



The impact of colchicine in preventing post-pericardiotomy syndrome; a double-blind clinical trial study

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Abstract

Introduction: Post-pericardiotomy syndrome is a relatively common complication after open heart surgery. In recent years, colchicine had a good effect on treatment of the pericarditis.

Objectives: This study aimed to study the effect of colchicine to prevent post-pericardiotomy syndrome in patients who had open heart surgery.

Patients and Methods: This double-blind clinical trial study was conducted on 240 patients undergone open heart surgery. Eligible patients were selected by simple sampling and randomly divided into two groups; 120 subjects in the experimental group receive colchicine (1 mg for patients greater than 70 kg and 0.5 mg for patients lower than 70 kg) and 120 subjects in the control group who received the placebo. Patients were followed up regarding the incidence of post-pericardiotomy syndrome after the surgery during hospitalization and in follow up visits in one month and six months after hospital discharges.

Results: In total, the incidence rate of post-pericardiotomy syndrome was 33.7% (81 subjects). A significant difference of post-pericardiotomy syndrome between two groups was seen. We found post-pericardiotomy syndrome in 12.1% (29 patients) of colchicine group versus 21.6% (52 patients) in the placebo group (chi-square test). The incidence rate based on the Kaplan-Meier curve, in the second week to one month after the surgery, was lower in colchicine group while in third to the sixth month it had a constant trend.

Conclusion: Colchicine is effective for prevention the post-pericardiotomy syndrome without any life-threatening complication.

Trial registration: Registration of trial study has been approved in the Iranian Registry of Clinical Trial (identifier: IRCT20141209020258N70; <https://irct.ir/trial/28142>, ethical code; IR.ARAKMU.REC92-148-11).

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Introduction

Post-pericardiotomy syndrome (PPS) is a relatively common complication after open heart surgery with the occurrence time of days to weeks after surgery (1,2). This syndrome was first described by Janton et al as a disease including fever and pleuritic chest pain after rheumatic mitral valve repair (3, 4). However, it was also observed in non-rheumatic heart diseases and after heart surgery with or without cardiopulmonary bypass. PPS is currently recognized as an inflammatory complication of immune response which occurs following surgical trauma to the pericardium, pleura or both, due to the release of stimulant antigens of immune response and ultimately inflammation (2,5). PPS usually occurs during the early weeks after surgery, but may also occur 6 to 12 months after surgery with less prevalence (6,7). Symptoms of the disease vary depending on its severity and can be manifested as atrial fibrillation, pleural effusion, pericardial effusion, constrictive

Key point

In a double-blind clinical trial study conducted on 240 patients undergone open heart surgery, we found colchicine is effective for prevention the post-pericardiotomy syndrome without any life-threatening complication.

pericarditis and cardiac tamponade. Diagnosis of this syndrome is based on the presence of at least two criteria as follows; fever of unknown origin, pleuritic chest pain, friction rub, constrictive pericarditis, cardiac tamponade, atrial fibrillation and occurrence or exacerbation of pericardial effusion and pleural effusion (2,5,8,9). Very mild cases of this syndrome are usually without symptoms and are spontaneously resolved while in other cases, medical treatment is necessary. Common treatment for this complication is experimental and done using acetylsalicylic acid or non-steroidal anti-inflammatory drugs. Corticosteroids

are prescribed in the case of contraindications or failure to respond to these treatments (10-13). In recent years, the preventive modalities for this complication are under study and evaluation. Colchicine is one of the drugs under consideration for primary prevention. This drug was initially used in the study by Finkelstein et al, to reduce PPS occurrence in 163 patients having undergone open heart surgery. It was administered since the third day after surgery for one month, and in a three-month follow-up. It was specified that colchicine outperformed in favor of reducing post-pericardiotomy syndrome (9). Likewise, Imazio et al studied the effect of colchicine on treatment and prevention of PPS and concluded that colchicine reduced the occurrence of early postoperative pericardial and pleural effusion in cardiac surgery patients. Additionally, Mack et al analyzed all the papers published during 1966–2011, regarding the effect of colchicine on treatment and prevention of PPS as a systematic review. However, no adequate data indicating colchicine as a conventional treatment for PPS prevention in patients undergone open heart surgery was detected (1). In addition, Imazio et al in a systematic review, analyzed the effect and complications of colchicine for prevention of pericarditis in 127 related published papers (a total of 795 patients), and concluded that colchicine is effective and safe for primary and secondary prevention of pericarditis (14).

