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Effect of short-term colchicine treatment on endothelial function in patients with coronary artery disease

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ABSTRACT

Background: Inflammation is associated with endothelial dysfunction and plays an important role in the pathogenesis and development of cardiovascular diseases. It has been shown that colchicine, an anti-inflammatory drug, improves the cardiovascular outcome in patients with cardiovascular disease. The purpose of this study was to evaluate the short-term effect of low-dose colchicine on endothelial function in patients with coronary artery disease (CAD).

Methods: This was a double-blind, randomized, placebo-controlled, crossover-within-subject clinical trial. A total of 28 patients with CAD received low-dose colchicine (0.5 mg/day) or a placebo for 7 days with a washout period of at least 14 days. Flow-mediated vasodilation (FMD) and serum concentrations of high-sensitivity C-reactive protein (hs-CRP) were measured after the 7-day treatment with colchicine or the placebo.

Results: The serum concentration of hs-CRP was significantly decreased after administration of colchicine compared with that after administration of the placebo [median (interquartile range): 0.04 (0.02–0.08) mg/dL vs. 0.07 (0.04–0.11) mg/dL, P = 0.003], while there was no significant difference in FMD between the treatments [median (interquartile range): 3.1% (1.5–5.3%) vs. 3.3% (1.9–5.2%), P = 0.384]. Colchicine, however, significantly improved FMD in coronary artery disease patients with white blood cell (WBC) counts of ≥7500 WBC/mm^3 [median (interquartile range): 3.3% (2.1–6.6%) vs. 2.0% (1.4–3.8%), P = 0.043].

Conclusions: Administration of low-dose colchicine did not improve endothelial function in patients with CAD, but exploratory analysis suggested that endothelial function is significantly improved in patients with leukocyte activation.

1. Introduction

Endothelial dysfunction is the initial step in the process of atherosclerosis and plays an important role in the development of this condition [1,2]. Flow-mediated vasodilation (FMD), an index of endothelium-dependent vasodilation, in the brachial artery, has been widely used in clinical research for the assessment of endothelial function [3–6]. In addition, it has been shown that endothelial dysfunction is an independent predictor of cardiovascular events [7–10].

Although international guidelines recommend treatment of hypertension, dyslipidemia, and diabetes to prevent cardiovascular events, it is well known that patients with coronary artery disease have a high residual risk of cardiovascular events [11,12]. Inflammation is associated with endothelial dysfunction and plays an important role in the pathogenesis, maintenance, and development of atherosclerosis [1,2,13]. Recently, much interest has been shown in treatments targeting inflammation to prevent cardiovascular events [14,15].

Colchicine, an anti-inflammatory drug, is used to treat gout attacks and several inflammatory conditions [16,17]. It has been shown that colchicine inhibits the migration, adhesion, and cytokine secretory function of leukocytes [16,17]. Interestingly, a previous study showed that low-dose colchicine (0.5 mg/day) therapy stabilizes coronary plaque [18]. It has also been shown that colchicine reduces the risk of

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cardiovascular events [19,20]. The experimental study demonstrated the synergistic protective effects of colchicine and atorvastatin on endothelial function in a rat model of hyperlipidemia [21]. However, there is no information on the effects of colchicine on endothelial function. Therefore, in this study, we evaluated the short-term effects of low-dose colchicine on endothelial function in patients with CAD. In addition, as exploratory analysis in a subgroup we focused on patients with leukocyte activation who have a high risk of cardiovascular events.

