Efficacy of Colchicine Preloading in Mitigating Contrast-Induced Nephropathy in Diabetic Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) remains a significant complication in patients undergoing percutaneous coronary intervention (PCI), particularly among those with diabetes mellitus (DM). Colchicine, a potent anti-inflammatory agent, has been hypothesized to reduce the incidence of CIN through its anti-inflammatory properties. **Objective:** This study aimed to evaluate the effectiveness of colchicine loading in reducing the incidence of CIN in diabetic patients undergoing elective PCI. **Patients and methods:** A simple random sampling method was used, employing a computer-generated table. A total of 200 diabetic patients complaining of chronic coronary syndrome and scheduled for elective PCI were randomly assigned to receive an antihistamine, an antiemetic, and a colchicine loading dose of 1.5 mg administered 1 to 2 hours before PCI, with an additional 0.5 mg of colchicine given either 1 hour after or immediately following the procedure or to standard clinical practice, which included antihistamine and antiemetic without colchicine. The patients were randomized into two groups: the colchicine group (n=100) and the control group (n=100). **Results:** The primary endpoint, CIN incidence, was significantly lower in the colchicine group (12%) compared to the control group (28%) (P=0.005). Serum creatinine 48 hours post-contrast was significantly lower in the colchicine group (0.88 ± 0.22 mg/dL) compared to the control group (1.01 ± 0.24 mg/dL, P=0.006). Similarly, eGFR was notably higher in the colchicine group (77.76 ± 14.70 ml/min) than in the control group (70.20 ± 17.38 ml/min, *P*=0.021). **Conclusion:** Colchicine loading before PCI significantly reduced the incidence of CIN in diabetic patients, suggesting a potential role for colchicine in protecting renal function in this high-risk population.

Keywords: Colchicine, Diabetes mellitus, Contrast-induced nephropathy, Percutaneous coronary intervention.

INTRODUCTION

Contrast-induced nephropathy (CIN) is a potential adverse event following the administration of radiographic contrast agents. CIN is clinically defined by a significant rise in serum creatinine (Scr) levels, specifically an increase of more than 25% or at least 0.5 mg/dL (44 μmol/L) from baseline. This change occurs within 48 hours of contrast exposure and requires the exclusion of other causes of renal impairment, such as nephrotoxic drug exposure, hypotensive episodes, urinary tract obstructions, or atheroembolic events. While, the incidence of CIN is generally below 2% in the general population, it increases significantly, reaching up to 50%, in high-risk groups. These groups include individuals with pre-existing chronic kidney disease, diabetes mellitus, congestive heart failure, or advanced age, with nearly half of the cases occurring in those undergoing coronary angiography or percutaneous coronary intervention (PCI). CIN accounts for approximately 11% of in-hospital acute kidney injury cases, leading to extended hospital stays and higher healthcare costs. Notably, nearly 50% of these cases involve patients who have undergone coronary angiography or PCI. CIN is also a significant prognostic factor for mortality, highlighting its clinical importance [(1 - 3)]. The pathophysiology of CIN is multifactorial and not fully understood. However, substantial evidence from large-scale studies consistently supports intravenous hydration, the use of low-osmolar contrast media, and minimizing contrast medium volume as effective strategies to reduce CIN risk [(4)]. Mechanical injury to the vasculature during PCI triggers a rapid influx of neutrophils to the affected area. This inflammatory response can be observed as early as one-hour post-procedure, marking the beginning of a complex inflammatory cascade [(5)].

Colchicine is an alkaloid extracted from the plant *Colchicum autumnale*. It has been used to treat acute gouty arthritis, familial Mediterranean fever (FMF), Behcet's syndrome, scleroderma, chronic constipation, amyloidosis, erythema nodosum, and acute pericarditis [(6)]. Colchicine is considered a safe drug with rare side effects, which include hypersensitivity, diarrhea, vomiting, and abdominal pain [(7)]. Emerging research suggests that colchicine may have broader therapeutic applications across various cardiovascular conditions than previously thought. These conditions include pericarditis, atrial fibrillation, chronic coronary syndrome, and the prevention of coronary artery restenosis following PCI [(8)]. The inflammatory response that occurs during PCI has the potential to raise the risk of myocardial injury associated with the procedure, which is known to be linked to higher long-term death rates from any cause. Colchicine directly suppresses the inflammasome and reduces the formation of neutrophil-platelet aggregates. If left unregulated, these clusters have the potential to accumulate in the narrow blood channels after a heart attack, which could worsen cardiac damage following PCI [(5, 9)].