Objectives

Considering the fact that studies on colchicine had contradictory results, and while no other drug has been introduced for PPS prevention and treatment, we sought

to evaluate the effect of colchicine on the prevention of PPS in an intervention study with a six-month follow-up period in patients who underwent open heart surgery.

Patients and Methods

Study design

In this double-blind clinical trial study, 240 patients underwent open heart surgery (2013 to 2014) in Amir-Almomnin hospital, Arak, Iran. Participants were randomly assigned to treatment by a central computer-based, automated sequence. All participants and trial investigators were blinded to randomized treatment. Age of more than 18 years and the indication of open heart surgery were the study inclusion criteria. Patients with a contraindication of colchicine, such as severe liver disease or high levels of liver enzymes, serum creatinine of greater than 2.5 mg/dL, heart failure, anemia, gastrointestinal disease, pregnancy and breastfeeding, and known sensitivity to colchicine or recent intake of this drug were excluded from the study. The case group received colchicine on the first day after surgery at the dose of 1 mg twice per day for first day, and then received 1 mg daily for one month in patients more than 70 kg and 0.5 mg in patients less than 70 kg. The control group received placebo. All patients were evaluated by clinical examination, ECG monitoring, chest X-ray and echocardiography at one day after surgery at the time of discharge and one month and also six months after discharge by a cardiologist unaware of the treatment groups. The flowchart of the patients included in the study is shown in Figure 1.

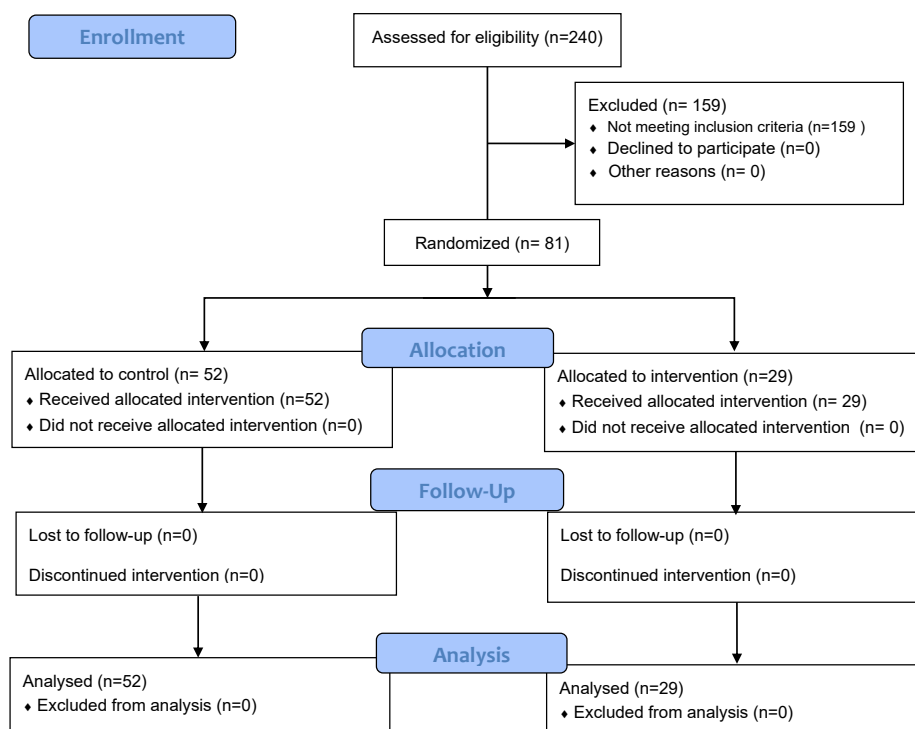


Figure 1. Flowchart of the study.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was approved in the Ethics committee of Arak University of Medical Sciences (#IR.ARAKMU.REC92-148-11). The trial study was also approved in the Iranian Clinical Trials Registry identifier: IRCT20141209020258N70; <https://irct.ir/trial/28142>). Accordingly, informed consent was obtained from the patients. This study is the result of the residential thesis by Navidreza Mashayekhi (Thesis# U-925).

Statistical analysis

After collecting the necessary data, they were analyzed using SPSS 18 software. Accordingly, t-test or its non-parametric equivalent (Chi-square test) and observation iteration test were used. The Fisher's exact test was applied, wherever appropriate. All *P* values were 2-tailed, and the values of less than or equal to 0.05 were considered statistically significant.

