compare our results.

Incidence of contrast induced nephropathy

Regarding this study we revealed that lower incidence of contrast induced nephropathy in treatment group than controls, however, the difference in incidence of CIN did not reach the statistical significance, (P . value > 0.05). The overall incidence of CIN is approximately 1%–6% in the general population according to some studies [57-58]. In patients with moderate renal dysfunction, however, CIN incidence is 11% to 44% as reported by other studies.(59). While in other study found the incidence of CIN was 28% in patients with mild or moderate renal impairment and chronic stable angina. In a group of patients who some of them were taking Trimetazidine (TMZ) drug (treatment group) and others who didn't (control group), the incidence of CIN was 8% to 20% respectively. The present study demonstrates that CM administration may induce CIN following CAG or PCI implantation. However, Trimetazidine reduce the incidence of

CIN from 15.6% to 9.1% but did not reach the statistical significance, (P. value >0.05).

Limitations of the study 1

Despite the presence of many studies that measured SCr concentrations after 24 hours, the way actually to estimate the incidence of contrast induced nephropathy is to measure the concentrations of SCr after 72 hours of contrast exposure. The problem originates here from the fact that the patients are normally discharged from the hospital after 1 or 2 of days following PCI, making it difficult for researcher to measure SCr concentrations after 2-3 days of angiography or PCI procedure so many contrast induced nephropathy cases will be missed in this period. 2. The sample size in this study was not considered large enough for determination contrast induced nephropathy incidence and may undoubtedly limit the value of our findings, and the study was based on patients enrolled from a single center, so a more systematic and theoretical analysis is required in order to follow up this results.

CONCLUSION

Our study concluded that Trimetazidine reduce the acute kidney injury response and systemic inflammatory response induced by contrast administration after coronary angiography and percutaneous coronary intervention.

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