

Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial

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Published online: 15 September 2011
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Abstract There is a need for more effective therapies to reduce morbidity and mortality from cardiovascular disease. Inflammation plays a central role in the pathogenesis of atherosclerosis but no randomized studies have evaluated anti-inflammatory therapy in patients with acute coronary or cerebrovascular disease. We performed a pilot randomized controlled trial comparing the effect of colchicine 1 mg per day with placebo on high sensitivity C-reactive protein (CRP) levels and platelet function in 80 patients with acute coronary syndrome or acute ischemic stroke who were followed for 30 days. Clinical status was ascertained for 74 (92.5%) patients and CRP levels were obtained in 68 (85%) of patients at follow up. Colchicine

did not significantly reduce absolute hs-CRP at 30 days [median 1.0 mg/l (range 0.2, 162.0) versus 1.5 mg/l (0.2, 19.8), $P = 0.22$] or difference in CRP from baseline to 30 days [absolute difference 7.0 mg/l (−61.0, 87.8) vs. 7.1 mg/l (−1.0, 144), $P = 0.64$]. The proportion of patients with CRP <2 mg/l at follow up did not differ according to treatment allocation (77% vs. 62%, X^2 1.84, $P = 0.18$). There was also no difference in platelet function assessed using platelet aggregation with ADP (5 μ mol), arachidonic acid (0.5 mmol), collagen (1 μ g/ml) and collagen (5 μ g/ml) ($P = 0.86$, $P = 0.64$, $P = 0.76$, $P = 0.20$, respectively), and urine dehydrothromboxane B2 ($P = 0.54$). Colchicine was associated with an excess of diarrhoea (X^2 4.14, $P = 0.04$). In conclusion, our pilot study provided no evidence that colchicine 1 mg daily for 30 days compared with placebo suppresses inflammation in patients with acute coronary syndrome or acute ischemic stroke.

Electronic supplementary material The online version of this article (doi:10.1007/s11239-011-0637-y) contains supplementary material, which is available to authorized users.

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Keywords Colchicine · Inflammation · Acute coronary syndrome · Atherothrombosis · Ischemic stroke

Introduction

Cardiovascular disease is expected to remain the leading cause of death worldwide during the next two decades despite the widespread use of effective primary and secondary preventive strategies [1]. One approach to further reduce the risk developing cardiovascular disease and prevent its complications is to identify and treat new or emerging risk factors.

Inflammation plays a central role in the pathogenesis of atherosclerosis [2]. Damage to the vascular endothelium by established cardiovascular risk factors such as

hypertension, dysglycemia, dyslipidemia and smoking triggers an inflammatory response leading to the influx of macrophages and lymphocytes, migration and proliferation of smooth muscle cells, secretion of cytokines and other mediators of inflammation that induce further damage. Rupture of an “inflamed” and unstable atherosclerotic plaque leads to exposure of sub-endothelial proteins and the release of tissue factor that results in platelet and coagulation activation and superimposed thrombus formation [2, 3].

High sensitivity C-reactive protein (hs-CRP) is a simple non-specific laboratory marker of inflammation that can be readily measured in most clinical laboratories. Consistent evidence from prospective cohort studies indicates that increasing baseline blood levels of hs-CRP are independently associated with increasing risk of future cardiovascular events [4–7], including patients with recent acute coronary syndrome (ACS). Blood levels of hs-CRP have been incorporated into risk prediction models [8] and elevated hs-CRP (>2 mg/l) levels have been used to identify individuals who may benefit from statin therapy even in the absence of hyperlipidemia [9]. However, a causal role for hs-CRP in the pathogenesis of atherothrombosis is unproven and it remains to be determined whether treatments that reduce hs-CRP or inflammation prevent cardiovascular events.

