International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Effect of Colchicine in Maintenance of Sinus Rythm and Left Atrial Volume Index in Patients with Atrial Fibrillation after Cardioversion

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Abstract

Atrial fibrillation (AF) is the commonest form of sustained arrhythmia. It increases the risk of stroke, heart failure, and mortality. However, AF rhythm control agents are not very useful due to a high recurrence of AF, low adherence, and common adverse effects. The aim of this work was to investigate the potential benefit of colchicine in the maintenance of rhythm control and left atrial volume index (LAVI) in AF patients after cardioversion. This prospective comparative study was carried out on 80 patients aged above 18 years old, with paroxysmal and Persistent non-valvular AF, who recover to sinus rhythm medically, electrically or spontaneously, received amiodarone post cardioversion to sinus rhythm. Patients were divided into two equal groups: group A received colchicine + anti-arrhythmic drugs and group B received placebo + anti-arrhythmic drugs. There was no significant difference between colchicine group and placebo group as regard LAVI at baseline (mean ± SD 36.06 mm/m^2 vs 37.02 mm/m^2 respectively), p value 0.6. But after 3 months there was significant decrease in LAVI in patients received colchicine's vs placebo, (mean ± SD 32.53 mm/m^2 vs 36.55 mm/m^2 respectively), p value 0.01. AF was founded in 85% of colchicine group vs 80% in placebo group but within 3 months AF founded in 42.5% of colchicine group vs 72.5% of placebo group, p value 0.01. The use of Colchicine was safe and effective in preserving AF after cardioversion. Colchicine resulted in significant reduction in LAVI and the incidence of AF compared to placebo.

Keywords: Atrial Fibrillation, Cardioversion, Colchicine, Left Atrial Volume, Sinus Rhythm.

Full length article **Corresponding Author*, e-mail: ptrservices2022@gmail.com

1. Introduction

Atrial fibrillation (AF) is the commonest form of sustained arrhythmia. It increases the risk of stroke, heart failure, and mortality. However, AF rhythm control agents are not very useful due to a high recurrence of AF, low adherence, and common adverse effects. Colchicine decreases interstitial myocardial fibrosis by interfering with collagen accumulation and reverses the contractile function in failing hearts. Therefore, colchicine may attenuate myocardial remodeling by decreasing ECM accumulation and prevent AF occurrence [1]. Recent studies have indicated that inflammation might play a significant role in the initiation, maintenance, and perpetuation of AF. Inflammatory markers such as interleukin-6 and C-reactive protein are elevated in AF and correlate to longer duration of AF, success of cardioversion, and thrombogenesis. Furthermore, the inflammatory process might be modulated by the use of statins, angiotensin-converting enzyme inhibitors, or glucocorticoids [2]. Colchicine is a widely available and potent anti-inflammatory drug that is approved for the treatment and prevention of acute gout, as well as other inflammatory conditions, such as pericarditis. It inhibits the infiltration of neutrophils in the heart of rats after acute myocardial infarction. It also suppresses NLRP3 inflammasome activation and IL-1β secretion in patients with acute coronary syndrome. Recently, colchicine has been shown to reduce the occurrence of post operative AF and early AF recurrence after pulmonary vein isolation (PVI) as well as the level of proinflammatory biomarkers CRP and IL-6 [3]. Although M-mode left atrial dimension is easy to acquire, its validity has recently been challenged. Because the left atrium is an asymmetrical cavity, left atrial size is more accurately reflected by a measurement of volume rather than area or linear dimension. Furthermore, left atrium dilatation might not be evenly distributed in all planes, and measurement of antero-posterior dimension is likely to be insensitive to changes in left atrial size [4]. The aim of this work was to investigate the potential benefit of colchicine in the maintenance of rhythm control and left atrial volume index (LAVI) in AF patients after cardioversion.

2. Patients and Methods

This prospective comparative study was carried out on 80 patients aged above 18 years old, with paroxysmal and persistent AF, non-valvular AF, who recover to sinus rhythm medically, electrically or spontaneously, received amiodarone post cardioversion to sinus rhythm. The study was done after approval from the Ethical Committee Aswan University Hospitals, Egypt. An informed written consent was obtained from the patients. Exclusion criteria were moderate to severe mitral stenosis and mechanical valve prosthesis, active inflammatory or infectious disease, malignancy, left ventricular ejection fraction < 40%, corticosteroid or other immunosuppressive or immune-modulatory therapy, pregnant and lactating women, women of childbearing potential not protected by a contraception method, atrial flutter was also excluded unless there is history of coexisting AF, contraindication to colchicine e.g., hypersensitivity to drug, sever hepatic and renal impairment, refusal of consent. Patients were further divided post cardioversion in to two equal groups:

- Group A: received colchicine (0.5 mg daily) + cordarone for maintenance of sinus rhythm.
- Group B: received cordarone for maintenance of sinus rhythm+ placebo.