Results

This study showed that the two groups had identical

Table 1. Comparison of quantitative variables at the beginning of research in two groups

Variable	Colchicine (n=29)	Placebo (n=52)	<i>P</i> value*
Age (y)	64.1±9.2	59.2±10.1	0.08
BMI (kg/m ²)	27.6±2.1	26.3±1.9	0.4
Pump time (min)	88.5±22.5	86.3±26.1	0.6
Cross clamp time (min)	55.5±19.2	52.6±16.3	0.14
Serum creatinine (mg/dL)	1.3±0.3	1.1±0.2	0.3

BMI; body mass index.

Data are presented as Mean±SD. * *t* test independent.

Table 2. Comparison of frequency distribution of qualitative variables at the beginning of research

Variable	Group		<i>P</i> value*	
	Colchicine (n=29)	Placebo (n=52)		
Gender	Male	12 (42.3)	22 (43.1)	0.34
	Female	17 (57.7)	30 (56.9)	
Medical history	Hypertension	20 (69.4)	35 (67.2)	0.58
	Diabetes	7 (25)	12 (22.7)	
	Smoking	3 (11.9)	8 (15)	
	Previous MI	6 (21.6)	10 (19.3)	
Drugs	β-Blockers	17 (57.7)	29 (55.8)	0.47
	Amiodarone	3 (10.2)	4 (7.9)	
	ACE Inhibitors/ARBs	14 (47.9)	29 (55.6)	
	Other drugs	12 (39.8)	24 (45.2)	
NYHA functional class	II	20 (68.4)	29 (63.5)	0.59
	III	6 (22.3)	12 (23.6)	
	IV	3 (9.3)	7 (12.9)	
Type of surgery	CABG	27 (93.2)	49 (96.2)	0.9
	Valvular diseases	1 (3.4)	1 (1.9)	
	Aortic disease	1 (3.4)	1 (1.9)	
Method of surgery	On pump	29 (100)	52 (100)	0.9
	Off pump	0 (0)	0 (0)	

Data are presented as No. (%).

*Chi-square.

distribution at the beginning of the study in terms of some confounding and intervening variables based on independent group's *t* test (Table 1).

Additionally, comparison of frequency distribution of qualitative variables such as gender ratio, patient functional class according to NYHA classification and some other qualitative variables at the beginning of research (based on chi-square test) are presented in Table 2.

The occurrence of PPS, based on the presence of at least two criteria of fever of unknown origin, pleuritic chest pain, friction rub, constrictive pericarditis, cardiac tamponade, atrial fibrillation, and occurrence or exacerbation of pericardial effusion and pleural effusion, was 12.1 percent (*n* = 29) in colchicine group versus 21.6 percent (*n* = 52) in placebo group (*P* < 0.05). Occurrence of primary and secondary consequences of PPS was studied during hospitalization, one and six months later. The results are given in Table 3.

Likewise, the incidence of PPS showed no significant difference regarding the time immediately and one week after surgery in two groups (*P* > 0.05; Kaplan-Meier curve), however in the second week up to one month later, it was significantly lower in the colchicine group (*P* < 0.05) while it was stable in both groups in the third to the sixth months of follow up (Figure 2).

The most prevalent complication of colchicine was gastrointestinal complications. The frequency distribution of other complications is illustrated in Table 4.

Discussion

In this double-blind clinical trial study, we sought to determine the effect of colchicine on the prevention of post-pericardiotomy syndrome. We found both groups

Table 3. Occurrence of consequences and diagnostic criteria of PPS within six months

Variable	Group		P value*	
	Colchicine (n=29)	Placebo (n=52)		
Primary outcomes	Fever of unknown origin for more than a week	1(3.3%)	2(3.9%)	0.38
	Pleuritic chest pain	1(3.9%)	7(12.8%)	0.002
	Friction rub	1(2.7%)	4(8.3%)	0.001
	Pleural effusion	4(12.2%)	13(25.6%)	0.001
	pericardial effusion	4(12.8%)	12(22.8%)	0.002
	Atrial fibrillation	7(23.9%)	13(25.7%)	0.059
	Cardiac tamponade	1(0.06%)	1(1.7%)	0.237
Secondary outcomes	Constrictive pericarditis	0(0%)	0(0%)	0.9
	Recurrent pleural or pericardial effusion	1(0.9%)	1(2.1%)	0.001
	Readmission because of PPS	2(2.2%)	3(6.2%)	0.003
Mortality	1(1.3%)	1(1.9%)	0.592	

Data are presented as No. (%).