Colchicine is a simple, inexpensive yet potent anti-inflammatory drug that is approved for the management of patients with acute gout. The mechanism of action of colchicine has not been fully explored but it is reported to inhibit membrane expression of adhesion molecules on T cells and endothelial cells [10], synthesis of TNF α and IL6 [11], monocyte migration and secretion of matrix metalloproteinase-9 [12]. By disrupting the cytoskeleton, colchicine is believed to suppress secretion of cytokines and chemokines and in vitro platelet aggregation [13, 14]. More recent observational data have suggested that low-doses of colchicine suppress blood levels of hs-CRP in patients with stable coronary artery disease [15]. However, the effects of colchicine on hs-CRP have not been tested in a randomized controlled trial and it remains to be demonstrated that reducing inflammation prevents cardiovascular events.

We hypothesized that treatment of patients presenting to hospital with an acute vascular syndrome using low-doses of colchicine would reduce inflammation and thereby decrease the risk of subsequent cardiovascular events. To begin testing this hypothesis we performed a pilot randomized controlled trial to determine whether colchicine compared with placebo could suppress hs-CRP in patients admitted to hospital with either an acute coronary syndrome or acute ischemic stroke. We also examined whether colchicine suppresses platelet function.

Methods

Study design

The colchicine compared with placebo to reduce hs-CRP in patients with acute coronary syndromes or ischemic stroke—targeting inflammation in atherosclerosis (COOL) study was a double-blind pilot randomized controlled trial that compared 30 days of colchicine given at a dose of 1 mg once daily with placebo in patients with acute coronary syndrome or acute ischemic stroke. The study was registered at www.clinicaltrials.gov (NCT00754819).

Study patients

Adult patients (>18 years) admitted with a diagnosis of acute coronary syndrome were eligible for inclusion. In a subsequent protocol amendment prompted by slower than expected recruitment, the eligibility criteria were expanded to include patients with acute ischemic stroke. The diagnosis of acute coronary syndrome was based on meeting at least two of the following three criteria: ischemic chest pain occurring at rest or increasing in frequency and lasting >10 min; ECG changes of ischemia with ST elevation, ST depression or new left bundle branch block; or elevated cardiac biomarkers. Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 h. CT scan or MRI imaging results were reviewed for all patients with stroke to confirm the absence of haemorrhage prior to enrolment.

Exclusion criteria were hypersensitivity to colchicine; moderate renal dysfunction (creatinine clearance <50 ml/min) or hepatic dysfunction (ALT > 1.5 $\times$ upper limit of normal range); thrombocytopenia or leukopenia; pregnant or lactating women and women at risk of pregnancy. To reduce the risk of colchicine accumulation and toxicity we also excluded patients taking moderate-strong CYP3A4 inhibitors (Appendix A). Patients already taking colchicine, those with evidence of active infection or inflammatory conditions that might be associated with markedly elevated hs-CRP levels in the blood (e.g., active rheumatoid arthritis) and those taking other anti-inflammatory therapies (e.g., corticosteroids) were also excluded.

The study was conducted at the Hamilton General Hospital and was approved by the Institutional Review Board. All patients provided written informed consent.

Randomization

We used computer generated randomization with variable block sizes to assign patients in a 1:1 ratio to colchicine or placebo. Colchicine was over-encapsulated by an

independent trial pharmacist so that active drug and placebo had identical appearances, thereby blinding investigators, study coordinator and patients to treatment allocation. Patients were issued study drug immediately after randomization using sequentially numbered bottles of study drug. At enrolment patients were provided with a list of food and drugs that should be avoided during the study because of potential interaction with colchicine and a copy of the list was faxed to the patients' General Practitioner.

Follow up and outcome measures

All patients were contacted by telephone 5–7 days after discharge from hospital to ensure adherence and tolerability of the study drug. A final follow up appointment was scheduled at 30 days. Patients were encouraged to contact the investigators to report adverse or outcome events during the course of the study. An independent unblinded data and safety monitor reviewed adverse and outcome events after approximately one-third of patients had been enrolled.

