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REVIEW ARTICLE

Effects of colchicine on pericardial diseases: a review of the literature and current evidence

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Colchicine, extracted from the colchicum autumnale plant, used by the ancient Greeks more than 20 centuries ago, is one of the most ancient drugs still prescribed even today. The major mechanism of action is binding to microtubules thereby interfering with mitosis and subsequent modulation of polymorphonuclear leukocyte function. Colchicine has long been of interest in the treatment of cardiovascular disease; however, its efficacy and safety profile for specific conditions have been variably established in the literature. In the subset of pericardial diseases, colchicine has been shown to be effective in recurrent pericarditis and post-pericardiotomy syndrome (PPS). The future course of treatment and management will therefore highly depend on the results of the ongoing large randomized placebo-controlled clinical trial to evaluate the efficacy and safety of colchicine for the primary prevention of several postoperative complications and in the perioperative period. Also, given the positive preliminary outcomes of colchicine usage in pericardial effusions, the future therapeutical use of colchicine looks promising. Further study is needed to clarify its role in these disease states, as well as explore other its role in other cardiovascular conditions.

Keywords: *Colchicine*; *Pericardial*; *Diseases*; *Pericardium*; *Cardiac*; *Review*

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Colchicine, an ancient drug prescribed even today, comes from a plant named colchicum (1). It is not only the drug of choice in inflammatory diseases like gout but also is prescribed in diseases like Behcet's disease, an anti-inflammatory disease (2, 3). The main mechanism of action of colchicine is by binding to microtubules which interferes with mitosis ultimately leading to dysfunctional polymorphonuclear leukocyte (3, 4). Other proven hypothesis regarding colchicine mechanism includes inhibiting the production of chemotactic factors and affecting the transcellular movement of collagen (3). Some studies also suggest that colchicine maybe involved in changing the binding characteristics of several membrane proteins, thereby making the proteins non-functional (3). Colchicine has long been of interest in the treatment of cardiovascular disease; however, its efficacy and safety profile for specific conditions have been variably established in the literature. In this review, we examine the literature and current evidences behind the most common usages in pericardial diseases.

Pericarditis

Acute pericarditis is a common, benign disease (Table 1). Presence of a pericardial friction rub, pleuritic chest pain with positional changes, and characteristic findings on ECG are specific for diagnosing pericarditis in the clinical setting. However, in developed countries like the United States, more than 80% of cases of pericarditis are idiopathic (5).

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Table 1. Acute/Chronic and Recurrent Pericarditis

Author, year	PMID	Study design	Sample	Follow-up (months)	Mean age (years)	Male (%)	Intervention (dosage, interval)	Primary outcome variable	Outcome measure	Secondary outcome variable	Outcome measure
Guindo J et al., 1990	2205414	Open-label prospective study	9	24.3	41.7	78	Colchicine (1 mg/day) daily	Difference between the symptom-free periods before and after treatment with colchicine	(p less than 0.002)	N/A	N/A
Adler Y et al., 1994	8184826	Open-label prospective study	8	3	42	62.5	Colchicine (1 mg/day) daily	Preventing recurrences of pericarditis	(p less than 0.0001)	N/A	N/A
Imazio M et al., 2005	16186437	COPE trial (prospective, randomized, open-label design)	120	18	56.9	47	Colchicine (1.0 to 2.0 mg for the first day and then 0.5 to 1.0 mg/day, for 3 months)	Recurrence rate	$p = 0.004$	Symptom persistence at 72 h	$p = 0.003$
Imazio M et al., 2005	16186468	CORE trial (prospective, randomized, open-label design)	84	20	51	34.5	Colchicine (1.0–2.0 mg the first day and then 0.5–1.0 mg/day, for 6 months).	Recurrence rate	$p = 0.02$	Symptom persistence at 72 h	$p = 0.03$
Imazio M et al., 2011	21873705	CORP trial (Prospective, randomized, double-blind, placebo-controlled multicenter trial)	120	18	47.5	45.5	Colchicine (1.0 to 2.0 mg on the first day followed by a maintenance dose of 0.5 to 1.0 mg/day, for 6 months).	Recurrence rate at 18 months	Absolute risk reduction, 0.31 [95% CI, 0.13 to 0.46]; relative risk reduction, 0.56 [CI, 0.27 to 0.73]	Symptom persistence at 72 h	Absolute risk reduction, 0.30 [CI, 0.13 to 0.45]; relative risk reduction, 0.56 [CI, 0.27 to 0.74]
Imazio M et al., 2013	23992557	ICAP trial (multicenter, double-blind trial)	240	3	52	60	Colchicine at a dose of 0.5 mg twice daily for 3 months for patients weighing >70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg	Incessant or recurrent pericarditis	Relative risk reduction in the colchicine group, 0.56; 95% confidence interval, 0.30 to 0.72; number needed to treat, 4; $p < 0.001$	Rate of symptom persistence at 72 h, the number of recurrences per patient, and the hospitalization rate	Rate of symptom persistence at 72 h ($p = 0.001$), the number of recurrences per patient ($p = 0.001$), and the hospitalization rate $p = 0.02$)

