Impact of Trimetazidine on Incidence of Contrast Induced Nephropathy in Diabetic Patients with Renal Insufficiency Undergoing Percutaneous Coronary Intervention

Najah R. Hadi[1*], Khalid I. Amber[2], Hussein A. Alsalkhi[3], Bashaer M. Muhammad-Baqir[4], Mustafa H. Ahmed[5]

[*1]Department of Pharmacology & therapeutics, Faculty of Medicine, University of Kufa, Iraq, E mails: drnajahiraq@gmail.com

[2]Al-Sader Teaching hospital, Al-Najaf center for cardiac Surgery and Trans Catheter Therapy, Iraq, E mail: khalidamber4@gmail.com

[3]Department of Pediatric Cardiology, Faculty of Medicine, University of Kufa, Iraq, E mail: azarhussein@yahoo.com

[4]Department of Clinical Pharmacy, Faculty of Pharmacy, University of Kufa, Iraq, E mail: bashaerdrugs@gmail.com

[5]Al-Sader Teaching Hospital, the specialist centre for Nephrology and Kidney Transplantation, Iraq, E mail: mustafaasd8@gmail.com

Corresponding Author E-mail: drnajahiraq@gmail.com

ABSTRACT

The main objective of this study is 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 , starting 48 hours before surgical procedure and for 24 hours post the procedure.

Trimetazidine significantly reduce the elevation in serum levels of nuclear factor kappa B , high-mobility group box 1, expression of Toll-like receptor 2 (p<0.05) while insignificantly reduce the elevation in serum levels of creatinine and urine level of Neutrophils gelatinase-associated lipocalinis (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, Coronary artery disease, Percutaneous coronary intervention, Creatinine, Neutrophils gelatinase-associated lipocalinis, High-mobility group box 1, Toll-like receptor 2.

Correspondence:
Najah R. Hadi
Department of Pharmacology & Therapeutics, Faculty of Medicine
University of Kufa, Iraq
E-mail: drnajahiraq@gmail.com
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INTRODUCTION

Percutaneous coronary intervention (PCI) remains one of the best therapies available to treat coronary heart disease (CHD) which seems to be a common problem in the world wide [1]. Renal complications, such as contrast-induced nephropathy (CIN), are still possible outcomes after administration of contrast media (CM) during coronary angiography (CAG) and PCI procedures [2]. Contrast media is simply a chemical substance that helps showing the image of internal body parts and distinguishing the healthy tissue from the diseased tissues [3]. The level of toxicity, osmolality, and anaphylactic reaction is noticeably higher in ionic contrast media comparing to non-ionic contrast media [4]. Most early studies as well as current study focus on the relative ($\geq 25\%$) or absolute (≥ 0.5 mg/dl $= 44$ μmol/l) increase in serum creatinine (SCr) is taken as a reference to define CIN following the intravascular injection of CM with absence of an alternative etiology to explain renal injury. Usually, SCr level increases during the 1-2 days, reaches the peak within 3-5 days, and returns to normal status within 1-3 weeks [5]. Early diagnoses and accurate recognition of CIN is important to improve the treatment outcomes and prevent CIN from happening in the first time place [6]. The overall incidence of CIN is approximately 1%–6% in the general population

according to some studies [7]. In patients with moderate renal dysfunction, however, CIN incidence is 11% to 44% as reported by other studies [8]. Many reasons to prevent using SCr as an indicator for AKI include , Firstly creatinine concentration needs many days to achieve a new steady state in the acute cases, so the creatinine concentration will not be able to show the real level of renal impairment [9].Secondly , non renal factors can affect SCr level, such as hydration status, muscle mass, gender, age, drugs, and nutritional habits [10]. 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), besides depending on pre-procedure measurements of SCr level as baseline. The patients were categorized into three different categories: those who having normal renal function (eGFR >60), those with mild chronic kidney disease (CKD) (eGFR 45 to 60), those with moderate CKD (eGFR 30 to 45), and those with severe CKD (eGFR<30) [11]. Contrast media causes direct and indirect effects on the reduction of renal perfusion, and toxic effects on the tubular cells inside the kidney [12]. Both the endothelial and tubular cells are susceptible to death and apoptosis due to cytotoxicity associated with iodine content in the contrast media [13]. The risk for CIN increases