The primary outcome was the blood level of hs-CRP at 30 days, measured by nephelometry (Cardiophase hs-CRP Dade Behring). Secondary outcomes were platelet function measured by turbidimetric platelet aggregometry (Chronolog Series 500 whole blood lumi-aggregometer) using ADP (5 μ mol), arachidonic acid (0.5 mmol) and collagen (1 and 5 μ g/ml) as agonists and urinary 11-dehydrothromboxane B2 concentrations by commercial enzyme linked immunosorbent assay. Secondary clinical outcomes were the occurrence of death, myocardial infarction or stroke at 30 days. We monitored the safety of colchicine by measuring a full blood count and creatinine kinase at the end of the study and by recording adverse events, particularly diarrhoea, myopathy, neuropathy and rhabdomyolysis.

Statistical analyses

The primary analysis aimed to compare the proportionate reduction in hs-CRP at 30 days in the colchicine versus placebo group using Student's *t*-test. Statistical significance was set at two sided alpha of 5%. Additional analyses comparing hs-CRP at 30 days and non-parametric analyses were added because of the skewed data and exploratory nature of the study. Similar analyses were planned for platelet aggregation and urinary 11-dehydrothromboxane B2 (11-dTXB2). The rates of clinical outcomes were compared using Chi square test. Analyses were performed according to the intention-to-treat principle.

We planned to enrol 80 patients estimating that this would provide 80% power to demonstrate a 40% reduction in hs-CRP, assuming a 10% study drug discontinuation rate.

Role of the funding source

The study was funded by Hamilton Health Sciences New Investigator Fund. The funding source was not involved in the planning, conduct or analysis of study data.

Results

Characteristics of the study patients

Between April 2008 and August 2009 we enrolled 82 patients. One patient with elevated ALT was erroneously enrolled before the results of liver function testing were available. He did not receive any study drug and declined follow up. A second patient withdrew consent to receive study drug after having been randomized but agreed to follow up by telephone to ascertain clinical and vital status. She did not receive study drug.

Of the remaining 80 patients, 40 were randomly allocated to receive colchicine and 40 were allocated to receive placebo. 73/80 (91%) had acute coronary syndrome and 7 (9%) had stroke. Baseline characteristics are summarized in Table 1. The mean age of the patients was 57 years (SD

Table 1 Characteristics of study patients

	Colchicine (<i>n</i> = 40)	Placebo (<i>n</i> = 40)
Mean Age (SD) (years)	57.2 (11.7)	57.2 (8.7)
Median Age (range) (years)	55.5 (37,83)	58.0 (42,77)
Male	34 (85)	37 (92.5)
Weight (kg)	89.8	90.4
Diagnosis, <i>n</i> (%)		
Unstable angina	8 (20)	3 (7.5)
Myocardial infarction	27 (67.5)	35 (87.5)
Ischemic stroke	5 (12.5)	2 (5)
Diabetes	7 (17.5)	6 (15)
Hypertension	19 (47.5)	15 (37.5)
Hyperlipidaemia	19 (47.5)	19 (47.5)
Previous angina or MI	8 (20)	6 (15)
Previous stroke	3 (7.5)	0 (0)
Peripheral vascular disease	3 (7.5)	1 (2.5)
Heart failure	1 (2.5)	0 (0)
Family history of premature heart disease	22 (55)	19 (47.5)
Smoking		
Current	18 (45)	17 (42.5)
Ex-smoker	13 (32.5)	15 (37.5)
Nonsmoker	9 (22.5)	8 (20)
Aspirin	40 (100)	40 (100)
Clopidogrel	34 (85)	34 (85)
Statin	40 (100)	38 (95)

10 years) and 89% were male. 78/80 patients received statin therapy.

Follow-up

Patient follow up was completed in September 2009. The mean duration of follow up was 31 days (SD 17 days). 74/80 (92.5%) patients completed follow up; 68 attended a follow up appointment and six were followed by telephone only as they either declined or repeatedly failed to present for clinical review and blood collection. Patients who declined to come in cited inconvenience because of distance or work as the primary reason. Of the remaining six

patients, four were lost to follow up and two withdrew citing excessive stress and refusing follow up (Table 2, Fig. 1).

