

Colchicine's promise in post-ablation atrial fibrillation: a meta-analysis

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Abstract

Introduction: Catheter ablation for restoration of sinus rhythm is limited by the high rates of arrhythmia due to inflammation caused by the procedure. Colchicine, a microtubule polymerisation inhibitor, reduces inflammation and may decrease atrial arrhythmia recurrence. We conducted a meta-analysis of RCTs and observational studies to assess the efficacy of colchicine in reducing atrial fibrillation (A fib) recurrence and pericarditis.

Methods: We identified seven studies through the systematic search of the PubMed, Embase, and Cochrane databases from inception to March 2024. Eligible articles had to be RCTs or observational studies comparing the effectiveness of colchicine with placebo in patients who underwent catheter ablation. Outcomes included A fib recurrence, atrial tachycardia, need to perform cardioversion or re-ablation, gastrointestinal (GI) adverse effects, pericarditis, and repeat hospitalisation. A random effects model was used to analyse binary outcomes, and the Mantel-Haenszel method was used to calculate the odds ratio with a 95% confidence interval.

Results: Data from 2165 patients were analysed. Colchicine reduced A fib OR = 0.61 ($p = 0.001$), pericarditis OR = 0.54 ($p = 0.07$), and the need for re-ablation OR = 0.53 ($p = 0.36$). However, it increased GI adverse effects OR = 3.15 ($p = 0.008$). There was no statistical difference in the need for cardioversion, repeat hospitalisation, and atrial tachycardia between the two groups.

Conclusions: Although colchicine significantly reduced the recurrence of A fib, further investigation is needed for a comprehensive understanding of the efficacy of colchicine in patients with catheter ablation.

Key words: atrial fibrillation, atrial tachycardia, catheter ablation, colchicine, meta-analysis, systematic review.

Introduction

Atrial fibrillation (AF), the most prevalent arrhythmia globally, affecting approximately 2–3% of the population, and it is linked to significant

morbidity and mortality [1, 2]. Catheter ablation has emerged as a widely accepted intervention for restoring sinus rhythm in AF patients [3]. However, the challenge of recurrence remains, leading to prolonged hospital stays, increased morbidity and mortality rates, and escalating healthcare costs. These recurrences are often attributed to inflammatory responses incited during the procedure. Inflammation, while potentially beneficial for healing, can result in incomplete ablation lines, leading to iatrogenic arrhythmia, AF, and post-ablation pericarditis. The conventional approach to prevent arrhythmia recurrence after ablation involves the use of antiarrhythmic drugs, but these are often accompanied by some severe side effects.

Colchicine, a medication with anti-mitotic, anti-inflammatory properties, has been used historically for gout and autoimmune disorders. Preliminary evidence suggests that post-catheter ablation administration of colchicine may improve cardiovascular outcomes by reducing both early and late electrocardiographic AF recurrence and pericarditis. However, the lack of definitive trials and concerns regarding side effects, notably diarrhoea, has limited its widespread use. Furthermore, the efficacy of colchicine has shown inconsistencies across prior studies.

Therefore, this meta-analysis of randomised controlled trials (RCTs) was undertaken to comprehensively assess the efficacy and safety of colchicine versus placebo in preventing atrial fibrillation recurrence and pericarditis in patients undergoing catheter ablation.

Methods

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The meta-analysis was not registered on PROSPERO.

Search strategy and screening

We conducted a systematic search in the Cochrane, Embase, and PubMed databases from inception to March 2024. The specific search strategy used to obtain relevant studies has been included in Supplementary 3. Following the initial screening results, title and abstract screening was performed with subsequent full-text screening. The citations of relevant studies were also screened to find additional articles. Finally, we included 4 RCTs and 3 observational studies, as shown in the PRISMA flowchart in Figure 1. The screening process was performed by 2 investigators (IB and MA). Any discrepancies were resolved through discussion.