*Chi- square.

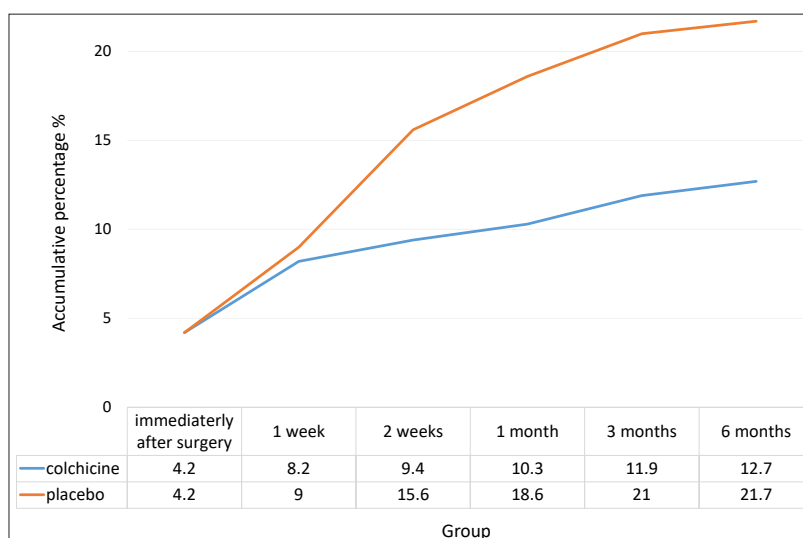


Figure 2. Accumulative percentage of post-pericardiectomy occurrence in terms of time.

had identical distribution at the beginning of the study regarding the distribution frequency of qualitative and quantitative variables, and homogeneity of both groups regarding possible confounding variables. Functional level of patients before surgery was generally at class 2 of New York classification, and the most prevalent reason for surgery was coronary artery bypass graft (CABG). The disease was a little more incident in women, but the difference was not significant. Overall, PPS occurrence in all the subjects was 33.7% (n = 81), 12.1 % (n = 29) in the colchicine group and 21.6 percent (n = 52) in placebo group.

In the six-month follow-up, fever, constrictive pericarditis, cardiac tamponade, and atrial fibrillation had identical occurrences in both groups, but pleuritic chest pain and friction rub occurred less in the colchicine group. Regarding the secondary outcomes, recurrence and re-hospitalization were less in the colchicine group, but showed no change in mortality in both groups.

PPS occurrence in terms of time, immediately after surgery and one week after surgery showed no significant

difference in both groups. However, in the second week up to one month later, it was lower in the colchicine group, while a stable and similar trend was observed in both groups during the third month to the sixth month.

The most prevalent complication of colchicine was gastrointestinal disorder. Using this drug with the dosage used in this work showed no life-threatening liver or kidney complications.

The results of this study are similar to those of most studies (15-22) suggesting the efficacy and safety of colchicine in preventing PPS. In a few studies, there are also different and contradictory results (23).

The potential efficacy of colchicine in preventing PPS was first introduced in 2002 (9). In this study, colchicine with a dose of 1.5 mg/day was compared to placebo, which began on the third day after surgery on 163 patients undergoing heart surgery since 52 patients (31.9%) were excluded from the study at the beginning of the trial due to postoperative complications or non-cooperation or gastroenteritis. During the next three months, 19 patients (17.1%) conflicted by PPS. From 19 patients, 5 were in the

Table 4. Side effects of colchicine in both groups

Complications	Group		P value
	Colchicine	Placebo	
Gastrointestinal*	5 (16.9)	3 (5.1)	0.001
Liver **	1 (1.7)	1 (0.9)	0.392
Renal ***	1 (2.2)	2 (3.8)	0.51
Other	6 (19.7)	5 (10.1)	0.001
Life threatening complications	0 (0)	0(0)	0.9

Data are presented as n (%).

* Incidence of diarrhea, nausea, vomiting and abdominal pain;

** Any abnormal increase in ALT and bilirubin higher than normal range;

*** Any increase beyond normal range in serum creatinine or abnormal GFR reduction.

colchicine group and 14 ones were in the placebo group. Results showed that colchicine is probably effective in PPS prevention, which is consistent with the findings in the current study.