Compliance with study drug was assessed by questionnaire and pill count for the patients attending follow up. (Table 2) In patients for whom complete adherence data were available, 54/68 took >90% and 57/68 took >70% of pills. Seven patients (five colchicine, two placebo) took <25% of study pills with two patients allocated to colchicine not taking any study drug. Reported reasons for non-compliance included adverse reactions (rash, $n = 1$; diarrhoea, $n = 3$), concomitant therapy that could interact with colchicine (Diltiazem, $n = 1$) and miscellaneous reasons ($n = 3$).

Table 2 Completeness of follow up and compliance according to drug allocation

	Colchicine	Placebo
All patients (n)	36	38
Mean follow up, days (SD)	28 (19)	34 (14)
Median follow up, days (range)	31 (30,59)	33 (30,71)
Patients with hs-CRP results at follow up (n)	31	37
Mean follow up, days (SD)	33 (7)	36 (9)
Median follow up, days (range)	31 (17,59)	34 (25,71)
Compliance (% pills taken) ^a (n)	31	37
>90%	22 (71%)	32 (86%)
<25%	5 (16%)	2 (5%)

^a Compliance for patients with hs-CRP at follow up only

Primary outcome

The lower limit of detection for hs-CRP was 0.2 mg/l; thus values below 0.2 mg/l have been analyzed as 0.2. Median hs-CRP at baseline was 9.9 mg/l (range 0.2, 168) and at follow up was 1.25 mg/l (0.2, 162). The change in hs-CRP from baseline value was not different between patients treated with colchicine or placebo [median absolute difference 7.0 (−61.0, 87.8) vs. 7.1 (−1.0, 144.0) mg/l; $P = 0.64$] (Table 3). One patient with an extremely high hs-CRP of 162 mg/l was hospitalized at the time of follow up. Removal of this outlying result did not materially change the results [median absolute difference 7.8 (−0.1, 87.8) vs. 7.1 (−1.0, 144); $P = 0.81$] (Fig. 2).

The absolute hs-CRP at 30 days was not significantly different between the two groups irrespective of whether this was evaluated by the t -test ($t = -0.90$, 95% CI

Fig. 1 Flow chart describing completeness of follow up

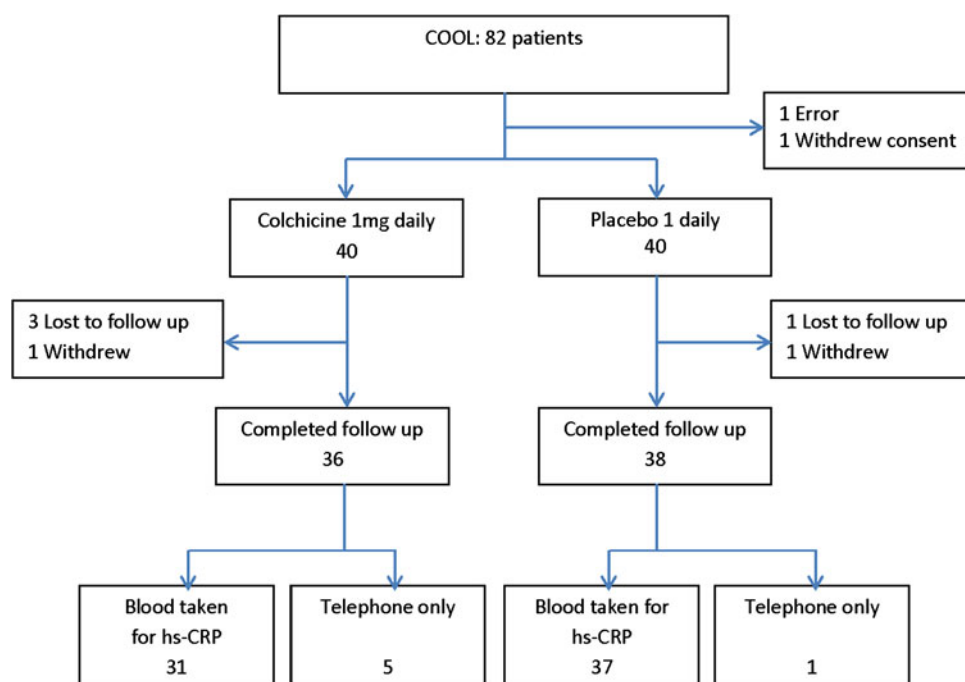
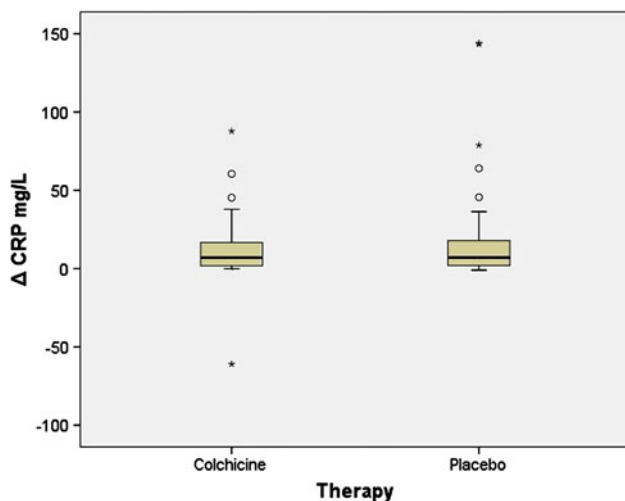