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Table 1 (*Continued*)

Author, year	PMID	Study design	Sample	Follow-up (months)	Mean age (years)	Male (%)	Intervention (dosage, interval)	Primary outcome variable	Outcome measure	Secondary outcome variable	Outcome measure
Imazio M et al., 2014	24694983	CORP-2 trial (multicenter, double-blind trial, randomized trial)	120	6	48	50	Colchicine (0.5 mg twice daily for 6 months for patients weighing more than 70 kg or 0.5 mg once daily for patients weighing 70 kg or less)	Recurrent pericarditis	Relative risk 0.49; 95% CI, 0.24 to 0.65; $p = 0.0009$	Symptom persistence at 72 h Remission at 1 week Incessant course	Symptom persistence at 72 h 53 (44.2%) 23 (19.2%) $p = 0.0001$ Remission at 1 week 71 (59.2%) 100 (83.3%) $p = 0.0001$ Incessant course 32 (26.7%) 10 (8.3%) $p = 0.0004$

Use of colchicine in patients with pericarditis is its most studied cardiovascular intervention. While it had been used for many years prior, it wasn't until 1990 when Guindo et al. first proved the usefulness of colchicine in patients with recurrent pericarditis (6). The open-label prospective study among nine patients who were treated with colchicine (1 mg/day) to prevent recurrences, showed a significant reduction in the frequency of recurrence rate. Interestingly, all patients previously had suffered at least three relapses despite treatment with other anti-inflammatories, such as prednisone, aspirin, or a combination of both. This was explained by authors as an action of colchicine independent of traditional anti-inflammatory pathways. This action of colchicine prevented recurrences although once the flare-up attack was controlled by a steroid, permitting the withdrawal of the steroid after a short period of treatment (6). Four years later, a similar study done on eight patients with recurrent pericarditis showed that in half of the patients, flare-up of pericarditis occurred when colchicine was stopped after a few months, without any alternative therapy, thereby stressing on the use of colchicine in preventing recurrent pericarditis. All of the patients who developed recurrent pericarditis developed it within 1 to 12 weeks (7, 8). One important limitation in this study was the number of follow-up months which was just three as compared with the previous study done by Guindo et al. which had a follow-up for 24 months. These preliminary results, however, needed to be verified in larger, randomized, placebo-controlled trials.

In 2005, the results of two important studies were made available, the CORE (COlchicine for REcurrent pericarditis) trial and the COPE (COlchicine for PEricarditis) trial (9). In the CORE trial, the effect of aspirin alone (or prednisone when aspirin was contraindicated) or aspirin plus colchicine was investigated in patients with first time recurrent pericarditis. The patients were randomly assigned to anti-inflammatory drugs, which were given for 3–5 weeks (progressively tapered), and colchicine (1 mg per day) for 6 months. The results were impressive with a significant effect. Recurrence rates at 18 months for the conventional treatment group was 50.6% while the rates for conventional treatment plus colchicine group was 24% ($p = 0.022$). This explained an important clinical benefit of colchicine over conventional treatment in patients with first time episode of recurrent pericarditis. In the same year, the COPE trial recommended prescribing colchicine not only for recurrent pericarditis but also after the first pericarditis attack (10). This trial conducted on 120 patients with a mean follow-up of 1.5 years reported significant recurrence rate reductions in patients with a first episode of acute pericarditis being treated with conventional treatment plus colchicine group (10.7%) to conventional group (32.3%) ($p = 0.004$).

These results confirmed those of a preliminary French study of 19 patients published in 1991 (11).