2. Methods

2.1. Study participants

Between April 2015 and December 2015, we enrolled 28 patients with CAD at two general hospital in Japan (Supplementary Text). CAD was defined as history of myocardial infarction, angina pectoris with organic stenosis of at least one coronary artery confirmed by diagnostic imaging (i.e., coronary angiography or coronary computed tomography), history of percutaneous coronary intervention, or history of coronary artery bypass grafting. Hypertension was defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg, in a sitting position, on at least 3 different occasions. Diabetes mellitus was defined according to the American Diabetes Association [22]. Dyslipidemia was defined according to the third report of the National Cholesterol Education Program [23]. Estimated glomerular filtration rate (eGFR) was calculated by the following equation: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ (×0.739 if women) [24]. The inclusion criteria were as follows: 1) age ≥20 years, 2) patients with CAD. The exclusion criteria were as follows: 1) treatment with moderate-strong CYP3A4 inhibitors, 2) eGFR, <30 mL/min/1.73 m^2, 3) serious hepatic dysfunction, 4) a history of malignant disease within five years prior to the study, and 5) pregnancy or possible pregnancy. This study was approved by the ethical committees of each hospital. All patients gave written informed consent for participation in the study.

2.2. Study protocol

This was a double-blind, randomized, placebo-controlled, crossover-within-subject clinical trial. The organization of the study is detailed in the online-only Data Supplement (Supplementary Text). After a review of hospital records, we selected patients who met the inclusion criteria. Patients who provided written informed consent were randomized in a 1:1 ratio to receive 7-day treatment with colchicine (0.5 mg/day) or a placebo with crossover by a sealed envelope method (Fig. 1). Each study was separated by a washout period of at least 14 days. FMD was measured and blood sample was collected after 7 days of daily colchicine or placebo administration. The patients were instructed to abstain from eating, drinking alcohol, smoking and taking caffeine for at least 12 h prior to the measurements. The study began at 8:30 AM. Measurements were performed while each patient was in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22 °C–25 °C). Venous blood samples were obtained from the left antecubital vein. FMD was measured after 30 min of resting in the supine position. All participants and observers were blind to the form of examination.

2.3. Measurement of FMD

A high-resolution ultrasonography (UNEXEF18G, UNEX Co, Nagoya, Japan) was used to evaluate FMD. The protocol for measurements of FMD has been described in detail previously [25]. Briefly, the longitudinal image of the brachial artery was assessed before and after generation of vascular response to reactive hyperemia by a 5 min period of forearm occlusion to evaluate FMD. FMD was defined as the maximal percentage change in vessel diameter from the baseline value.

2.4. Measurement of blood samples

High-sensitivity C-reactive protein (hs-CRP) was measured by nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan).

2.5. Statistical analysis

Results are presented as means ± SD, median (interquartile range) for continuous variables and as percentages for categorical variables. Statistical significance was set at a level of $P < 0.05$. Differences in FMD and hs-CRP after administration of colchicine or placebo were evaluated using Wilcoxon signed-rank test. Relations between changes in FMD and changes in plasma colchicine levels were determined by Spearman rank correlation analysis. Since this was an exploratory study to evaluate the short-term effects of low-dose colchicine on endothelial function in a crossover design, the sample size was decided in accordance with the guideline for FMD from a report on the International Brachial Artery Reactivity Task Force [4]. We categorized patients into two groups according to the cutoff value of white blood cell (WBC) count for predicting patients with improved FMD after administration of colchicine: low group (<7500 WBC/mm^3) and high group (≥7500 WBC/mm^3). Cutoff value was derived from the receiver-operator characteristic curves and previous epidemiological data including our unpublished data. The data was processed using the software package Stata version 9 (Stata Co., College Station, Texas, USA).

3. Results

3.1. Clinical characteristics

Baseline characteristics of the patients are summarized in Table 1. The 28 patients included 27 men (96.4%) and 1 woman (3.6%), and 25 (89.3%) of the patients had hypertension, 10 (35.7%) had diabetes