Table 3 C-reactive protein and platelet function results according to drug allocation

	Colchicine	Placebo	<i>P</i> value
Δ hs-CRP mg/l	<i>N</i> = 31	<i>N</i> = 37	
Median (range)	7 (– 61.0,87.8)	7.1 (– 1.0,144)	0.64
Mean (SD)	12.2 (23.9)	20.9 (34.9)	0.24
hs-CRP at follow up mg/l	<i>N</i> = 31	<i>N</i> = 37	
Median (range)	1.0 (0.2,162)	1.5 (0.2,19.8)	0.22
Mean (SD)	7.2 (28.9)	2.9 (4.6)	0.37
Follow up hs-CRP <2 mg/l			
<i>n</i> (%)	24 (77)	23 (62)	0.18
% Platelet aggregation	<i>N</i> = 22	<i>N</i> = 27	
Median (range)			
ADP	39.5 (9–91)	35 (0–75)	0.86
Arachidonic acid	2 (1–85)	2 (1–75)	0.64
Collagen 1 μ g/ml	17.5 (1–84)	19 (0–72)	0.76
Collagen 5 μ g/ml	64 (14–85)	59 (0–81)	0.20
Urine thromboxane B2	<i>N</i> = 27	<i>N</i> = 31	
Median (range)	49 (21–287)	52 (26–189)	0.54

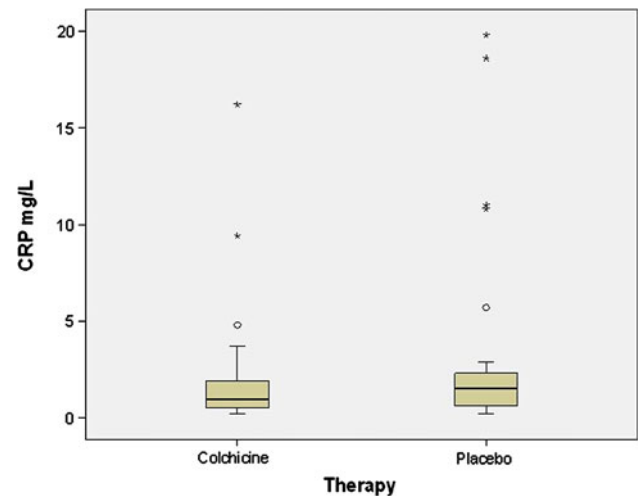
Δ hs-CRP difference in hs-CRP from baseline

**Fig. 2** Comparison of change in hs-CRP from baseline to follow up (Δ hs-CRP) between patients allocated to colchicine and placebo

–2–90,1.09; $P = 0.37$) or non-parametric analyses (median 1.0 (0.2,162.0) versus 1.5 (0.2,19.8) mg/l; Mann–Whitney test, $P = 0.22$ (Fig. 3).