No specific drug has been introduced currently for the treatment and prevention of PPS (24, 25). However, according to European guidelines on diagnosis and treatment of pericarditis (2004), colchicine is the first medical step for chronic pericarditis (class I indication) and it is a relatively common modality for treating acute pericarditis (class IIa indication) (26). Similarly, in the COPP study (6), colchicine was also introduced as an effective and safe drug for prevention and treatment of PPS. Our study showed that most complications of PPS (85%) occur in the first month after surgery. Therefore, using colchicine for 4 weeks does not provide serious complications; however the risk of gastrointestinal complications and especially gastroenteritis is high. Diarrhea is a common complication of this drug (10% of the patients) that can be controlled and reduced by adjusting the dose and choosing the right patient.

In the COOP2 study (27), colchicine had an acceptable preventive effect on this syndrome. However, similar to the results of our study, no reduction in the incidence of atrial fibrillation, pericardial effusion and pleural effusion was seen. The probability of gastrointestinal complications was also high in this study, while 20 percent of the patients were not able to continue the study,

The exact mechanism of colchicine subsiding of PPS is not still properly clear. However, its effects are mostly ascribed to inhibition and destruction of microtubules (28). Colchicine contributes to formation process of microtubules, and ultimately leads to establishment of colchicine - tubulin complex by formation of b-tubulin. This occurs in the mitotic phase or the interphase phase. Thus, colchicine leads to inhibition of intracellular granules and the release of various substances (29). By this mechanism, colchicine can inhibit various functions of leukocytes and finally anti-inflammatory function. In addition, colchicine is able to accumulate in leukocyte, thereby its concentration in leukocytes is 16 times higher than plasma levels. This mechanism influences its medical effects.

Various and different treatments have been utilized for PPS prevention including aspirin, corticosteroids, and colchicine. In a meta-analysis on 894 patients, colchicine was reported as an effective drug in preventing from this syndrome (25,30,31), while aspirin and corticosteroids have milder effects. In a single-center study with a sample size of 822 subjects treated with dexamethasone or placebo, it was found that corticosteroids had a little preventive effect on the appearance of PPS (32). However, administration of colchicine has been shown to have preventive effects on the simultaneous increase in C-reactive protein and the development of anti-inflammatory properties. This anti-inflammatory mechanism justifies that it should not be expected that colchicine influences all PPS complications such as atrial fibrillation or fluid effusion (8). On the other hand, this overall anti-inflammatory mechanism of colchicine justifies the occurrence of this syndrome at the first week after surgery in the current study, and later, the syndrome probability reduces with the emergence of anti-inflammatory effects. The occurrence of complications and non-cooperation of patients are the main obstacles to lack of early initiation of colchicine. However, considering the emergence of anti-inflammatory effects of this drug within two or three days, it is logical to start the drug up to two days before surgery with an adjusted dosage (6).

Postoperative atrial fibrillation is one of the most common complications after heart surgery and leads to increased morbidity, prolonged hospitalization and medical expenses (8-33). Pathophysiology of this fibrillation is also numerous and includes cases such as pericardial inflammation, disturbance of postoperative autoimmune balance and fluid shift (34-36). Microtubules play a significant role in the intracellular transmissions since colchicine is also effective in controlling this activity. On the other hand, colchicine influences the activity of neutrophils, and migration to the affected area (36). Therefore, it is expected that use of this drug is also effective in preventing fibrillation too. Additionally, other mechanisms may be involved in the development of this complication, which require separate recognition and intervention.

Conclusion

Administration of colchicine is effective in prevention of most complications and symptoms of post-pericardiotomy syndrome without any life-threatening complications. Of course, chance of patient non-compliance is high particularly due to gastrointestinal complications that can be controlled by adjusting the dose. In addition, the relatively high incidence of PPS at the first week after surgery in the placebo group may denote the anti-inflammatory mechanism of colchicine in preventing this syndrome and early prescription of this drug (for example, one week before elective surgeries) may be effective to prevent PPS.

Limitations of the study

According to low number of valve replacement surgery in this study, it was not possible to differentiate the incidence of PPS in subgroups of CABG against valve replacement. Also, due to the fact that the follow up period in this study was six months, it was not possible to investigate the incidence of late PPS complications. Likewise, multi-centered studies, studies with larger sample size and longer follow-up, or studies on specific groups and surgeries and conducting further meta-analysis are necessary for identifying the preventive effects of colchicine on PPS complications and symptoms.

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Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. NRM and AA designed the protocol of study. AS developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by AR, PS and NM. Analysis of data was performed by AR. All authors read and approved the final paper.

Conflicts of interest

The authors declare that they do not have any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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