Selection criteria and study outcomes

Studies fulfilling the following criteria were included for analysis: (1) RCTs with colchicine or placebo intervention and observational studies; (2) patients who underwent catheter ablation for atrial fibrillation; (3) primary outcomes – recurrence of AF and post-ablation pericarditis; and (4) secondary outcomes – gastrointestinal (GI) adverse effects, need for rehospitalisation for cardiologic reasons, cardioversion, atrial tachycardia, and repeat ablation.

Studies excluded were duplicates, case reports or series, reviews, meta-analyses, letters to the editor, and publications with only abstracts available.

Data extraction

Six authors (IB, MA, GN, BK, ZT, and AA) independently extracted data from studies that met the inclusion criteria and recorded the findings in a designated Google Sheet. Extracted data encompassed details of the study design, including first author's name, publication year, country, event counts in the colchicine and placebo groups, GI adverse effects, intervention method, follow-up duration, surgical method, primary outcome, and population characteristics (median age, gender, BMI, congestive heart failure, diabetes mellitus [DM], smoking history, hypertension, and coronary artery disease). Disagreements were resolved through consensus between all authors.

To perform the analysis, the comprehensive R archive network-R (CRAN-R) software (R Statistical Software [4.1.2; R Core Team 2021]) was used. Means with standard deviations (SD), frequencies, and percentages of baseline comorbidities and demographics were reported. The Mantel-Haenszel with inverse variance method was used to calculate the pooled odds ratio, and a probability value of $p < 0.05$ was considered statistically significant. The “test for overall effect” was reported as a Z-value corroborating the 95% confidence interval (CI). Higgins I-squared (I^2) was determined to measure statistical heterogeneity where values of $\leq 50\%$ corresponded to low heterogeneity, while values $\geq 75\%$ indicated high heterogeneity. The quality of the RCTs was assessed using the Cochrane Risk of Bias Tool [4] and observational studies using the Newcastle-Ottawa Scale.

Additionally, subgroup analysis for RCTs and non-RCTs was performed. We used the inverse variance method with a random effects model. Heterogeneity among subgroups and across all studies was measured using Higgins I-squared, tau-squared, and p -value of Cochran's Q statistic. Furthermore, the χ^2 test was used to test for subgroup differences, and a p -value of less than 0.1 was considered significant.

Results

The search strategy retrieved a total of 142 references from three databases. Subsequently, 15 duplicates were identified and removed. The initial screening of titles and abstracts led to the exclusion of 116 references; the remaining 11 studies were deemed eligible for full-text review. After a thorough assessment, 4 RCTs and 3 observational studies were included in the analysis. A detailed breakdown of the study selection process, including the reasons for exclusion, is presented in the accompanying PRISMA flowchart in Figure 1.

The detailed forest plots, Egger's p -value, funnel plots, and heterogeneity tests are provided in Supplementary 4, Supplementary 5, Supplementary 6, and Supplementary 10, respectively.

Study and patient characteristics

Four RCTs (Benz *et al.* 2024 [5], Ahmed *et al.* 2023 [6], Deftereos *et al.* 2014 [7], Deftereos *et al.* 2012 [8]) and three Observational studies (Mohanty *et al.* 2023 [9], Campbell *et al.* 2023 [10], Iqbal *et al.* 2023 [11]) were included in the analysis, encompassing a cohort of 2165 patients, of whom 1150 were assigned as controls. The primary outcomes under investigation were AF recurrences; pericarditis whereas secondary outcomes were GI adverse effects, need for rehospitalisation for cardiologic reasons, cardioversion, atrial tachycardia, and need for repeat ablation procedures. A comprehensive

summary of the included studies is provided in Table I, and patient baseline characteristics are presented in tables within Supplementary 12.

AF recurrence

Data regarding atrial fibrillation recurrence were extracted from three RCTs and three observational studies comprising 1799 patients. The analysis revealed a statistically significant decrease in AF reoccurrence (OR = 0.6117 [0.4565; 0.8198], p -value = 0.0010). There was low heterogeneity among studies (I^2 = 23%). The forest plot is shown in Figure 2.