Comparison of hs-CRP in patients compliant (taking >90% of study pills) with study drug also showed no difference in hs-CRP at 30 days (colchicine $n = 22$, placebo $n = 32$; Mann–Whitney test $P = 0.41$).

24/31 (77%) patients randomised to colchicine and 23/37 (62%) patients randomised to placebo had a hs-CRP ≤ 2 mg/l at follow up (X^2 1.84, $P = 0.18$).

**Fig. 3** Boxplots comparing C-reactive protein levels between patients allocated to colchicine and placebo at follow up. The outlying follow up hs-CRP result (162 mg/l in colchicine group) has been removed

Other outcomes

Platelet aggregation

Platelet aggregation studies were available for 22 and 27 patients treated with colchicine and placebo, respectively. Platelet aggregation with ADP (5 μ mol), arachidonic acid (0.5 mmol), collagen (1 μ g/ml) and collagen (5 μ g/ml) was not different whether patients were on colchicine or placebo ($P = 0.86$, $P = 0.64$, $P = 0.76$ and $P = 0.20$, respectively) (Fig. 4).

Urine 11-dehydrothromboxane B2

Urine 11-dTXB2 levels were available for 27 and 31 patients on colchicine and placebo, respectively at follow up. Treatment with colchicine did not result in a difference in urine 11-dTXB2 levels at follow up compared with placebo ($P = 0.54$) (Fig. 5).

Clinical outcomes

No patient died during follow up. One patient on colchicine with myocardial infarction was readmitted with unstable angina and one patient on placebo was admitted with an occipital stroke.

Safety outcomes

Diarrhoea was twice as common in the colchicine group (14 vs. seven patients) (X^2 4.14, $P = 0.04$), however only four patients (three colchicine, one placebo) ceased study drug because of diarrhoea. Most patients with diarrhoea

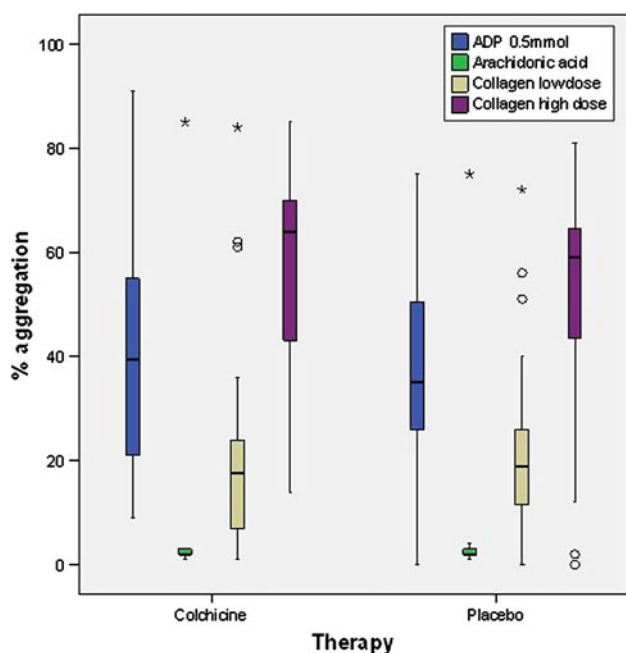


Fig. 4 Comparison of platelet aggregation at follow up in patients treated with colchicine and placebo

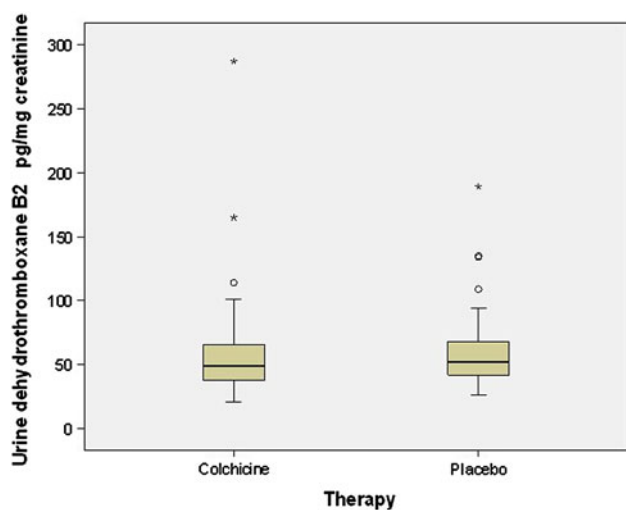


Fig. 5 Comparison of urine 11-dehydrothromboxane B2 at follow up in patients treated with colchicine and placebo