Since, then, multiple studies testifying for the efficacy of colchicine have been performed. The Colchicine for Recurrent Pericarditis (CORP) trial, done on 120 Italian patients with a first recurrence of pericarditis, reported a recurrence rate of 24 and 55% with colchicine group and placebo group, respectively. There was a significant relative risk reduction of 0.56 [CI, 0.27 to 0.73] when both groups were compared (12). Imazio and Adler, the scientists who have been working tirelessly since the past decade on colchicine and anti-inflammatories later suggested that aspirin and NSAIDs (non-steroidal anti-inflammatories) should be the mainstay of treatment for acute and recurrent pericarditis with the possible adjunct of colchicine, especially for recurrences (13). Their past trials also showed that colchicine use was associated with a reduced risk of pericarditis during follow-up either for primary or secondary prevention without a significant higher risk of adverse events compared with a placebo (14).

In the recent years, Imazio et al. concluded that the data from controlled clinical studies supported the use of colchicine as effective, efficient, and safe means of treatment in recurrent pericarditis. They, however, suggested that there was less evidence that supported the use of colchicine in the treatment of acute pericarditis (15). Similar studies evaluating the current evidence from different prospective, randomized, controlled trials suggested a role for colchicine in the secondary prophylaxis for recurrent pericarditis (16). A recently concluded trial and a continuation of the CORP trial (CORP-2) with 240 patients who were being treated in colchicine and placebo groups (120 patients in each group) reported recurrent pericarditis in 26 (21.6%) and 51 (42.5%) patients, respectively, with a significant clinical difference (relative risk 0.49; $p = 0.0009$), which spoke highly of the use of colchicine in these patients (17). Conversely, in other trials, pretreatment with corticosteroids substantially attenuated the efficacy of colchicine, leading to significantly longer therapy periods and more recurrences (18). This hypothesis was tested in a large multicenter all-case analysis. The results suggested that there were significantly more relapses after colchicine treatment as compared to those with previous corticosteroid treatment. The authors of the study suggested that pretreatment with corticosteroids exacerbates and extends the course of recurrent pericarditis (19). However, over the recent years, large randomized controlled trials have shown that colchicines had statistically significant beneficial effect on the hospitalization rate ($p = 0.02$), on symptom persistence at 72 h ($p = 0.001$), and the number of recurrences per patient (20). Thus, this has been the main topic of debate – whether to use colchicine with or without anti-inflammatories in recurrent pericarditis? While colchicine should be recommended for the prevention of recurrent pericarditis, questions concerning the long-term usage of colchicine in patients having pretreatment with corticosteroids need to be further elucidated.

In conclusion, many recent trials evaluating the role of colchicine with and without addition of aspirin or NSAIDs in the treatment of acute pericarditis and prevention of recurrence are still pending. Till then, colchicine should probably be regarded as a first-line treatment in the absence of contraindications (21).

Postpericardiotomy syndrome

Postpericardiotomy syndrome (PPS), occurring in 10–45% of patients after a cardiac surgery, is a common complication, developing in days to months after pericardial injury which can often lead to disability (Table 2) 22–25.

Use of colchicine in PPS is not well studied. In a small randomized trial in 2002, colchicine was not shown to be clinically effective at preventing PPS (26). However, in 2010, COPPS Trial reported that colchicine significantly reduced the incidence of the PPS compared with placebo at 12 months' interval. These initial results were encouraging and were a huge development since no drug had been proven efficacious and safe enough to prevent PPS (27). There was also no known optimal method of prevention of PPS. A meta-analytic pooling showed that colchicine was associated with decreased risk of PPS (OR 0.38, 0.22 to 0.65); however, the clinical evidence for primary prevention of PPS was limited to a few studies of variable quality, leading to individual biases among different studies. Nevertheless, available data at that time suggested a beneficial profile for colchicine (28). Follow-up studies did not confirm the results of COPPS trial, suggesting that the use of colchicine as primary prophylaxis in PPS is indeterminate; thus, colchicine should not be recommended routinely until large, randomized, controlled trials confirm the efficacy of colchicine (16, 29). However, many studies favoring the use of colchicine in PPS have recently been published with the most influential being a meta-analysis study which showed a lower incidence of PPS with a 56.6% relative risk reduction in colchicine group as compared with the conventional therapy group. The reduction in the incidence of pericarditis alone was even more striking in this study with a relative risk reduction rate of 57.4% (30).