Both groups received other medication not including non-dihydropyridine calcium channel blocker or digoxin. All patients were subjected to: Full history (personal data, the existence of classical cardiovascular risk factor such as age, gender, diabetes mellitus, hypertension, dyslipidemia, family history of premature CAD and smoking, onset of AF, and, previous medication as diuretics, ACE inhibitors /ARB and beta blocker), clinical examination (general and local).

2.1. Electrocardiography (ECG)

12 lead ECG to detect rhythm, heart rate, p wave dispersion, ST segment –T wave changes).

2.2. Transthoracic echocardiography

Transthoracic echocardiography was performed for each patient to exclude RHD, evaluate left ventricular ejection fraction, diastolic function, LAVI, left ventricular (LV) dimension and thickening, valve morphology and function). All measurements were done using a commercially available machine (Vivid 7, GE Medical System, Horten, Norway) with a 3.5 MHz transducer. In the apical four chamber view, the Simpson method was used to assess LVEF, LV volumes and LAVI. LAVI was assessed by the following equation:

$$\text{LAVI}=\text{LA volume} / \text{BSA}$$

$$\text{LA volume} = (8 / 3\pi) \times (A1 \times A2 / L) = 0.85 \times (A1 \times A2 / L)$$

2.3. Trans-esophageal echocardiography

Trans-esophageal echocardiography (TEE) was performed for patients who presented after 48 hours from the onset of AF to exclude left atrial appendage (LAA) thrombus, then electrical cardioversion was done after exclusion of LAA by trans-esophageal echocardiography.

2.4. Intervention

Trans-esophageal echo was performed as:

Electrodes were placed on patient‘s chest to watch heart electrical activity, blood pressure cuff was placed on patient‘s arm and pulse oximeter on patient‘s finger to check oxygen level, I.V Sedative was given to help patient to relax, local anesthetic spray through patient‘s throat was given to prevent feeling of pain during TEE, nasal cannula was used to provide oxygen to patient, then patient was lied on left side on the exam table, transesophageal echo probe which is long, thin, flexible tube was inserted into patient‘s mouth using lubricant to slide down easily through esophagus, on TEE, the LAA is best visualized in the mid-esophageal two –chamber view (80-100̊) and the mid esophageal aortic valve short-axis view (30-60). In most patients, these two views allow satisfactory imaging of LAA and therefore the recommended views for this purpose.

2.5. Method of cardioversion

It was done after exclusion of LAA thrombus using TEE, there were 60 patients regained sinus rhythm pharmacologically by amiodarone 300 mg IV as bolus dose then 900 mg IV by continuous infusion for 24 hours ,12 patients were cardioverted electrically after failure of pharmacological cardioversion by synchronized direct-current cardioversion using 150 J after sedation, 28 patients regained sinus rhythm spontaneously without any intervention

2.6. Follow-up visits

All Patients were followed up after 6 months, any patient reported symptoms suggestive of dysrhythmia at any time during follow up period, was evaluated by ECG and 24 hours Holter monitoring, transthoracic echocardiography was done after 6 months to evaluate LA dimensions and LAVI.

2.7. Statistical analysis

Statistical analysis was done by SPSS v20. Quantitative variables were presented as mean and standard deviation (SD). Qualitative variables were presented as number and percentage (%). Kruskal-Wallis’ test was used to assess the statistical significance of the difference of a non-parametric variable between more than two study. correlation was done by Pearson's correlation or Spearman's. A two tailed P value < 0.05 was considered significant.

3. Results and Discussion

There were insignificant differences between two groups as regard sex, age, risk factors and anthropometric measurement (Table 1). Colchicine can rapidly reduce the level of inflammation biomarkers, specially hs-CRP. Thus, a reduction in the risk for cardiovascular events is expected after taking colchicine [5]. Recent evidence has demonstrated that colchicine reduces adverse events in patients with cardiovascular disease. Some clinical trials and meta-analyses suggested that colchicine has the potential to prevent the occurrence of postoperative AF [6-7]. Papageorgiou et al., published a meta-analytic result of 4 studies, and, showed that treatment with colchicine significantly reduced the risk of AF recurrence after cardiac surgery or pulmonary vein isolation [8]. Literature showed that LAVI to the subjects’ body surface area (LAVI) is a superior metric of left atrial dimension in terms of predicting cardiovascular outcomes [9-11].