dramatically in patients with diabetes and renal failure due to low levels of endogenous vasodilators, such as nitric oxide and prostaglandins. The reduction in these endogenous vasodilators causes reduces in glomerular filtration rate and kidney blood flow [14]. Recently, the standard guidelines to prevent CI-AKI are focusing on increasing volume expansion by giving fluids at speed of 1 ml/kg per hour in patients with chronic kidney disease. The fluids should be given 12 hours before diagnostic cardiac catheterization or PCI, and 24 hours after the procedure is complete [15]. It is important to remember that serum creatinine changes are not accurate enough to determine acute alteration in renal function [16]. So the early diagnosis of CI-AKI requires a serious investigation such as a real and distinctive renal biomarker [17]. The levels of Neutrophils gelatinase-associated lipocalinis (NGAL) protein in urine increase before any noticeable increase happens in levels of serum creatinine following acute renal injury [18]. It is easier to detect NGAL in nephrotoxicity renal injuries and in human urine, blood, and kidney cortical tubules. The reason behind this comes from that fact that the NGAL is known originally for its resistance to degradation and its small molecular size, which doesn't exceed 25 kDa only [19]. After the contrast administration, serum NGAL level increases within 2 hours and urinary NGAL level increases within 4 hours [20]. High mobility group box-1(HMGB1) is stored typically in the nuclei of cells and belongs to category of damage-associated molecular pattern proteins that play a vital role in inflammation [21]. Some researchers suggest HMGB1 to be a potential causative factor of kidney damage [22]. Hypoxia and oxidative stress can cause the cells excretion more HMGB1 [23] particularly in the kidney [24]. Nuclear factor kappa from B cells originally belongs to a family of pleiotropic transcription factors involved in transcriptional regulation of many genes related to inflammation [25]. A link between experimental and human kidney diseases and NF-κB is established, especially in case of several path-physiological triggers in renal cells are involved in activation of NF-κB by ischemia reperfusion when kidney injury occurs [26]. According to some animal studies are focused on explaining that NF-κB inhibitors reduce the induction of renal inflammation and injury [27]. Toll-like receptors (TLRs), which induce inflammatory response through the activation of NF-kB, are also believed to participate in inflammation [28]. Among the 11 human TLRs, TLR2 is involved in the pathogenesis of renal diseases, although expression levels of TLR2 is observed at low levels in the kidney [29]. TLR2 was described as an essential initiator of inflammatory responses that result in renal injury [30]. Trimetazidine (TMZ) (piperazine derivative) can restore mitochondrial membrane stability and protect the cells from complications of ischemia. It can also restore glutathione peroxidase level and lower Ca2+ ion-induced mitochondrial damage. It as an anti-ischemia drug can enhance the heart function and improve exercise tolerance in patients who suffer from ischemic cardiomyopathy [31], this due to its effects on the energy substrate utilized by heart, and because TMZ is actually able to affect both the glucose oxidation stimulation and

fatty acid oxidation inhibition [32]. Contrast induced nephropathy also can be prevented byusing anti-ischemic drug with antioxidant properties such as TMZ. This idea can be further supported if the pathogenesis of contrast induced nephropathy is actually involving reactive oxygen radicals and renal medullar ischemia according to the general assumption [33].

METHODS AND 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 (Fujiflim/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 Reticulo- endotheliosis Viral Oncogene Homolog A (NFκB-ELISA) KIT ,were produced by (Cloud-Clone /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 Al-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) [34]. Eleven patients were excluded from this study mainly 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 is 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 amino glycoside, cisplatin, cyclosporine, amphoteicine 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 contrast media.