had it for a short duration (1–2 days) early in the study. Three patients all of whom were receiving colchicine had diarrhoea for the duration of the study but did not stop the study drug (Table 4).

Discussion

Our pilot study results indicate that hs-CRP levels are high in patients presenting with acute atherothrombosis and fall rapidly over the subsequent 30 days. Colchicine given in a

Table 4 Safety outcomes

	Colchicine (<i>n</i> = 36)	Placebo (<i>n</i> = 38)
Diarrhoea (<i>n</i>)	14	7
Neuropathy, myopathy, rhabdomyolysis (<i>n</i>)	0 ^a	0
Rash (<i>n</i>)	0	1 ^b
New neutropenia/thrombocytopenia (<i>n</i>)	0	0
Creatinine kinase	<i>N</i> = 26	<i>N</i> = 30
Normal (<i>n</i>)	20	28
>ULN (<i>n</i>)	4	2
>1.5 × ULN (<i>n</i>)	2	0
>2 × ULN (<i>n</i>)	0	0

^a One patient had myalgia without elevation of creatinine kinase enzyme

^b Rash probably due to Bupropion

dose of 1 mg/day did not significantly reduce blood levels of hs-CRP when compared with placebo. Colchicine was well tolerated when given as a single daily dose with no serious toxicity although it was associated with a higher rate of noncompliance and an excess of diarrhoea. We found no effect of colchicine on platelet function.

Preliminary observational data have suggested a suppressive effect of low-dose colchicine on hs-CRP levels in patients with established atherosclerosis [15]. Ours is the first randomised trial evaluating the effects of colchicine on inflammation in patients with acute atherothrombosis. Possible explanations for the lack of a measurable effect of colchicine therapy on hs-CRP in our study should be considered. There are numerous potential causes of hs-CRP elevation following an acute vascular event, some of which might not be sensitive to the effects of colchicine. The number of patients included in the COOL study might have been inadequate and further aggravated by incomplete follow up of patients. The majority of patients were treated with high dose statins which may have contributed to failure to detect an effect on hs-CRP. The dose and duration of colchicine evaluated in our study might have been insufficient to dampen overt inflammation in patients with acute atherothrombosis. Much larger doses of colchicine are required to suppress inflammation in patients with acute gout whereas low-doses can still be effective for the suppression of the long-term low-grade inflammation that is a feature of chronic atherosclerosis. Finally, incomplete compliance with study drug would have further reduced the power of the study to detect a treatment effect.

Low-dose colchicine has the potential to inhibit platelets by modulating the activity of phospholipase A2 and cyclooxygenases, thereby reducing thromboxane production, and by interfering with leukocyte–platelet interactions [16]. However, any modest platelet-inhibitory effect of colchicine on platelet function in our study might have

been masked by the use of aspirin in all patients and the additional use of clopidogrel in the majority.

Apart from an excess of diarrhoea, colchicine was well tolerated in our study and there were no serious adverse events. Several patients treated with colchicine elected to continue study drug despite experiencing diarrhoea, including three patients who had diarrhoea for the duration of the study. It is unclear whether using the same dose of colchicine in divided doses might have avoided the occurrence of diarrhoea.

In summary, our pilot study provides no evidence that low-dose colchicine initiated after admission to hospital with an acute atherothrombotic vascular event either suppresses hs-CRP or affects platelet function at 30 days. Additional studies evaluating colchicine [17] and novel anti-inflammatory therapies [18–20] in patients with chronic atherothrombosis are ongoing and will further clarify the role of anti-inflammatory treatments for the prevention of cardiovascular events.

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