The future course of treatment and management will therefore highly depend on the results of the COPPS-2 trial (COlchicine for prevention of the Post-pericardiotomy Syndrome and Post-operative Atrial Fibrillation) which will be the first large randomized placebo-controlled clinical trial to evaluate the efficacy and safety profile of colchicine for the prevention of several postoperative complications and in the perioperative period. This trial

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Table 2. Post-pericardiotomy syndrome

Author, year	PMID	Study design	Sample	Follow-up (months)	Mean age (years)	Male (%)	Intervention (dosage, interval)	Primary outcome variable	Outcome measure	Secondary outcome variable	Outcome measure
Finkelstein Y et al., 2002	12574898	Prospective, randomized, double-blind design	163	1	63.5	73	Colchicine (1.5 mg/day) or placebo for 1 month	Prevention of PPS in patients after cardiac surgery	($p < 0.135$)	N/A	N/A
Imazio M et al., 2010	20805112	COPPS trial (multicenter, double-blind, randomized trial)	360	12	65.7	66	Colchicine (1.0 mg twice daily for the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients $\geq$70 kg, and halved doses for patients $<$70 kg or intolerant to the highest dose)	Incidence of PPS at 12 months	$p = 0.002$; number needed to treat = 8)	Combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses	$p = 0.024$
Imazio M et al., 2013	23816016	COPPS-2 (multicenter, double-blind, placebo-controlled randomized trial)	360	1	N/A	N/A	Colchicine (0.5 mg twice a day for 1 month in patients weighing $\geq$70 kg and 0.5 mg once for patients weighing $<$70 kg or intolerant to the highest dose)	Incidence of PPS, postoperative effusions, and POAF at 3 months after surgery	N/A	Incidence of cardiac tamponade or need for pericardiocentesis or thoracentesis, PPS recurrence, disease-related admissions, stroke, and overall mortality	N/A

will evaluate the possible benefit of the early use of colchicine, starting before cardiac surgery, potentially providing stronger evidence to support the use of preoperative colchicine without a loading dose to prevent several postoperative complications (31). Given these positive preliminary outcomes, the future therapeutical use of colchicine looks promising and deserves to be studied further.

Effusions

Postoperative effusions (including pleural or pericardial) are relatively common after cardiac surgery complication (Table 3). Most of these effusions are perioperative, occurring within the first week as a direct consequence of the surgical procedure ('non-specific effusions'). They usually follow a benign course 32–34. Nevertheless, large symptomatic effusions may require medical therapy. As with PPS, use of colchicine in postoperative effusions have not yet been well studied. However, there have been some trials that have studied these uses to a limited scale.

A substudy of the COPPS trial suggested that colchicine significantly decreased the incidence of postoperative pericardial (relative risk reduction 43.9%) and pleural effusions (relative risk reduction 52.3%) as compared with the control subjects, despite similar baseline values (35). Case report–level literature has also shown effectiveness of colchicine even in large postoperative pericardial effusions with life-threatening complications, as compared with other drug therapies (36, 37). However, apart from the aforementioned large randomized trial and a few case reports, the effect of colchicine on effusions has not been extensively studied. Given these positive preliminary outcomes, the future therapeutical use of colchicine looks promising and deserves to be studied further.

Conclusion

Colchicine is an old drug with a well-established safety profile used in a variety of diseases that is becoming a drug of interest in cardiovascular diseases. In the subset of pericardial diseases, colchicine has been shown to be effective in recurrent pericarditis and to some extent in PPS. The future course of treatment and management will therefore highly depend on the results of the ongoing large randomized placebo-controlled clinical trial to evaluate the efficacy and safety of colchicine for the primary prevention of several postoperative complications and in the perioperative period. Given the positive preliminary outcomes of colchicine usage in pericardial effusions, the future therapeutical use of colchicine looks promising. Further studies are needed to clarify the role of colchicine in these disease states, as well as to explore its other roles in different cardiovascular conditions.

Table 3. Pericardial Effusions

Author, year	PMID	Study design	Sample	Follow-up (months)	Mean age (years)	Male (%)	Intervention (dosage, interval)	Primary outcome variable	Outcome measure	Secondary outcome variable	Outcome measure
Imazio M et al., 2010	20805112	COPPS trial (multicenter, double-blind, randomized trial)	360	12	65.7	66	Colchicine (1.0 mg twice daily for the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥ 70 kg, and halved doses for patients < 70 kg or intolerant to the highest dose)	Incidence of PPS at 12 months	$p = 0.002$; number needed to treat = 8	Combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses	$p = 0.024$

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