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 [35]. 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 as a period of three days, starting 48 hours before surgical procedure and for 24 hours post the procedure [36]. 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) for acute kidney injury markers and inflammatory markers. 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 TLR 2 in peripheral blood monocyte by flow- cytometry analysis, while the residual blood 3ml was allowed to clot in a clot activator gel tube (25-30) min. in room temperature at 37C° 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 NF-kB p65, serum HMGB1, while 3ml urine was be centrifuged at 3000 ×g for 5 minute that was be used for the assay of: urinary NGAL 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.

RESULTS
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).

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	
	No	2	4.4	1	2.3	0.570** (N.S)
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%	-
Medication	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 hypoglycemia	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. 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).
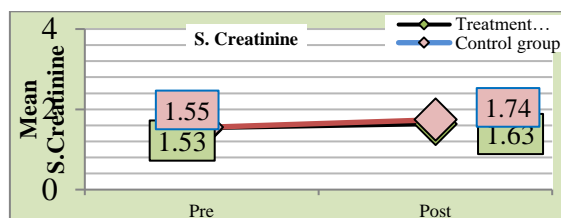
Figure 1: Graphical comparison of the mean Sr. creatinine (mg/dl) value in both studied groups (P-value < 0.05)
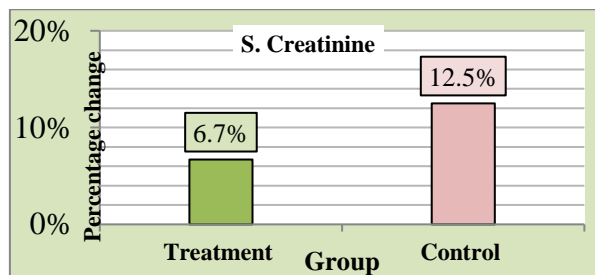
Figure 2: Bar chart comparing the percentage change in Sr. creatinine (mg/dl) level after treatment with TMZ in both studied groups (P-value < 0.05).

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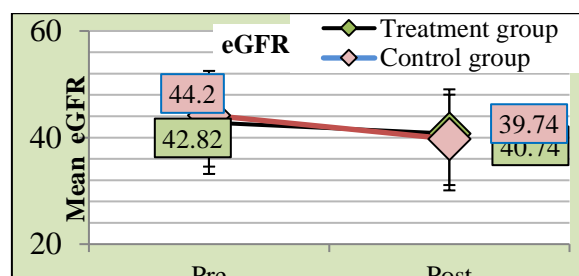

Figure 3: Graphical comparison of mean values and changes of eGFR (ml/min/1.73m^2) in both studied groups (P- value < 0.05)
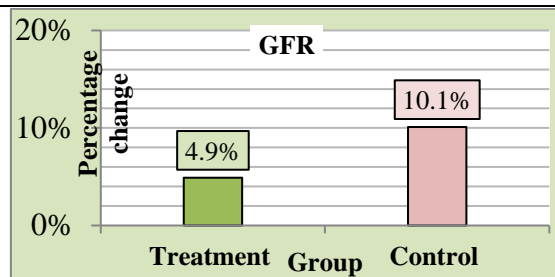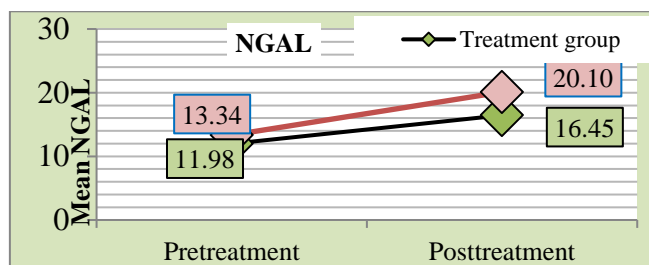
Figure 4: Bar chart comparing the percentages changes in eGFR (ml/ min/ 1.73 m^2) in both studied groups (P-value< 0.05)

Effect of contrast media and Trimetazidine on level of Urinary NGAL

In the present study, the mean urinary NGAL level was 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 was insignificant difference in level of urinary NGAL 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 =0.130), nonetheless the effect size was (0.41) indicated a moderate effect attributed to treatment with Trimetazidine in protection of further elevation in urinary NGAL level. All these changes are summarized in figures (5-6).