GI adverse effects

Analysis of data concerning GI Adverse effects from 1771 patients was extracted from six studies. Colchicine had a statistically significant increase in GI adverse effects (OR = 3.1541 [1.3491; 7.3740], p -value = 0.0080). High heterogeneity was observed among studies (I^2 = 79.5%). Figure 3 shows the forest plot of GI adverse effects.

Rehospitalization

Data were extracted from four studies, involving 1443 patients, and showed no statistically significant association with colchicine (OR = 1.0072 [0.6785; 1.4951], p -value = 0.9717). There was also no heterogeneity among studies (I^2 = 0.0%).

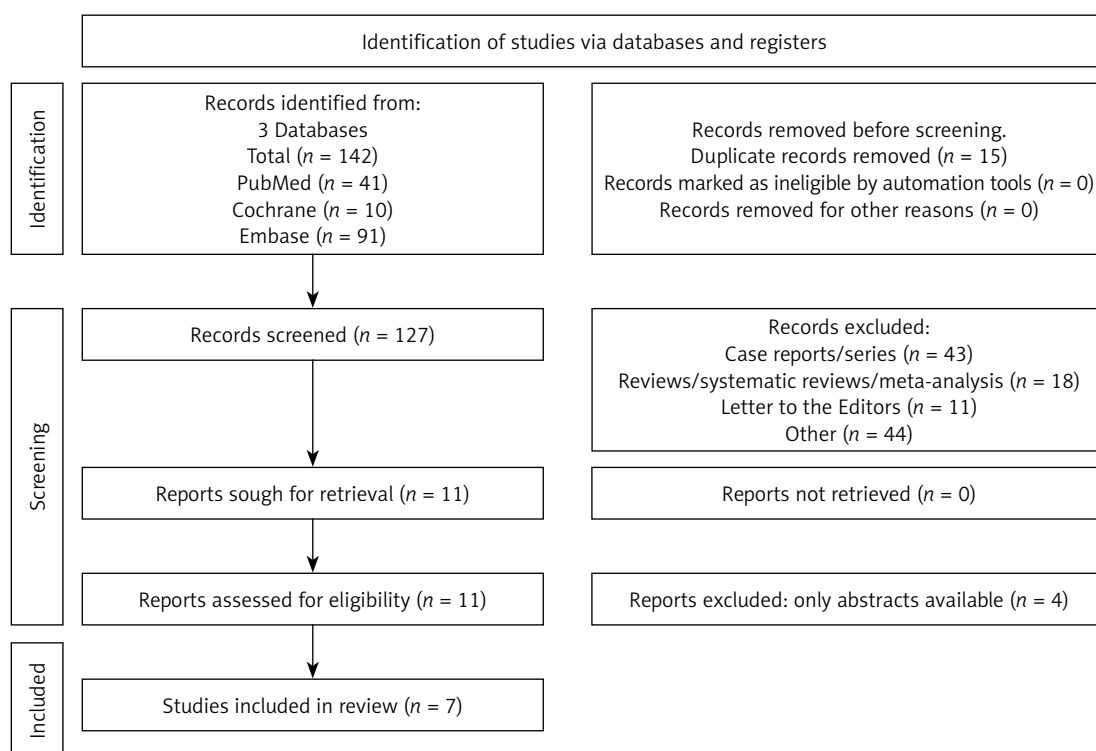


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram indicating the systematic identification, screening, and inclusion of studies