The current study results showed that mean LA volume/BSA (mL/m^2) and LA had insignificant differences between both groups but as regard EF there was significant decrease in colchicine group 59.18 compared to 61.33 in placebo group. There were insignificant differences between the two groups as regard mean LA volume/BSA and LA. While, there was significant decrease in colchicin group versus the placebo group as regard EF (Table 2). Regarding LAVI, there was no significant difference between the studied groups at baseline but at 3 months post-treatment the colchicine group have significantly lower LAVI than control group. The mean reduction of LAVI was significantly higher in colchicine group compared to control group. Pre-treatment AF was founded in 85% of colchicine group and 80% in placebo group without significant difference but within 3 months AF founded in 42.5% of colchicine group and 72.5% of placebo group with significant differences. As regard pre LAVI was 36.06 in colchicin group vs 37.02 in placebo with insignificant differences. While after 3 months there was significant decrease in colchicines 32.53 vs 36.55 in placebo group (Figure 1). AF recurrence within 3 months AF founded in 42.5% of colchicin group vs 72.5% of placebo group with insignificant differences (Table 3). Toufan et al., (2017) showed that LAVI is a powerful forecaster of the recurrence of AF after cardioversion [12]. In support to the current study results a study by Bessissow et al., (2018) showed that new Post-Operative Atrial Fibrillation (POAF) occurred in 5 (10.2%) patients in the colchicine group and 7 (13.7%) patients in the placebo group [13]. Also, Imazio et al., (2011) revealed that colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay [14]. Patients on colchicine had a reduced incidence of AF 12.0% versus 22.0% in control group. In concordance with the current study a meta-analysis of by Zhao et al., (2022) revealed that Colchicine significantly reduces the incidence of postoperative AF [15]. Also, the current study was consistent with the meta-analysis by Papageorgiou et al., (2017) who showed that treatment with colchicine is associated with lower recurrence of AF rates after cardiac surgery and ablation procedures [8]. However, gastrointestinal side effects were more common in patients treated with colchicine. This was in line with a meta-analysis by Verma et al., (2015) as they suggested that colchicine may reduce the composite rate of cardiovascular adverse outcomes in a range of patients with established cardiovascular disease [16]. However, in contrast to the current study results Shvartz et al., (2022) showed that baseline clinical, laboratory, instrumental, and intraoperative data did not differ statistically significantly between the groups [17]. POAF was detected in 9 patients (18%) of the treatment group and 15 subjects (29.4%) of the control group, which had no statistical significance. Also, in disagreement with the current study in Tabbalat et al., (2020) study, 81 patients received 1-mg dose of colchicine and 71 received placebo, both groups were similar in baseline data, the study revealed that POAF occurred in 13 patients (16.1%) in the colchicine group and 13 patients (18.3%) in the placebo group [18]. The study concluded that Low-dose colchicine did not prevent POAF in patients undergoing cardiac surgery. Similarly, Tabbalat et al., (2016) the studied groups were well-matched in baseline data [19]. The study showed that the primary end point of AF occurred in 63 patients (17.5%): 26 (14.5%) in the colchicine group and 37 (20.5%) in the no-colchicine group (relative risk reduction 29.3% [P = .14]). Diarrhea occurred in 54 patients, 44 (24.6%) on colchicine and 10 (5.5%) on no-colchicine (P < .001). Diarrhea led to discontinuation of colchicine in 23 (52%) of the 44 patients. Also, Zarpelon et al., (2016) revealed that Colchicine group patients showed no significant reduction in AF incidence as compared to control group patients [20]. As well, Imazio et al., (2014) showed that the use of colchicine result in no significant reduction in the incidence of AF [21]. The currents study showed that the use of colchicine in the maintenance of rhythm control and LAVI in AF patients after cardioversion was safe as it was not result in major adverse events. The meta-analysis by Andreis et al., (2021) as they revealed that Colchicine is associated with increased risk of gastrointestinal events and myalgias, but not of other adverse events [22].