There was a notable and meaningful decrease in the frequency of CIN in the subgroup of individuals with diabetes, as shown by statistical analysis. The occurrence of CIN was 32% in patients who had just undergone routine, guideline-based therapy. However, this occurrence was notably reduced to 7% among individuals who had undergone further colchicine medication, as reported in a study [(10)]. Therefore, this study aimed to assess the effect of colchicine loading on

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preventing CIN in diabetic patients scheduled for elective coronary angiography with PCI.

PATIENTS AND METHODS

Study design and duration: This prospective, randomized study was conducted on a cohort of patients undergoing PCI who received colchicine as an integral component of their therapeutic regimen. A simple random sampling method was used, employing a computer-generated table. A total of 200 patients complaining of chronic coronary syndrome and scheduled for elective PCI were randomly assigned to receive an antihistamine, an antiemetic, and a colchicine loading dose of 1.5 mg administered 1 to 2 hours before PCI, with an additional 0.5 mg of colchicine given either 1 hour after or immediately following the procedure or to standard clinical practice, which included antihistamine and antiemetic without colchicine. A single expert interventional cardiologist performed the procedure, and creatinine concentration was measured after 48 hours.

Inclusion criteria: Adult cases diagnosed with diabetes, characterized by HbA1c level of 6.5% or greater. Age of 18 years or older, presenting with suspected ischemic heart disease, and were referred for coronary angiography, with the potential for PCI, as part of their clinical evaluation.

Exclusion criteria: Use of oral steroids or NSAIDs other than aspirin within the greater of 72 hours or three times the agent's half-life, a GFR of less than 30 ml/min or dependence on dialysis, chronic colchicine use or a history of colchicine intolerance, myelodysplasia history, active malignancy or ongoing infection, previous episodes of CIN, and administration of a contrast volume of less than 120 ml.

Intervention studies: Elective PCI was performed by a single expert interventional cardiologist, adhering to established clinical protocols. Each patient was administered an initial bolus of 5000 units of heparin, with supplementary intraprocedural boluses provided as necessary. All patients were administered an ionic low-osmolality contrast medium specifically ioxaglate meglumine and ioxaglate sodium (Containing 320 mg of iodine per milliliter, Hexabrix, GuerbetR). Drug-eluting stents were deployed in all patients utilizing standard techniques, with the decision-making and specific procedural approach left to the discretion of the interventional cardiologist. The post-stenting antithrombotic regimen comprised the administration of aspirin and clopidogrel, both prescribed at standard therapeutic doses.

Serum creatinine levels were assessed prior to hospital admission, within the first 24 hours, and subsequently on a daily basis for patients remaining in the hospital. For those who were discharged, follow-up was conducted, and creatinine clearance was determined utilizing the Cockcroft-Gault formula to estimate renal function. Creatinine concentration was also measured again on the second day.

Baseline high-risk clinical characteristics for the development of CIN were identified by the presence of at least one of the following factors: An estimated creatinine clearance below 60 ml/min, an age of 75 years or older, a diagnosis of diabetes mellitus, and the administration of a contrast volume of 120 ml or greater. The study endpoint was CIN occurrence, defined as an elevation in serum creatinine levels surpassing 25% or an increase of 0.5 mg/dl (44 μmol/l) from baseline values [(11)].

Ethical considerations: The Ethics Committee of Ain Shams Faculty of Medicine approved this investigation. All participants gave their acceptances to participate in the study in a written form. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis

