Colchicine for Coronary Heart Disease: A Meta-Analysis of Randomized Controlled Trials

Chenchao Fu,1 Bin Wang2

1Department of Geriatrics, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China; 2Department Neurosurgery, The Affiliated Hospital of Southwest Medical University, Luzhou, Sichuan, China

ABSTRACT

Background: The efficacy of colchicine administration for coronary heart disease remains controversial. We conducted a systematic review and meta-analysis to explore the influence of colchicine administration versus placebo on treatment efficacy for coronary heart disease.

Methods: We have searched PubMed, Embase, Web of Science, EBSCO, and Cochrane Library databases through May 2021 for randomized controlled trials (RCTs) assessing the effect of colchicine administration versus placebo in patients with coronary heart disease. This meta-analysis was performed using the random-effects model.

Results: Six RCTs involving 6,321 patients were included in the meta-analysis. Overall, compared with control groups for coronary heart disease, colchicine intervention can significantly reduce major adverse cardiovascular events (odds ratio [OR] 0.74; 95% confidence interval [CI] 0.59 to 0.92; \( P = .006 \)), but revealed no obvious impact on mortality (OR=0.93; 95% CI 0.63 to 1.36; \( P = .69 \)), serious adverse events (OR 0.71; 95% CI 0.31 to 1.61; \( P = .41 \)), or restenosis (OR 1.02; 95% CI 0.63 to 1.64; \( P = .95 \)).

Conclusions: Colchicine treatment may be effective to reduce major adverse cardiovascular events in patients with coronary heart disease.

INTRODUCTION

Myocardial infarction has become a leading cause of mortality and morbidity, and percutaneous coronary intervention (PCI) is widely accepted as the most effective treatment strategy [Keeley 2003; Yang 2018; Russo 2018; Guo 2018; Echouffo-Tcheugui 2018]. Cardiomyocytes may be injured by acute restoration of myocardial blood flow [Ottani 2018; Cao 2018]. Vascular injury during PCI results in rapid neutrophil recruitment and subsequent inflammatory cascade that is associated with endothelial dysfunction and microvascular obstruction [Shu 2007; Aggarwal 2003]. Inflammation during PCI may also increase the risk of myocardial injury and mortality [Novack 2012].

Colchicine may have protective effects on coronary heart disease by inhibiting neutrophil chemotaxis and activity in response to vascular injury, active interleukin-1β (IL-1β) and neutrophil-platelet aggregates [Paschke 2013; Martinon 2006; Shah 2016]. A 2-dose regimen of colchicine (1.2 mg followed by 0.6 mg administered over an hour) showed rapid anti-inflammatory effects [Terkeltaub 2010]. In 1 randomized controlled trial (RCT) involving 4,745 patients, low-dose colchicine (0.5 mg once daily) after PCI resulted in a significantly lower risk of ischemic cardiovascular events than placebo [Tardif 2019].

Several studies have explored the efficacy of colchicine in patients with coronary heart disease, but the results were conflicting [Tardif 2019; Shah 2020; Akodad 2017]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of RCTs to investigate the efficacy of colchicine administration versus placebo for coronary heart disease.
extracted independently by 2 investigators, and discrepancies were resolved by consensus. We also contacted corresponding authors to obtain data when necessary.

The primary outcomes were mortality and major adverse cardiovascular events (defined as repeated revascularization, nonfatal myocardial infarction, and cardiac death). Secondary outcomes included restenosis and serious adverse events (including cardiovascular and noncardiovascular adverse events such as gastrointestinal event, infection, pneumonia, and septic shock).

Quality Assessment in Individual Studies
Methodological quality of the included studies was independently evaluated using the modified Jadad scale [Jadad 1996], which uses 3 items: randomization (0 to 2 points), blinding (0 to 2 points), and dropouts and withdrawals (0 to 1 point), for a maximum possible total of 5 points. An article with Jadad score ≤2 is considered to be of low quality, and Jadad score ≥3 suggests high quality [Kjaergard 2001].

Statistical Analysis
We estimated the odds ratio (OR) with 95% confidence intervals (CIs) for all dichotomous outcomes (mortality, major adverse cardiovascular events, restenosis and serious adverse events). The random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I2 statistic, and I2 > 50% indicated significant heterogeneity [Higgins 2002]. Whenever significant heterogeneity occurred, we searched for potential sources of heterogeneity by omitting 1 study in turn for the meta-analysis or performing subgroup analysis. Publication bias was not evaluated because of the limited number of included studies (<10). All statistical analyses were performed using Review Manager version 5.3 (The Cochrane Collaboration, Oxford, UK).

RESULTS

Literature Search, Study Characteristics, and Quality Assessment
Figure 1 is the detailed flowchart of the search and selection results. Initially, 348 potentially relevant articles were identified, and 5 RCTs were included in the final meta-analysis [Tardif 2019; Shah 2020; Akodad 2017; Zarpelon 2016; O’Keefe 1992; Tong 2020].

The baseline characteristics of the eligible RCTs in the meta-analysis are summarized in Table 1. The 6 studies were published between 1992 and 2020, and the total sample size was 6,321. Colchicine was administered at doses ranging from 0.5 to 2 mg daily. Among the 6 studies, 5 reported mortality [Tardif 2019; Shah 2020; Zarpelon 2016; Tong 2020; Briguori 2009], 3 reported major adverse cardiovascular events [Tardif 2019; Shah 2020; Tong 2020], 2 reported serious adverse events [Tardif 2019; Shah 2020], and 2 reported restenosis [Shah 2020; O’Keefe 1992]. Jadad scores of the 6 included studies varied from 3 to 5; thus all 6 studies were considered to be of high quality.