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Title	First author	Year of study	Type of study	Type of randomization	Total no. of patients screened	Total no. of patients enrolled		Intervention and dose	Duration of follow up	Control	Primary outcome	Secondary outcome
						Total	Intervention Group					
Colchicine to Prevent Atrial Fibrillation Recurrence After Catheter Ablation: A Randomised, Placebo-Controlled Trial	Benz [5]	2024	RCT	Double blinded	202	199	100	99	0.6 mg twice	10 days	Placebo	Atrial arrhythmia recurrence or AF associated clinical events Non-infectious diarrhoea, signs and symptoms of pericarditis, recurrence of AF, composite clinical endpoint (emergency department visit, hospitalisation for cardiovascular cause, cardioversion, repeat ablation for AF, atrial flutter or left-atrial tachycardia), all-cause mortality
Prophylactic Colchicine After Radiofrequency Ablation of Atrial Fibrillation: the PAPERS Study	Ahmed [6]	2023	RCT	Open Label	258	139	66	73	0.6 mg twice daily	7 days	Placebo	GI distress Pericarditis post-ablation pericarditis
Impact of Colchicine Monotherapy on the Risk of Acute Pericarditis Following Atrial Fibrillation Ablation	Mohanty [9]	2023	Non RCT	NA	4282	1075	607	468	0.3 mg twice daily	30 days	Placebo	Higher arrhythmia-free survival rate Lower risk of acute pericarditis and related hospitalization

Table I. Cont.

Title	First author	Year of study	Type of study	Type of randomization	Total no. of patients screened	Total no. of patients enrolled		Intervention and dose	Duration of follow up	Control	Primary outcome	Secondary outcome
						Total	Intervention Group					
Colchicine for the Prevention of Recurrent Arrhythmia After Catheter Ablation of Atrial Fibrillation: Results of a Single-Centre, Retrospective Study	Campbell [10]	2023	Non RCT	NA	180	180	90	0.6 mg daily	30 days	Placebo	AF recurrence	Hospitalisation
Colchicine usage for prevention of post atrial fibrillation ablation pericarditis in patients undergoing high-power, short-duration ablation	Iqbal [11]	2023	Non RCT	NA	294	205	104	0.6 mg twice daily	14 days	Placebo	Prevention of post-ablation pericarditis	Post-ablation chest pain, pericarditis, 30-day hospitalisation, ER visits, or AF recurrence or need of cardioversion
Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life	Deftereos [7]	2014	RCT	Double blinded	274	206	103	0.5 mg twice daily	3 months	Placebo	AF recurrence	Quality of life at 3 and 12 months
Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomised controlled study	Deftereos [8]	2012	RCT	Double Blinded	210	161	80	0.5 mg twice	3 months	Placebo	AF recurrence rate after the 3-month blanking period	Role of colchicine in the therapeutic management of patients undergoing catheter ablation for AF; GI side effects

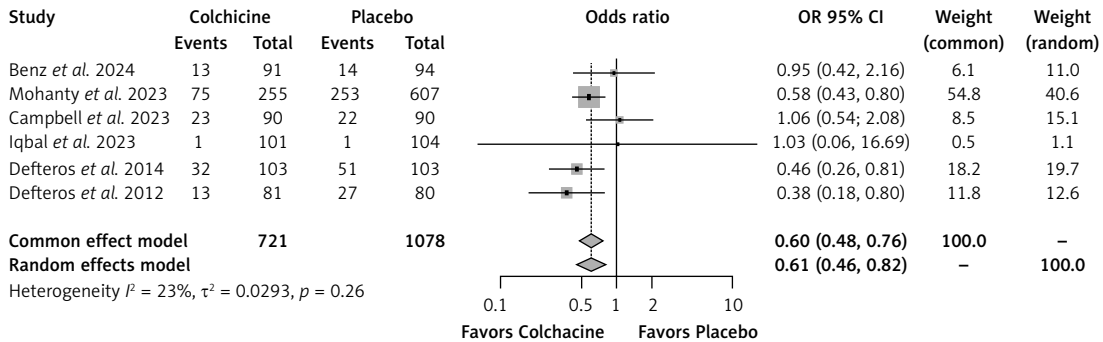


Figure 2. Forest plot of atrial fibrillation recurrence outcome and the odds ratio of colchicine when compared to placebo, both common and random effect models; the heterogeneity I^2 , τ^2 , and p -value for Cochran's Q statistic are also given