The statistical evaluation of the data was carried out utilizing SPSS version 27.0. Descriptive statistics were employed to summarize continuous variables, with results presented as the mean (X) and SD for normally distributed data or as the median and range for data exhibiting skewness. Qualitative data were presented as frequency with percentage (%). For inferential statistical analysis, an array of tests was employed to scrutinize various facets of the dataset. The Pearson Chi-square (χ^2) test was deployed to juxtapose multiple groups concerning a singular qualitative variable. However, in circumstances where the fundamental assumption of the Chi-square test—that no less than 80% of the expected frequencies surpass the threshold of five—was contravened (Notably in matrices exceeding the dimensions of 2 x 2), the Monte Carlo method was invoked as an alternative analytical strategy. Upon the confirmation of homogeneity and normality of variances through Levene's test and Shapiro-Wilk test, the independent samples t-test was employed to identify significant differences between two independent groups with normally distributed data. For comparisons between two independent groups with non-normal distributions, the Mann-Whitney U-test (Z test) was employed. To evaluate significant differences between two dependent groups with normally distributed data, the paired samples t-test was utilized. The significance threshold was set at a P-value of 0.05, with values equal or below this threshold being deemed statistically significant.

RESULTS

The mean age in the study group was 50.59 years and in the control group 52.1 years with no statistical difference between the two groups. Also, the gender distribution was not statistically different between the study group (male/female ratio 83/17) and the control group (male/female ratio 78/22), and there was no statistical difference between the two groups as regards body mass index (BMI) and traditional risk factors (Table 1).

Table (1): Comparison between the study groups regarding the demographic data

		Colchicine group N= 100	Control group No= 100	Test value	P-value	Sig.
Sex	**Male**	83 (83%)	78 (78%)	0.796 *	0.372	NS
	Female	17 (17%)	22 (22%)			
Age (Years)	**Mean ± SD**	50.59 ± 11.19	52.10 ± 9.74	0.695 *	0.562	NS
	Range	24 – 76	34 - 76			
BMI (kg/m^2)	**Mean ± SD**	27.17 ± 1.74	26.45 ± 1.73	0.662 *	0.254	NS
	Range	22 – 31.5	22.1 - 30			
Hypertension		31 (31%)	35 (35%)	0.362 *	0.574	NS
Smoking		53 (53%)	61 (61%)	1.306 *	0.253	NS
Dyslipidemia		28 (28%)	35 (35%)	1.135 *	0.287	NS
Positive family history		21 (21%)	18 (18%)	0.287 *	0.592	NS

P-value > 0.05: (NS)Non-significant; P-value < 0.05: (S) Significant; P-value < 0.01: (HS)Highly significant
*: Chi-square test; •: Independent t-test, BMI: Body mass index

Laboratory findings were comparable between the two groups (**Table 2**). Pre-procedural ejection fraction showed no statistical significance between the two groups, however, Mehran's score was slightly higher in the control group (3±2.14 vs 3.69±2.38, P=0.05). Regarding procedural parameters, there was no statistically significant difference between the two groups regarding the amount of contrast used and the coronary anatomy **(Table 3)**.

Table (2): Comparison between the study groups regarding pre-procedural laboratory parameters

		Colchicine group N = 100	Control group N = 100	Test value	P-value	Sig.
Hemoglobin (mg/dl)	**Mean±SD**	12.53±1.81	11.82±1.77	1.654*	0.102	NS
Platelets count (x10^3/uL)	**Mean±SD**	230.59±56.81	250.27±61.82	-1.188*	0.238	NS
Total leukocyte count (%)	**Mean±SD**	7.87±1.72	8.21±1.68	-0.731*	0.467	NS
Total cholesterol (mg/dl)	**Mean±SD**	203.78±23.37	199.04±17.16	0.662*	0.510	NS
Triglyceride (mg/dl)	**Mean±SD**	194.44±46.99	195.44±47.56	-0.179#	0.858	NS
LDL-C (mg/dl)	**Mean±SD**	157.91±22.11	156.70±19.72	-0.384*	0.702	NS
HDL-C (mg/dl)	**Mean±SD**	43.19±8.31	44.73±8.58	-0.362*	0.719	NS
RBG (mg/dl)	**Mean±SD**	135.97±20.85	140.95±18.37	-1.391*	0.168	NS
HbA1C (%)	**Mean±SD**	7.67±0.62	7.48±0.57	0.841*	0.403	NS

P-value > 0.05: (NS)Non-significant; P-value < 0.05: (S) Significant; P-value < 0.01: (HS)Highly significant.
*: Independent t-test; #: Mann-Whitney test, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol

Table (3): Comparison between the study groups regarding the pre-procedural ejection fraction, Mehran's risk score, and procedural parameters

