The COLCOT Trial: Colchicine For Secondary Post–MI Prevention!

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Abstract

Inflammation has long been known to raise the risk of plaque rupture, leading to acute coronary syndromes [1]. Multiple trials have been done in the past to show the benefits of inflammation reduction [2]. The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) trial showed that canakinumab can lower cardiovascular events when compared to placebo, due to inhibition of interleukin 1B [3]. The LoDoCo (Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease) trial demonstrated that patients receiving 0.5 mg daily of colchicine had fewer cardiovascular events than patients who did not receive colchicine [4]. Thus, with heart disease being the number one cause of death in many parts of the world, and the well-established relationship between cardiovascular events and inflammation, the COLCOT (Colchicine Cardiovascular Outcome Trial) was conducted to evaluate the ability of colchicine to lower the risk of subsequent acute coronary events [5].

An old drug dating back to 1500 B.C. to treat joint problems, colchicine has indications for Familial Mediterranean Fever, gout, and pericarditis [6]. The COLCOT trial was conducted in 167 centers, across 12 nations, and was presented at the American Heart Association 2019 Scientific Sessions in Philadelphia, PA.

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Study Design:

- Randomized, double-blind clinical trial
- Median time of follow up: 22.6 months
- 4745 patients were recruited within 30 days of having a myocardial infarction
  - 2366 patients received 0.5 mg of colchicine daily
  - 2379 patients received placebo daily

Primary Endpoint: Time to first event including death from cardiovascular (CV) causes, cardiac arrest, myocardial infarction (MI), stroke, or hospitalization for angina leading to revascularization.

Secondary Endpoint: components of primary composite of CV death, cardiac arrest, MI or stroke.

Inclusion criteria:

- Men and women over 18 years old
- Myocardial infarction within 30 days of enrollment
- Completed any planned revascularization procedures
- On guideline-directed medical treatment, including statin

Exclusion criteria:

- LV EF < 35%
- Stroke within 3 months
- Type 2 MI
- CABG (within previous 3 years or planned)
- IBS or chronic diarrhea
- Neuromuscular disease

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- Nontransient creatinine kinase level > 3x ULN
- Nontransient hematologic abnormalities
- Significant hepatic or renal disease
- Chronic corticosteroid therapy
- Drug/EtOH abuse
- Sensitivity to colchicine

Results

The mean age was 61 years. Overall, 20% of total participants were female, and 20% of total participants were diabetic. A total of 93% of patients underwent PCI during the index MI. ASA, another antiplatelet drug, and statin were taken by 98.8%, 97.9%, and 99% respectively.

The primary efficacy outcome demonstrated:

- Cardiovascular death, myocardial infarction, stroke, resuscitated cardiac arrest, or urgent hospitalization for unstable angina leading to revascularization happened in 5.5% of the colchicines group, versus 7.1% of the placebo group (p = 0.02)

The secondary outcomes demonstrated:

- *Cardiovascular death*: 0.8% in the colchicine group versus 1% of the placebo group
- *Stroke*: 0.2% in the colchicine group versus 0.8% in the placebo group
- *Urgent hospitalization for revascularization*: 1.1% in the colchicine group versus 2.1% in the placebo group
- *Infection*: 2.2% in the colchicine group versus 1.6% in the placebo group
- *Diarrhea*: 9.7% in the colchicine group versus 8.9% in the placebo group

Discussion

Low dose colchicine has shown reduction in cardiac death, myocardial infarction, stroke, and urgent hospitalization when compared to placebo (5.5% versus 7.1% respectively). The side effects of colchicine were largely GI -related symptoms. The colchicine group did not have significantly more patients with diarrhea when compared to placebo (9.7% versus 8.9%). Despite the positive effect of colchicine on preventing recurrent major cardiovascular events in the COLCOT trial, more studies are needed before it can be recommended as part of the routine post–MI medical therapy. The positive effect of colchicine may be related to the overwhelming number of patients already on appropriate medical therapy (statins and antiplatelet therapy) and having received appropriate revascularization (93% of patients from each group). In addition, the relatively short follow up time of 23 months did not allow for comprehensive review of risks versus benefits of long term use of colchicine. Therefore, further larger studies with longer follow up time are needed to assess the side effects of colchicine and to study colchicine's effect in other high risk patients without recent ACS.

Clinical Implications

The findings from the COLOCT trial do not come as a surprise for many physicians, as the harmful effects of inflammation are well known and manifest in several ways. Reduction of inflammation has been the target of many recent atherosclerosis therapeutic regimens [7]. Although colchicine has shown promise in its ability to mitigate inflammation and reduce events post MI [8], the safety of its long term use for cardiac indications remains in question [9] and further studies are needed to establish a definitive role for its use in atherosclerosis.

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