Figure 5: Graphical comparison of mean values and changes of urinary NGAL (ng/ml) in both studied groups (P- Value < 0.05)
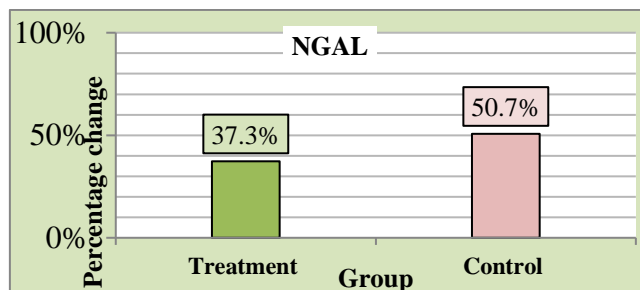

Figure 6: Bar chart comparing the percentages changes in urinary NGAL (ng/ml) level in both studied groups (P- Value < 0.05)

Effect of contrast media and Trimetazidine on levels of HMGB1 &NF-kB

In the present study, the mean serum HMGB1 & NF-κB levels were significantly increased at 24 hrs after contrast administration in both control & treatment groups [for HMGB1 (P. value < 0.001), for NF-κB (P. value =0.009 & 0.005, respectively)]. When compared between two studied groups, pre contrast administration, there were insignificant difference in levels of serum HMGB1& NF-κB between two groups. 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 = 0.004 & < 0.001, respectively), with a large effect sizes of (1.51) & (0.95), respectively, indicated the protective effect of trimetazidine to prohibit further elevation in both levels of serum HMGB1 &NF-κB. All these changes are shown in figures (7-10)
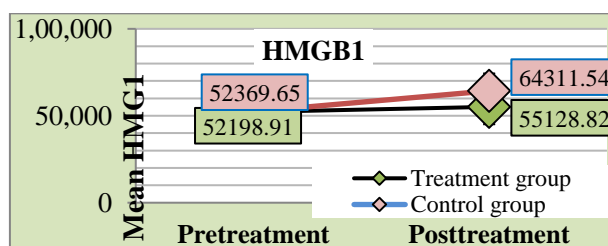

Figure 7: Graphical comparison of mean values and changes of serum HMGB1 (pg/ml) in both studied groups (P- value < 0.05)
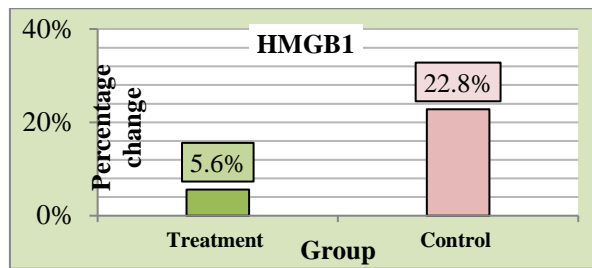
Figure 8: Bar chart comparing the percentages changes in serum HMGB1 (pg/ml) level in both studied groups (P- value < 0.05)
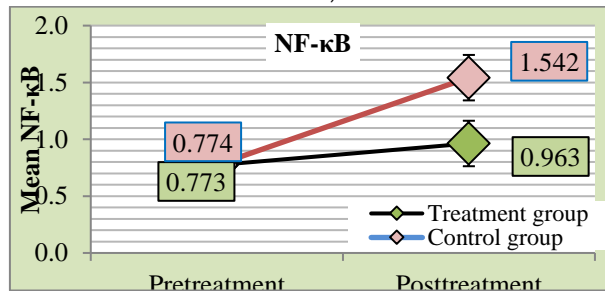

Figure 9: Graphical comparison of mean values and changes of serum RELA (ng/ml) in both studied groups (P- value < 0.05)
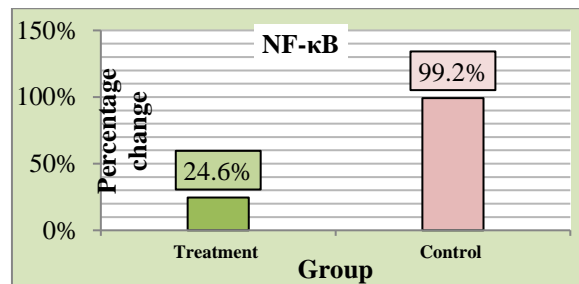

Figure 10: Bar chart comparing the percentages changes in RELA (ng/ml) level in both studied groups (p- value <0.05).