		Colchicine group N. = 100	Control group N. = 100	Test value	P-value	Sig.
Pre-procedural ejection fraction and Mehran's risk score						
Ejection fraction (%)	**Mean±SD**	49.52±5.03	50.51±6.02	-0.710 $^{\phi}$	0.420	NS
	Range	41-58	42 - 62			
Mehran's score	**Mean±SD**	3±2.14	3.69±2.38	-1.991#	**0.050**	**S**
	Range	1 - 8	1 - 9			
Procedural Parameters						
Contrast amount (ml)	**Mean±SD**	208.58±38.41	214.72±26.94	-1.252 $^{\phi}$	0.214	NS
	Range	150 - 300	150 - 250			
Culprit vessel	**Left anterior descending**	52 (52%)	64 (64%)	3.201*	0.210	NS
	Left circumflex artery	11 (11%)	10 (10%)			
	Right coronary artery	37 (37%)	26 (26%)			
Number of affected vessels	**Single vessel**	51 (51%)	37 (37%)	3.983*	0.136	NS
	Two vessels	33 (33%)	42 (42%)			
	Three or more vessels	16 (16%)	21 (21%)			

P-value > 0.05: (NS)Non-significant; P-value < 0.05: (S) Significant; P-value < 0.01: (HS)Highly significant, ϕ: Independent T-test, #: Mann - Whitney test*: Chi-square test

The basal serum creatinine level showed no statistically significant difference between the two groups. However, serum creatinine at 48 hours was significantly higher in the control group (1.01±0.24 vs. 0.88±0.22 mg/dl, P= 0.006) (**Figure 1)**.

The same went for the eGFR, there was no statistically significant difference at baseline but at 48 hours, the control group showed statistically significantly lower eGFR (70.20±17.38 vs. 77.76±14.70, P= 0.021) (**Figure 2)**. The incidence of CIN was statistically significant across the groups, occurring in 12% in the colchicine group and 28% in the control group (**Figure 3 and table 4**).

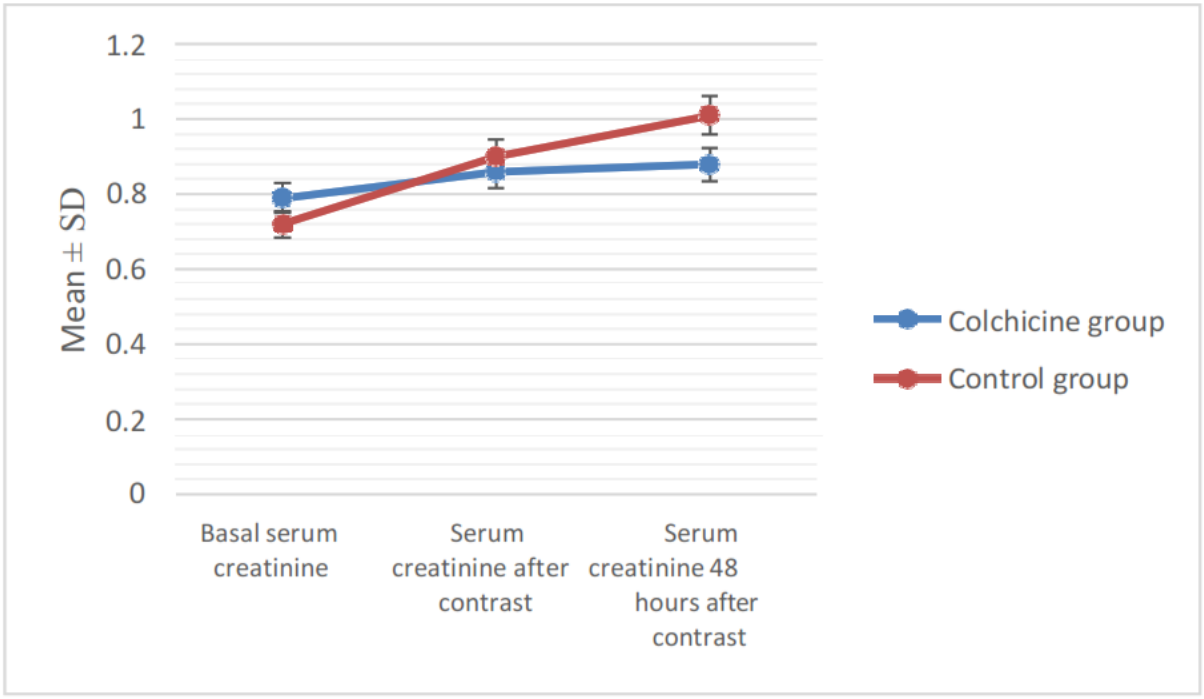

Figure (1): Comparison between the study groups regarding the follow-up of serum creatinine.