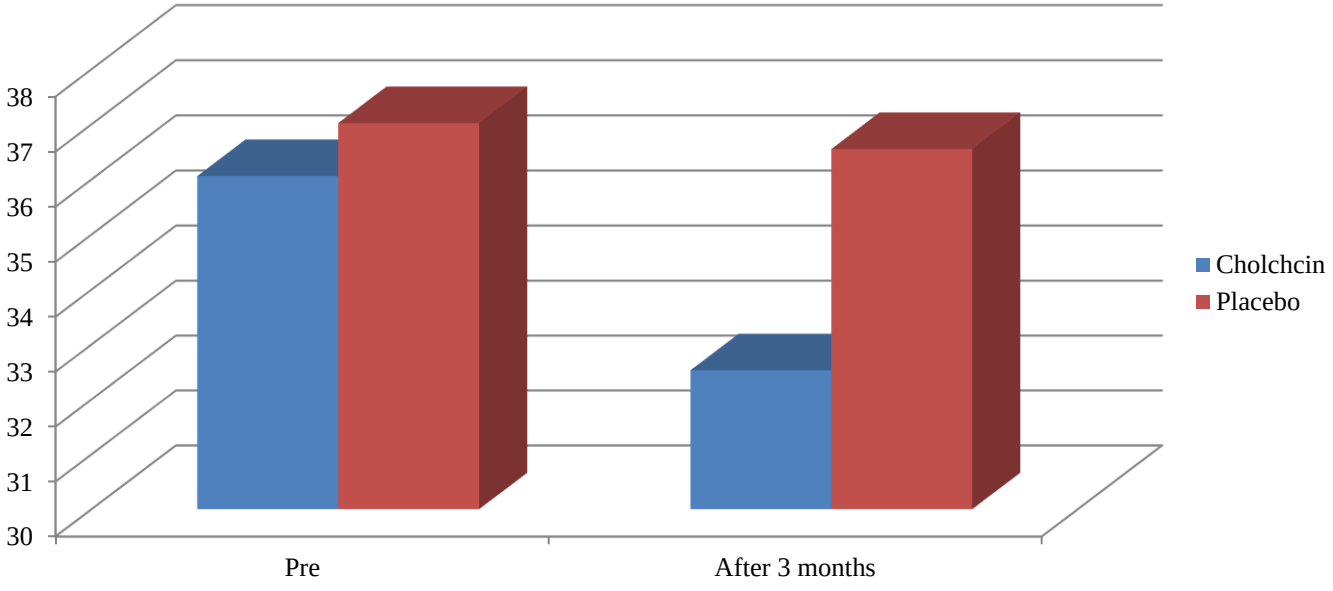

Figure 1: Comparison between the two studied groups according to LAVI.

Table 1: Demographic data, risk factors, and, anthropometric measurement of the studied patients (n = 80).

		Cholchcin (n = 40)		Placebo (n = 40)		Test of Sig.	p
Age (years)		56.40 ± 7.97		59.15 ± 9.78		t= 1.379	0.172
Sex	Female	15	37.5	14	35.0		
Risk factors	**Smoking**	14	35.0	16	40.0	χ^2=0.213	0.644
	IHD	16	40.0	12	30.0	χ^2=0.879	0.348
	DM	8	20.0	7	17.5	χ^2=0.082	0.775
	HTN	8	20.0	14	35.0	χ^2=2.257	0.133
	Stroke	5	12.5	3	7.5	χ^2=0.556	^{FE}p=0.712
Anthropometric measurement	**Weight (kg)**	76.68 ± 9.94		77.20 ± 9.48		t=0.242	0.810
	Height (cm)	168.13 ± 6.52		169.23 ± 7.07		t=0.723	0.472
	BMI (kg/m^2)	18.11 – 36.79		20.06 – 37.04		t=0.226	0.822
	Body surface area	1.88 ± 0.11		1.90 ± 0.12		t=0.653	0.516

Data are presented as mean ± SD or frequency (%). BMI: Body mass index, t: Student t-test, X^2: Chi square test, FE: Fisher Exact.

Table 2: Comparison between the two studied groups according to different parameters.

	Cholchcin (n = 40)	Placebo (n = 40)	t	p
LA volume/BSA (mL/m^2	67.68 ± 5.85	70.18 ± 6.87	1.753	0.084
LA	4.73 ± 0.44	4.74 ± 0.49	0.096	0.924
EF	59.18 ± 4.95	61.33 ± 4.44	2.046*	0.044*

Data are presented as mean ± SD or frequency (%). t: Student t-test.

Table 3: The presence of AF between the two studied groups.

AF	Cholchcin (n = 40)		Placebo (n = 40)		χ^2	p
	No.	%	No.	%		
Recurrence Within 3 months						
No recurrence	23	57.5	11	27.5	7.366*	0.007*
Yes recurrence	17	42.5	29	72.5		
^{McN}p	<0.001*		0.629			

McN: McNemar test, χ^2: Chi square test, p_0: p value for comparing between Pre and Within 3 months.

4. Limitations

The sample size was relatively small. The study was in a single center. The follow up of patients was limited for relatively short period. Future studies are needed to elucidate the optimal medication duration and dosage of colchicine to improve the treatment regimen and further comparative studies with larger sample size and longer follow-up are needed to confirm our results and to identify risk factors of adverse events.

5. Conclusions

The use of Colchicine was safe and effective in preserving AF after cardioversion. Colchicine resulted in significant reduction in LAVI and the incidence of AF compared to placebo.

Financial support and sponsorship
Nil.

Conflict of Interest
Nil

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