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 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).
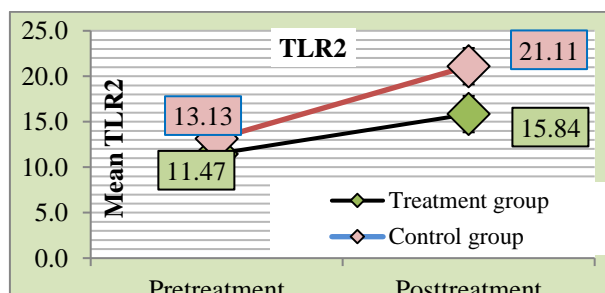

Figure 11: Graphical comparison of mean values and changes of mean TLR2 expression (% in peripheral monocyte) in both studied groups (P-value < 0.05)
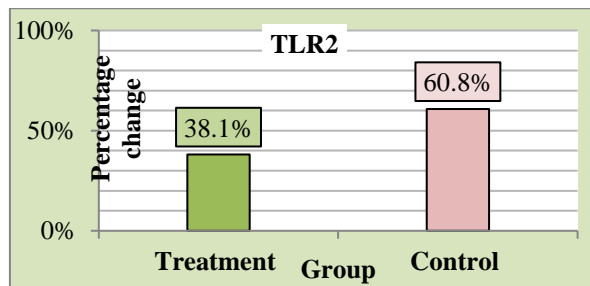
Figure 12: Bar chart comparing the percentages changes in TLR2 expression (% in peripheral monocyte) in both studied groups (P-value <0.05)
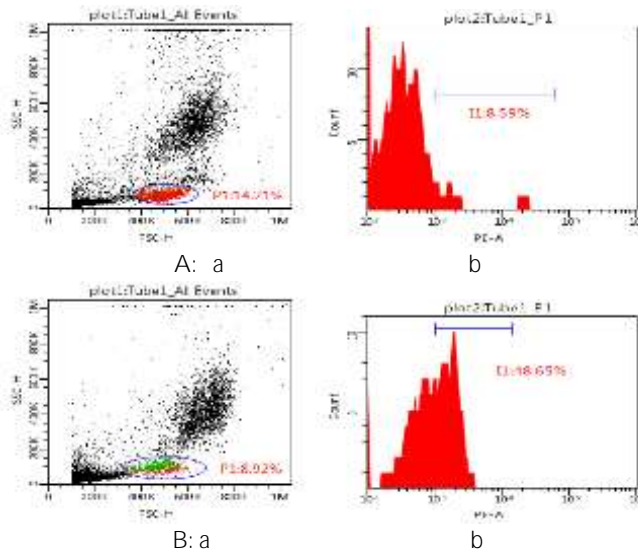

Figure 13: Expression of TLR2 in control group. A: before contrast administration B: 24 hour after contrast administration, where (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte) obtained by flow- cytometry with MR flow software.
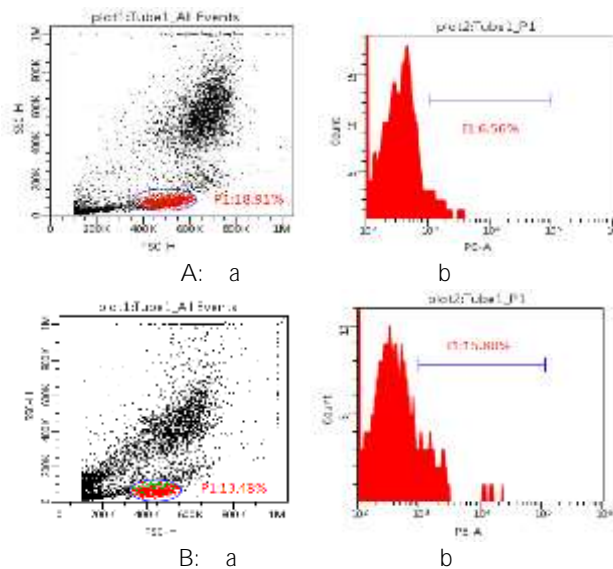

