Long-Term Care Updates

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Colchicine and Cardiovascular Diseases

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Introduction

Colchicine is an anti-inflammatory medication best known for treating gout. Its anti-inflammatory properties stem from its ability to inhibit microtubule polymerization and alter leukocyte responsiveness.[1] Considering inflammation plays an integral role in the development of cardiovascular (CV) diseases, there has been increased interest in the impact colchicine might have on CV outcomes. While many treatment options are already on the market with proven safety and efficacy for preventing and treating CV diseases, the risk of stroke, myocardial infarction (MI), and vascular death remain high.[2]

In this newsletter, we will discuss the safety and efficacy of colchicine on CV outcomes.

Clinical Evidence

The first study evaluating this relationship was a systematic review and meta-analysis assessing the safety and efficacy of colchicine on CV outcomes in any patient population and those with high CV risk (established coronary heart disease, secondary prevention of CV disease events). Investigators searched electronic databases for randomized control trials (RCTs) and pseudorandomized trials comparing colchicine to placebo, no treatment, or any other active treatment for a minimum of 6 months. The primary outcomes were all-cause mortality, MI, and adverse events. A total of 39 RCTs consisting of 4992 subjects met inclusion criteria; only 4 (n=1230) of which studied colchicine in a CV setting. A majority (69%) of these RCTs studied colchicine at doses $\leq$1mg/day, while most others studied doses of 1.2mg/day. Thirty studies (n=4174) evaluated all-cause mortality and had consistent results (I^2=27%), with colchicine showing no statistically significant effect (RR 0.94; 95% CI 0.82-1.09). MI was evaluated in 2 studies (n=652), and colchicine was associated with a significantly lower occurrence of MI relative to comparators (RR 0.20; 95% CI 0.07-0.57; $I^2 \leq$13%). Adverse events were reported in 11 studies (n=1313), with colchicine having no statistically significant effect (RR 1.52; 95% CI 0.93-2.46) and results being more heterogenous than the other primary outcomes (I^2=45%). However, colchicine was associated with significantly more gastrointestinal (GI) side effects in 11 studies (n=1258) compared to controls (RR 1.83; 95% CI 1.03-3.26), with results being highly heterogenous (I^2=74%). However, heterogeneity for this specific type of side effect was substantially reduced to 19% after removing one study that reported high GI events in both groups. Secondary outcomes included CV mortality, stroke, heart failure, non-scheduled hospitalizations, and non-scheduled CV interventions; however, colchicine only significant reduced non-scheduled hospitalizations for any reason relative to comparators (RR 0.87; 95% CI 0.77-0.99; I^2=0%), and this was reported from two studies (n=599).

Lower doses of colchicine (0.5 to 1mg/day) resulted in significantly reduced all-cause mortality ($p=0.03$) compared to higher doses (up to 2mg/day). Researchers concluded that colchicine may have substantial CV benefits, especially with regard to MI; however, there is enough uncertainty about its safety and efficacy in CV disease to warrant the need for large-scale trials before these results can be interpreted without caution.[3]

Further research on the efficacy of colchicine on CV outcomes was conducted in a more recent meta-analysis which focused only on patients with high CV risk. Investigators performed a literature search for clinical trials studying colchicine's impact on CV events between January 1990 and October 2019. The primary outcome was stroke incidence, and secondary outcomes included the occurrence of MI, all-cause mortality, and CV mortality. A total of 9 RCTs involving 6630 subjects met inclusion criteria, with 3359 in the treatment group and 3271 in the control group. Patient populations amongst studies consisted of those with stable coronary heart disease (3 studies), heart failure with reduced ejection fraction (1 study), postcardiac surgery (2 studies), and those after acute coronary syndrome (3 studies). Colchicine doses ranged from 0.5mg/day to 1mg/day. Six studies ($n=5958$) reported stroke incidence which was found to be significantly lower in the colchicine group compared to placebo (OR 0.33; 95% CI 0.15-0.70; $I^2=0\%$). No significant reduction difference in MI (OR 0.45; 95% CI 0.13-1.60; $I^2=73\%$), all-cause mortality (OR 0.85; 95% CI 0.60-1.42; $I^2=17\%$), nor CV mortality (OR 0.42; 95% CI 0.70-2.61; $I^2=58\%$) was observed between colchicine and placebo amongst 5 ($n=5598$), 9 ($n=6630$), and 6 studies ($n=5794$), respectively. Heterogeneity was only significant for MI ($p=0.03$), and side effects were not addressed. The authors concluded that while colchicine's tolerability and benefits should be confirmed in ongoing clinical trials, it could be considered for secondary prevention of atherosclerotic cerebrovascular disease, as it significantly reduced stroke risk in subjects with high CV risk.[2]