Primary Outcomes: Mortality and Major Adverse Cardiovascular Events
Outcome data were analyzed with the random-effects model, and the results suggest that compared with control groups for coronary heart disease, colchicine had no obvious
impact on mortality (OR 0.93; 95% CI 0.63 to 1.36; \( P = .69 \)), with no heterogeneity among the studies (I² = 0%, heterogeneity \( P = .56 \)) (Fig. 2), but significantly reduced major adverse cardiovascular events (OR 0.74; 95% CI 0.59 to 0.92; \( P = .006 \)), with low heterogeneity among the studies (I² = 5%, heterogeneity \( P = .35 \)) (Fig. 3).

**Sensitivity Analysis**

Low or even no heterogeneity was observed among the included studies for the primary outcomes; thus we did not perform sensitivity analysis.

**Secondary Outcomes**

Compared with control groups for patients with coronary heart disease, colchicine revealed no obvious impact on serious adverse events (OR 0.71; 95% CI 0.31 to 1.61; \( P = .41 \)) (Fig. 4) or restenosis (OR 1.02; 95% CI 0.63 to 1.64; \( P = .95 \)) (Fig. 5).

**DISCUSSION**

Anti-inflammatory therapy remains a promising option to reduce cardiovascular risk in patients with coronary heart disease. Preprocedural administration of high-intensity statin therapy has been documented to decrease myocardial injury and myocardial infarction in patients with acute coronary syndrome [Briguori 2009; Pasceri 2004; Patti 2007]. The anti-IL-1β antibody canakinumab was associated with reduced major adverse cardiovascular events by lowering IL-6 and high-sensitivity C-reactive protein concentrations in patients with prior myocardial infarction [Ridker 2017]. A rapid-acting anti-inflammatory agent may be beneficial for patients with myocardial infarction [Borden 2011; Silva 2006].

Colchicine, an anti-inflammatory agent, was traditionally used to treat gout, suppress neutrophil homotypic adhesion, modulate neutrophil deformability, decrease neutrophil extravasation, suppress an enzymatic component of the inflammatory, and reduce IL-1β and IL-6 [Paschke 2013]. Decreased levels of neutrophil-platelet aggregates were observed after

### Table 1 Characteristics of included studies

| No. | Reference | Colchicine group | Control group | Jadad Score |
|-----|-----------|------------------|---------------|-------------|
|     |           | \( N \) | Age (y) | Male (n) | History of myocardial infarction (n) | History of PCI (n) | Methods | \( N \) | Age (y) | Male (n) | History of myocardial infarction (n) | History of PCI (n) | Methods |
| 1   | Tong 2020 | 396 | 59.7 ± 10.2 | 322 | 59 | 51 | Colchicine 0.5 mg twice daily for the first month, then 0.5 mg daily for 11 mo | 399 | 60.0 ± 10.4 | 310 | 59 | 50 | Placebo | 5 |
| 2   | Shah 2020 | 206 | 65.9 ± 9.9 | 193 | 51 | 75 | Preprocedural oral administration of colchicine 1.8 mg | 194 | 66.6 ± 10.2 | 181 | 52 | 75 | Placebo | 5 |
| 3   | Tardif 2019 | 2,366 | 60.6 ± 10.7 | 1,894 | 370 | 392 | Colchicine 0.5 mg once daily after surgery | 2,379 | 60.5 ± 10.6 | 1942 | 379 | 406 | Placebo | 5 |
| 4   | Akodad 2017 | 23 | 60.1 ± 13.1 | 19 | - | 1 | Colchicine 1 mg once daily after surgery | 21 | 59.7 ± 11.4 | 16 | - | 1 | Placebo | 3 |
| 5   | Zarpelon 2016 | 71 | 61.5 ± 10.3 | 49 | 15 | 11 | Colchicine 1 mg orally, twice daily, preoperatively, and 0.5 mg, twice daily, until hospital discharge | 69 | 60.3 ± 8.1 | 46 | 17 | 9 | Placebo | 4 |
| 6   | O’Keefe 1992 | 130 | 59 | 111 | - | - | Colchicine 0.6 mg twice daily after surgery | 67 | 62 | 58 | - | - | Placebo | 4 |
colchicine intervention and improved outcomes after PCI [Nidorf 2007]. Our meta-analysis suggests that colchicine can substantially reduce the major adverse cardiovascular events in patients with coronary heart disease but reveals no obvious influence on mortality, serious adverse events, or restenosis.

Although there was no significant heterogeneity in this meta-analysis, different doses and methods of colchicine administration may have produced some bias. Colchicine was administered at doses ranging from 0.5 to 2 mg daily. Colchicine was found to decrease major adverse cardiovascular events for coronary heart disease, but there is no benefit of colchicine on mortality, which may be attributable to the low dose and only preoperative use of colchicine. In 1 RCT involving 140 patients with coronary heart disease, colchicine was used at a dose of 1 mg orally, twice daily, preoperatively, and 0.5 mg, twice daily until hospital discharge. The results revealed that colchicine was associated with a lower death rate compared with placebo (5.6% versus 10.1%) [Zarpelon 2016]. These data indicate that high doses may provide improved benefits to reduce mortality.

This meta-analysis has several potential limitations. First, our analysis is based on only 6 RCTs, and more RCTs with large samples should be conducted to confirm these results. Next, the doses and methods of colchicine intervention were different, which may have an influence on the pooling results. Finally, the ideal methods of colchicine intervention remain elusive.

Conclusions
Colchicine intervention may reduce major adverse cardiovascular events in patients with coronary heart disease.

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