Figure 14: Expression of TLR 2 in treatment group. A: before contrast administration B: 24 hour after contrast administration, where (a: percentage of monocyte in all blood, b: percentage of TLR2 in monocyte) obtained by flow cytometry with MR flow software.

Incidence of contrast induced nephropathy
Further analysis, revealed that lower incidence of CIN, 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).
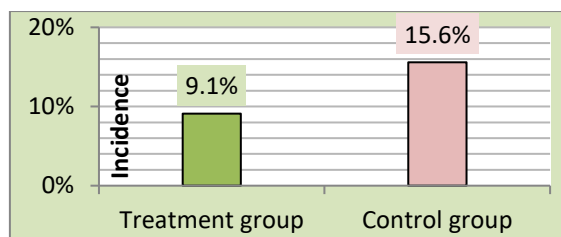
Figure 15: Bar-chart for the comparison of incidence rate of Contrast induced Nephropathy in both studied groups, (P-value < 0.05)

DISCUSSION

Effect of contrast media and Trimetazidine on levels of serum creatinine 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 was 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). According to study of [37] described no significant difference in serum creatinine was detected after 24 hours of patients undergoing CAG and having CAD who have already normal SCr Level. Compared with baseline levels, a significant increase in the levels of SCr was observed within 1-2 days after contrast media administration in patients without chronic renal failure, according to study was denoted by [35]. [38] Considered Trimetazidine as a good pharmacological choice to protect the renal function in patients who undergo CAG or PCI and who already suffer from mild to moderate renal dysfunction. According to study of [39], patients with renal impairment subjected to cardiac intervention procedures can also benefit from an oral dose of TMZ combination with oral co enzyme Q10. 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 in addition, 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 NGAL

In the present study, the mean urinary NGAL 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 differences between both groups did not reach the statistical significance, (P. value = 0.130). Serum NGAL can be used as a marker to diagnose contrast-induced AKI within four hours of starting PCI procedure [40]. In chronic kidney disease patients who undergoing coronary procedure, serial urinary NGAL usually increases during

3 hours after procedure, and peaked after 18 hours [41]. A noticeable increase in NGAL levels has been documented by (42) after 24 hours of CAG procedure. Four hours after cardiac catheterization, urinary NGAL level increased remarkably in patients with CIN as reported by [43]. To reach a precise diagnosis of CI-AKI in CKD patients undergoing elective coronary procedures, [44] used urinary NGAL and described it as an excellent marker for this purpose. Data analyzed by [45] showed that urinary NGAL concentrations increase significantly in patients with CI-AKI within 1 day after cardiac intervention. Also [46] recommended urinary NGAL as an accurate parameter for the early diagnosis of CIN. Actually, the increase of urinary NGAL levels during 1-2 days after CAG or PCI can be seen as a detection of CIN. Urinary NGAL levels also increase after PCI procedure as mentioned by study of [47]. Comparing to pre procedurally urinary NGAL level ratio measurements in patients with CI-AKI, a significant increase in urinary NGAL level was reported by (48) after 12 hours of angiography. The same study also reported a decrease in the risk of CI-AKI incidence by 8% in CKD patients who are given TMZ with normal saline injection, while the risk of CI-AKI incidence in the control group was 24%. From our findings, it is clear that all these studies as referred above are consistent with this study. As result the present study now provides evidence to support that contrast agent administration lead to elevation of NGAL level as well as trimetazidine reduce the elevation of NGAL following CM administration in CAG or PCI procedures.