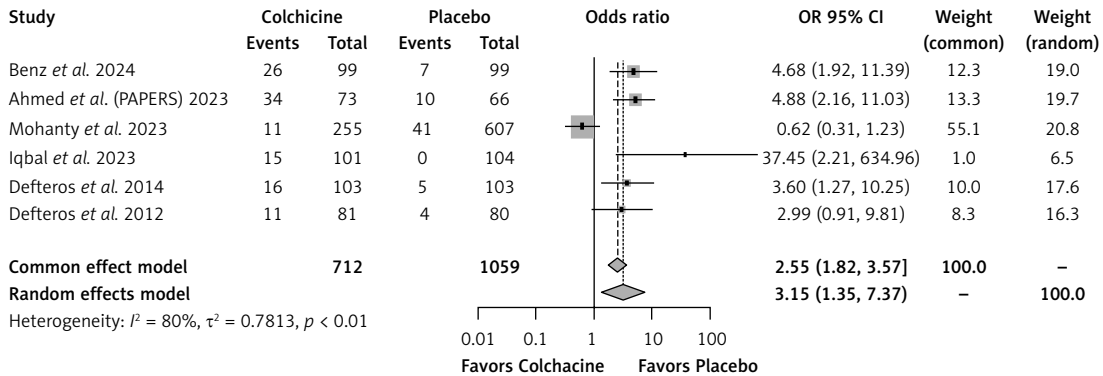


Figure 3. Forest plot of GI adverse effects outcome and the odds ratio of colchicine when compared to placebo using both common and random effect models; the heterogeneity I^2 , τ^2 , and p -value for Cochran's Q statistic are also given

Cardioversion

Analysis of cardioversion was performed on data extracted from two studies, encompassing a total of 404 patients. No statistically significant association was found (OR = 1.0204, p -value = 0.9559), and no heterogeneity was present among studies ($I^2 = 0.0\%$).

Pericarditis

Four studies were evaluated to assess data on pericarditis, involving 1404 patients. Colchicine use was found to be statistically insignificant with the rate of pericarditis (OR = 0.5384, p -value = 0.0715), and moderate heterogeneity was present among studies ($I^2 = 56.1\%$).

Atrial tachycardia

Analysis of data regarding atrial tachycardia was extracted from two studies, consisting of 365 patients. The occurrence of atrial tachycardia was found to be statistically insignificant (OR = 1.2655 [0.2047; 7.8244], p -value = 0.8000). Low heterogeneity was observed ($I^2 = 19.3\%$).

Repeat ablation

Two studies were extracted for data analysis of the need for repeat ablations, comprising 378 patients. The analysis of the data showed that colchicine decreased the need for re-ablation but was statistically insignificant (OR = 0.5294 [0.1354; 2.0697], p -value = 0.3605), while moderate heterogeneity ($I^2 = 61.2\%$) was observed.

Sub-group analysis

The studies were divided into two groups based on their study design. Group 1 consisted of four RCTs [5–8] whereas Group 2 comprised three observational studies [9–11]. The subgroup analysis was insignificant in all outcomes, which shows that the effect sizes of observational studies were similar to randomised controlled trials and that non-RCTs did not affect the quality of the meta-analysis. Detailed subgroup analysis is provided in Supplementary 7.

The risk of bias assessment of RCTs using the Cochrane ROB2 tool is given in Supplementary 8. The Newcastle Ottawa Scale used for observational studies is given in Supplementary 9.

Discussion

This systematic review and meta-analysis including seven studies analysed data from 2165 patients treated with colchicine.

Our findings are consistent with recent randomised trials, including Benz *et al.* (2024) and the PAPERS study, which demonstrated a reduction in early AF recurrence with colchicine therapy [5, 6]. However, the improved outcome observed in this pooled analysis appears greater, which may reflect differences in study design, inclusion of observational data, and variability in follow-up duration. These factors may also explain the lack of statistically significant effects observed in secondary outcomes such as atrial tachycardia and repeat ablation.