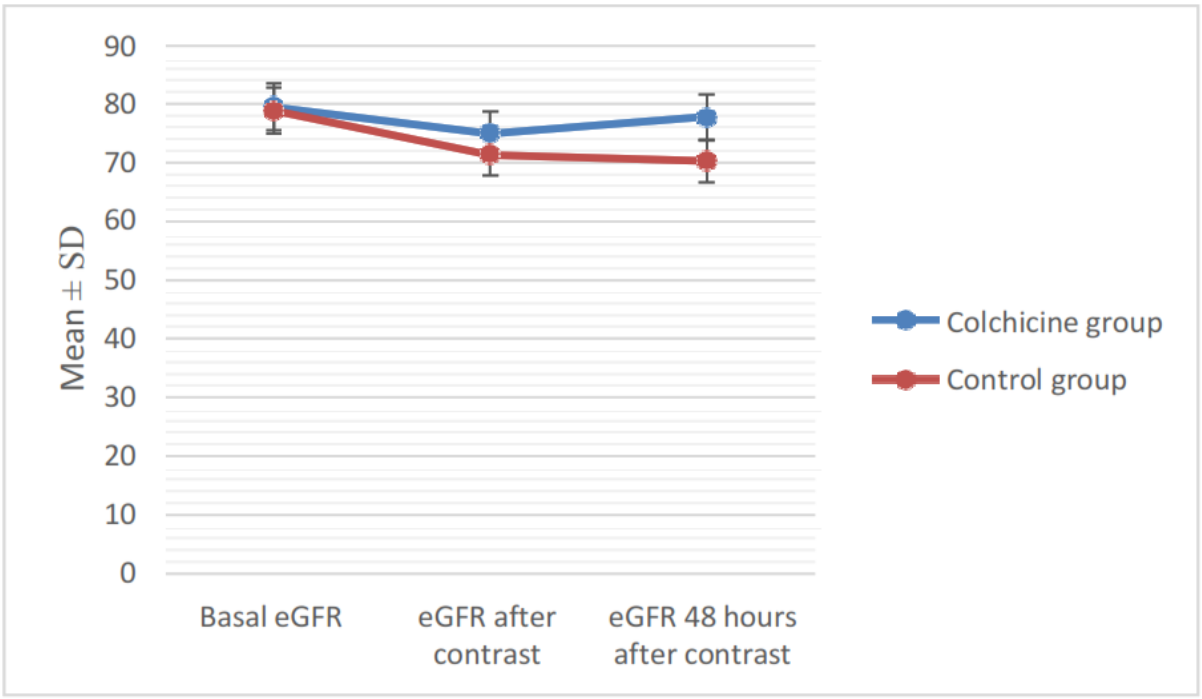

Figure (2): Comparison between the study groups regarding the follow-up of eGFR.