Most recently, one multi-center, double-blind, placebo-controlled RCT (LoDoCo2), which was not included in the previous meta-analyses, was published in August 2020 that looked at whether low-dose colchicine 0.5mg once daily prevented CV events in patients with chronic coronary disease. A total of 6528 eligible subjects participated in a one month open-label run-in phase, during which they received colchicine 0.5mg once daily. Of these subjects, 5522 who reported compliance and no unacceptable adverse effects and remained in stable condition and willing to participate were randomized to receive colchicine 0.5mg once daily ($n=2762$) or matching placebo ($n=2760$) for a median duration of 28.6 months. GI upset was the most common reason why subjects in the open-label run-in phase did not undergo randomization. All patients who were randomized were well treated at baseline with respect to their chronic coronary disease, with most or a majority taking an antiplatelet agent or anticoagulant (99.7%), a lipid-lowering agent (96.6%), a beta-blocker (62.1%), or a renin-angiotensin system inhibitor (71.7%). The primary outcome was a composite of CV death, spontaneous (non-procedural) MI, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary outcome was a composite of CV death, spontaneous MI, or ischemic stroke. The primary outcome occurred in 187 subjects (6.8%) in the colchicine group and 264 subjects (9.6%) in the placebo group, with colchicine having a 31% lower risk (HR 0.69; CI 0.57-0.83; $p<0.001$). The key secondary outcome occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group, with colchicine having a 28% lower risk (HR 0.72; 95% CI 0.57-0.92; $p=0.007$). Other secondary outcomes evaluated were the composite of spontaneous MI or ischemia-driven coronary revascularization, the composite of CV death or spontaneous MI, ischemia-driven coronary revascularization, spontaneous MI, ischemic stroke, death from any cause, and CV death. All other secondary outcomes except ischemic stroke and CV death were significantly lower in the colchicine group compared to placebo ($p\leq0.01$). On the other hand, death from any cause was higher in the colchicine group compared to placebo, but this was not statistically significant.[1] Hazard ratios and 95% CIs for the primary and secondary outcomes are outlined in Table 1 on the next page.

Table 1. Hazard ratios for CV events

Outcome	Colchicine n=2762	Placebo n=2760	HR (95% CI)	P Value
Primary Outcome				
CV death, MI, ischemic stroke, or ischemia-driven coronary revascularization	6.8%	9.6%	0.69 (0.57-0.83)	<0.001
Key Secondary Outcome				
CV death, MI, or ischemic stroke	4.2%	5.7%	0.72 (0.57-0.92)	0.007
Additional Secondary Outcomes				
MI or ischemia-driven coronary revascularization	5.6%	8.1%	0.67 (0.55-0.83)	<0.001
CV death or MI	3.6%	5.0%	0.71 (0.55-0.92)	0.01
Ischemia-driven revascularization	4.9%	6.4%	0.75 (0.60-0.94)	0.01
MI	3.0%	4.2%	0.70 (0.53-0.93)	0.01
Ischemic stroke	0.6%	0.9%	0.66 (0.35-1.25)	0.2
Death from any cause	2.6%	2.2%	1.21 (0.86-1.71)	NR
CV death	0.7%	0.9%	0.80 (0.44-1.44)	NR

NR=not reported

Non-CV death was the only adverse event that occurred more frequently in subjects taking colchicine compared to placebo (HR 1.51; 95% CI 0.99-2.31); however, this was not statistically significant. Additionally, while myalgia was reported more frequently in subjects on colchicine compared to placebo (HR 1.15; 95% CI 1.01-1.31), this adverse event was only collected from patients in the Netherlands. Researchers concluded that the occurrence of CV events was significantly lower with low dose colchicine compared to placebo in patients with chronic coronary disease, most of whom were already taking proven secondary prevention therapies.[1]

While each of the studies above came to diverse conclusions relative to colchicine's effect on specific CV outcomes, the fact that the results of all three were based on RCTs, minimizes the risk of bias and provides increased confidence in the investigators' findings. Additionally, results from the two meta-analyses provides increased power and a more precise estimate of colchicine's effect on CV outcomes. On the other hand, each study also has inherent limitations. In the first meta-analysis, while MI was significantly lower in subjects taking colchicine relative to comparators, this result was mainly driven by one study specifically designed for CV effects. Moreover, varying doses of colchicine and follow-up times were analyzed amongst the RCTs included in both meta-analyses. Lastly, the study population in LoDoCo2 was predominately male which reduces the generalizability of the study's results to females. The American College of Cardiology and American Heart Association's (ACC/AHA) clinical practice guidelines do not address colchicine's place in therapy for CV risk reduction.

Conclusion

Patients with a history of CV diseases, especially those who are elderly, are at increased risk for experiencing additional poor CV outcomes. Although the studies outlined demonstrated mixed results regarding colchicine's effect on MI, stroke, and CV death, it is clear colchicine exerts anti-inflammatory effects which have the potential to improve patient-oriented CV outcomes. Thus, it may be reasonable to consider adding colchicine as adjunct secondary prevention in patients with high CV risk.

References

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