Post-ablation A fib is a common complication following cardiac ablation procedures. It is important to evaluate the efficacy of colchicine in managing post-ablation A fib [12]. Our meta-analysis demonstrates that colchicine significantly reduces recurrence of A fib after catheter ablation (OR = 0.61), supporting the hypothesis that post-procedural inflammation may contribute to the process of arrhythmogenesis. This may be explained by colchicine's inhibition of the NLRP3 (NOD-like receptor protein 3) inflammasome, a multiprotein complex responsible for activating interleukin-1 β and interleukin-18 [13]. Colchicine binds to tubulin, preventing microtubule formation. This disruption halts the spatial convergence of the NLRP3-ASC-caspase-1 complex. When caspase-1 activation is inhibited, interleukins are not converted to their active form [14]. Colchicine also directly inhibits ASC.

However, it is important to consider its GI adverse effects. Common GI adverse effects of colchicine include diarrhoea, nausea, vomiting, and abdominal pain. More severe adverse effects such as GI bleeding and ulceration can also occur, although they are less common [15].

Colchicine exerts its GI adverse effects through its inhibitory action on microtubule polymerisation, which disrupts the function of cells with a high turnover rate, such as the GI mucosa. The disruption of microtubule polymerisation leads to increased intestinal motility causing diarrhoea. Additionally, colchicine can directly irritate the GI mucosa, resulting in symptoms such as nausea, vomiting, and abdominal pain [16]. It is crucial for healthcare providers to thoroughly educate patients about the potential GI adverse effects of colchicine and to monitor them closely during treatment.

Furthermore, a high heterogeneity was noted in the outcome of GI adverse effects. The observed heterogeneity ($I^2 = 79.5\%$) may be due to variability in colchicine dosing regimens, duration of therapy, and patient tolerance and gut sensitivity across studies.

Our study had a few considerable strengths, which include analysis of a large patient population ($n = 2165$). We also included both observational studies and RCTs, enhancing generalisability while maintaining internal validity through subgroup consistency.

However, a few limitations should also be considered. Some of the outcomes had moderate to high heterogeneity. Secondly, the inclusion of observational studies introduces potential confounding despite consistent subgroup findings. Furthermore, an optimal colchicine regimen cannot be determined due to differences in colchicine dosing and treatment duration across studies. Several studies have reported on the potential benefits of colchicine in reducing the incidence of atrial tachycardia and other arrhythmias following ablation procedures, but the results of this study did not show any significant improvement in atrial tachycardia and arrhythmias. This can be considered as a limitation of this study because no conclusive results were found in these outcomes due to less statistical power [17].

The outcome of mortality was not reported in all studies, so this outcome could not be analysed. Mortality, especially pertaining to cardiac causes, is an important outcome because it validates the safety of such a drug as well as the prognosis of the disease. Hence, it should be used as an appropriate endpoint in trials of A fib [18].

Our findings suggest that colchicine may be beneficial in patients at higher risk of inflammation-mediated AF recurrence. However, its routine use should be individualised due to the increased risk of gastrointestinal intolerance and the absence of demonstrated benefit in several secondary outcomes. Future randomised trials should be conducted on a larger scale with a focus on stratified patient populations and standardised dosing protocols. Additionally, there is a need to further investigate other factors such as underlying diseases and potential drug interactions when determining the appropriateness of colchicine therapy for patients with post-ablation A fib.

In conclusion, the findings of this meta-analysis suggest that administering colchicine following catheter ablation is associated with reduced recurrence of A fib. Nonetheless, significant GI adverse events were associated with colchicine use. However, the results did not show significant differences in the occurrence of atrial tachycardia, or the need for rehospitalisation or cardioversion.

To conclusively establish these benefits and ascertain the optimal colchicine dosage and treatment duration for the patient population, further investigation is warranted through large-scale RCTs with well-defined patient subgroups.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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