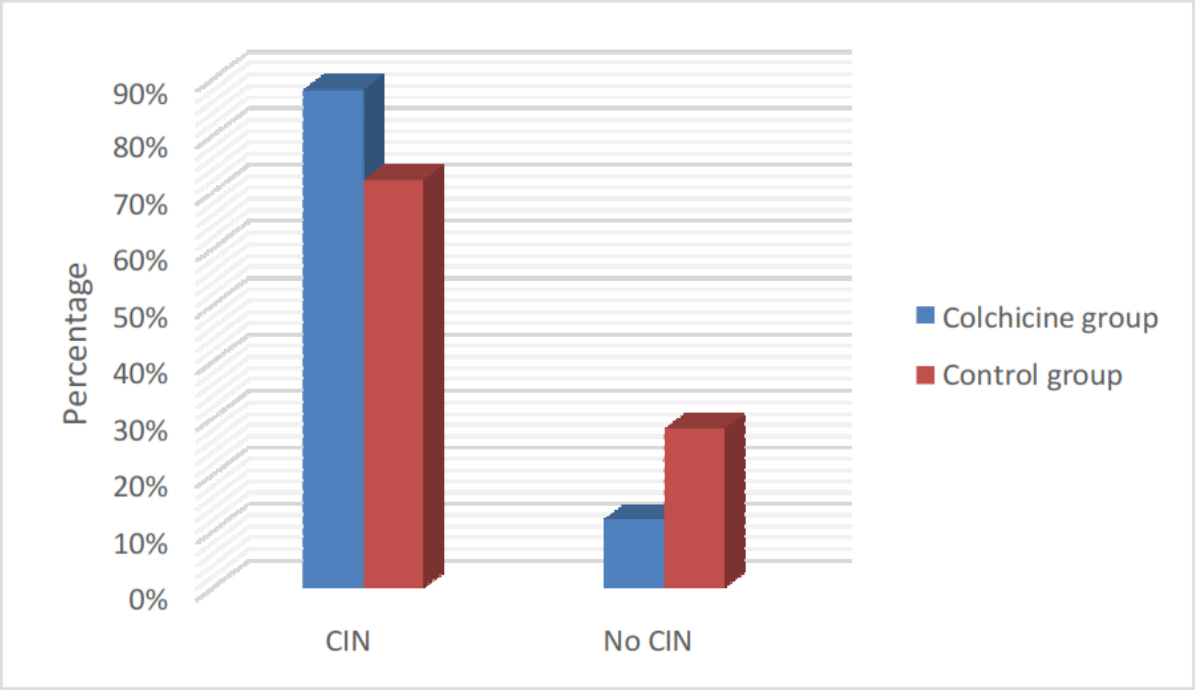

Figure (3): Comparison between two study groups regarding the incidence of CIN.

Table (4): Comparison between two groups regarding the follow-up of serum creatinine and eGFR and the incidence of CIN

		Colchicine group N = 100	Control group N = 100	Test value	P-value	Sig.
Serum Creatinine at baseline, same day after procedure, and at 48 hours follow-up						
Basal serum creatinine (mg/dl)	**Mean±SD**	0.79±0.19	0.72±0.18	1.864*	0.066	NS
Serum creatinine post-procedure (mg/dl)	**Mean±SD**	0.86±0.21	0.90±0.22	-0.925#	0.358	NS
Serum creatinine 48 hrs. post-procedure (mg/dl)	**Mean±SD**	0.88±0.22	1.01±0.24	-2.751#	**0.006**	**S**
Paired samples t-test (Basal and at 48 hours)		0.138 (NS)	**0.010 (S)**			
eGFR at baseline, same day post-procedure, and at 48 hours follow-up						
Basal eGFR (ml/min)	**Mean±SD**	79.47±11.94	78.86±11.86	0.219*	0.327	NS
eGFR post-procedure (ml/min)	**Mean±SD**	74.95±14.22	71.33±15.47	1.391*	0.168	NS
eGFR 48 hrs. post-procedure (ml/min)	**Mean±SD**	77.76±14.70	70.20±17.38	2.362*	**0.021**	**S**
Paired samples t-test (Basal and at 48 hours)		0.764 (NS)	**0.021 (S)**			
Incidence of CIN						
Incidence of CIN	**No**	88 (88%)	72 (72%)	8.002 $^{\Phi}$	**0.005**	**S**
	Yes	12 (12%)	28 (28%)			

P-value > 0.05: (NS)Non-significant; P-value < 0.05: (S) Significant; P-value < 0.01: (HS)Highly significant
*: Independent t-test: #: Mann - Whitney test, $^{\Phi}$: Chi-square test, CIN: Contrast-induced nephropathy

DISCUSSION

CIN remains one of the most devastating complications after PCI, particularly among those with diabetes mellitus. Colchicine, a potent anti-inflammatory agent, has been hypothesized to reduce the incidence of CIN through its anti-inflammatory properties [(12)]. This study aimed to evaluate the effectiveness of colchicine loading in reducing the incidence of CIN in diabetic patients undergoing elective PCI.

The pathophysiological mechanism underlying CIN remains unclear. It is believed that multiple mechanisms contribute to the development of CIN. Yet, research has shown that tubular toxicity [(13)], vasoconstriction, and renal hypoxia brought on by an unbalanced amount of vasoconstrictor and vasodilator mediators[(14)], oxidative stress [(15)], inflammation, and renal tubular obstruction [(16)] are the main causes of CIN.