Effect of contrast media and Trimetazidine on levels of HMGB1 & NF-kB

In the present study, the mean serum HMGB1 & NF-κB 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 = 0.004 &< 0.001,respectively). The level of HMGB1 increases in patients with acute kidney injury as documented in study of [49]. Inflammatory processes are involved in pathogenesis of CIN according to several experimental studies (50), but the precise mechanism is still not fully understood by researchers, although many of them were successful in providing an insight about the activation of the inflammatory receptor TLR2 and the release of HMGB1 by contrast media [51]. There is no data

presented about the effect of contrast media on the level of HMGB1in patients undergoing CAG or PCI but in the study of other design [52] observed the passive release of HMGB1 by CM following the necrotic and damaged epithelial cells in human renal proximal tubule. The cultured supernatant cells in the study were containing a determined level of HMGB1 after adding contrast media. Overall these findings are in accordance with findings reported by the present study which supports that contrast agent administration lead to elevation of HMGB1level. No previous research have been performed at yet to show the effect of Trimetazidine on the level of HMGB1 following CM administration and coronary intervention to compare our results in this study. To the best of our knowledge, there have been no articles found to report the effect of contrast media on level of NF-κB, but in a study of other design. The experiment of [53] reveled a possible activation of NF-κB in renal tissue after 6 hours of giving contrast media to a group of rats. This of course hints to the possibility that CM can indeed damage renal tubular–interstitial, which seems more dominant in the outer medulla. The question of how the radio contrast can lead to nephropathy can be answered by remembering the role of NF-κB in the renal inflammation after activation it. As well as [50] observed an increase in the phosphorylation of the transcription factor NF-KB after injecting human renal proximal tubule with both radio contrast media (Diatrizoate and Iomeprol) at 10 ,30 minutes respectively. Also (54) documented an increase in the translocation of NF-κB to the nucleus, establishing a possible link between NF- κB and kidney inflammatory response after CIN. Additionally, ten minutes of brief exposure to radio contrast can lead to remarkable increase in NF-κB according to study showed by (55). Statistically, the increase is five folds comparing to normal ranges. In spite of different in type of contrast media and other condition ,also (52) found after exposing the proximal tubule to contrast media for nearly 2 hours in different groups, there was an increase in level of NF-kB p65 in the nucleus comparing to other control group (p< 0.01). Contrast media exposure can lead to up regulation of macrophage chemokine, which also can be stimulated by activation of NFκB pathway, according to study demonstrated by (56). As result the present study supports that contrast agent administration lead to elevation of NFKB level. Indeed we did not find a study yet available about the effect of Trimetazidine on the level of NF-KB following CM administration and coronary intervention to compare our results.

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 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). In spite of different in type of contrast media and other condition, also [52], tried to assess the expression of TLR2 after exposing the 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 is no studies performed on the effect of CM on TLR2 expression following angiography 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 have performed to explain the effect of Trimetazidine on the TLR2 following CM administration and coronary intervention not found to compare our results.

Incidence of contrast induced nephropathy in patients of studied groups
Regarding this study we revealed that lower incidence of CIN in treatment group than control, however the difference in incidence of CIN did not reach the statistical significance, (P. value > 0.05). The incidence of CIN elevates by 50% in patients with advanced kidney disease, but the common incidence of CIN is around 5-10% in patients with mild to moderate chronic kidney disease according to study described by [57]. However, according to study of [58] illustrated the incidence of CIN is 20% or higher in patients with renal dysfunction and diabetes, and originally the incidence of CIN is around 3-14%. While in other study [36] 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, as reported by study of [38]. The present study demonstrates that contrast agent 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
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 CAG or PCI procedure so many CIN cases will be missed in this period. 2. The relatively low incidence of CI-AKI in our study population may be also explained by the low-intermediate risk, stable syndromes in the majority of cases, exclusion of patients with acute renal failure or end-stage renal disease requiring dialysis. In addition, patients enrolled in this study were hydrated with normal saline 1 ml/hour/kg body weight for at least 12 hours before and 24 hours after PCI procedure .3. 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 or percutaneous coronary intervention.

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