Numerous mechanisms are known to underlie the anti-inflammatory of colchicine [(17)]. Its anti-inflammatory properties come from preventing leukocyte migration, activation, and degranulation as well as from preventing the release of inflammatory mediators such as Interleukin 1(IL-1), tumour necrosis factor-alpha (TNF-alpha), leukotriene B4 (LTB4), prostaglandins E2 (PGE2), and thromboxane A2 (TxA2) [(18)]. Moreover, colchicine has been shown to reduce lymphocyte function and proliferation [(19-20)]. Also, colchicine has shown the ability to reduce the pro-inflammatory response of neutrophils, which when activated excessively is known to enhance tissue damage by disrupting microtubule polymerization, to lower the expression of adhesion molecules in membranes (L- and E-selectins), and to lessen the negative effects of neutrophils by blocking chemotaxis [(21)]. When neutrophils are overactivated, they release more cytokines, reactive oxygen species, proteases, elastases, and other enzymes, which in turn cause endothelial functions to be disrupted and vascular permeability to increase [(22-23)].

The presence of T2DM is acknowledged as a major predisposing factor for the onset of CIN [(24)]. This heightened risk is primarily due to the frequent occurrence of cardiovascular complications in T2DM patients, which often necessitate diagnostic and interventional procedures that may lead to CIN. Furthermore, nearly 7% of individuals are found to have albuminuria and varying degrees of renal impairment at the time of their T2DM diagnosis [(25)]. While not all patients with reduced eGFR are destined to develop CIN [(26)]. The CIN Consensus Working Panel advises that patients with an eGFR < 60 mL/min/1.73 m² undergo a thorough clinical evaluation and recommends exercising particular caution in individuals with an eGFR of less than 45 mL/min/1.73 m² [(27)].

In the current investigation, the incidence of CIN within the cohort receiving colchicine was observed to be 12%, a figure that represents a notable decrease in comparison with the 28% incidence documented in the controls (P = 0.005). This is consistent with a recent study by **Elhodhod *et al.* [(28)],** which examined 100 STEMI patients who received initial PCI. The fifty individuals were randomly assigned to a control group that received normal, guideline-based medical therapy or a research group that received it plus colchicine. The colchicine group had a trend toward a lower CIN rate, but the difference was not statistically significant. CIN occurred in 8% of the colchicine group compared to 20% in the control group (p = 0.083) with a 60% relative risk reduction. In the diabetic subgroup, CIN incidence decreased from 32% in the control group to 7% in the colchicine group (P = 0.033).

In a randomized, open-label study, **Oktay *et al.* [(29)]** found similar results in 280 elective PCI patients with an eGFR greater than 45 mL/min/1.73 m². In the trial, 140 patients were assigned to the colchicine therapy group (mean age: 60±9 years) and 140 patients were assigned to the control group (mean age: 61±7 years). The colchicine group had 6 patients (4%) with CI-AKI, while the control group had 13 patients (9%) (P=0.02). Additionally, the eGFR drop after PCI was considerably reduced in the colchicine-treated group compared to the control group (P<0.001). Logistic regression analysis indicated age (OR=1.3, 95% CI: 1.1-1.6, P=0.005), colchicine treatment (OR=0.84, 95% CI: 0.72-0.98, P=0.020), and diabetes mellitus (OR=2.24, 95% CI: 1.17-3.31, P<0.001) as independent predictors of CI-AKI [(29)].

Limitations: One of which is its single-center design, potentially restricting the applicability of its findings to broader populations and diverse healthcare environments. The relatively small sample size may not capture less common adverse events or allow for robust subgroup analyses. The short follow-up duration focuses on immediate outcomes, such as CIN, without assessing long-term renal function or mortality. The exclusion of patients with severe renal impairment or other significant comorbidities limits the applicability of the results to broader patient populations. Additionally, the reliance on a specific contrast agent may reduce the relevance of findings for procedures using different contrast media.

CONCLUSION

Colchicine loading before PCI significantly reduced the incidence of CIN in diabetic patients, suggesting a potential role for colchicine in protecting renal function in this high-risk population.

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