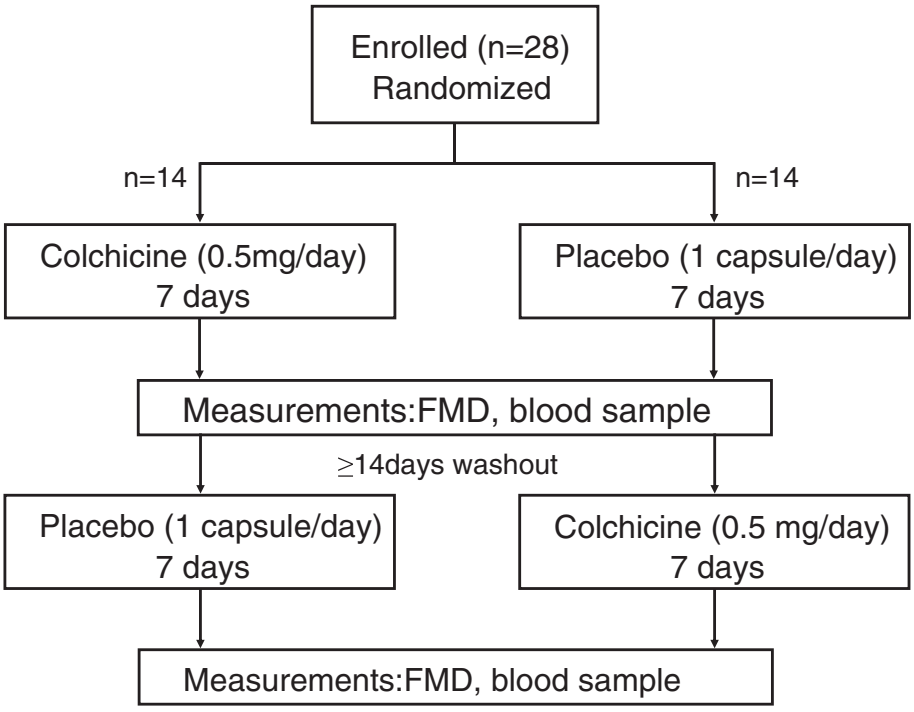

Fig. 1. Flow chart of study design.

Table 1
Clinical characteristics of the patients.

Variables	n = 28
Age, yr	68 ± 7
Sex, men/women	27/1
Body mass index, kg/m^2	24.7 ± 4.0
Systolic blood pressure, mm Hg	133 ± 21
Diastolic blood pressure, mm Hg	75 ± 13
Heart rate, bpm	67 ± 12
Total cholesterol, mg/dL	173 ± 22
Triglycerides, mg/dL	135 ± 66
HDL cholesterol, mg/dL	49 ± 10
LDL cholesterol, mg/dL	96 ± 20
HbA1c, %	6.4 ± 0.7
Glucose, mg/dL	120 ± 24
eGFR, mL/min per 1.73 m^2	65 ± 13
WBC count, WBC/mm^3	6539 ± 1490
hs-CRP, mg/dL	0.08 ± 0.05
Hypertension, n (%)	25 (89.3)
Diabetes mellitus, n (%)	10 (35.7)
Current smoker, n (%)	8 (28.6)
Former smoker, n (%)	27 (96.4)
History of acute myocardial infarction, n (%)	16 (57.1)
History of percutaneous coronary intervention, n (%)	20 (71.4)
History of coronary artery bypass grafting, n (%)	1 (3.6)
History of stroke, n (%)	1 (3.6)
Calcium-channel blockers, n (%)	16 (57.1)
Statins, n (%)	23 (82.1)
Nitrates, n (%)	6 (21.4)

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein. Results are presented as means ± SD for continuous variables and percentages for categorical variables.

Table 2
Clinical characteristics of the patients on the basis of WBC count.

Variables	Low group (<7500 WBC/mm^3)	High group (≥7500 WBC/mm^3)	P value
Age, yr	68 ± 6	68 ± 10	0.97
Sex, men/women	19/0	8/1	0.13
Body mass index, kg/m^2	24.3 ± 3.1	25.7 ± 5.7	0.49
Systolic blood pressure, mm Hg	128 ± 18	142 ± 24	0.14
Diastolic blood pressure, mm Hg	72 ± 9	81 ± 18	0.17
Heart rate, bpm	67 ± 12	67 ± 11	0.93
Total cholesterol, mg/dL	166 ± 15	181 ± 27	0.20
Triglycerides, mg/dL	102 ± 43	179 ± 69	0.02
HDL cholesterol, mg/dL	51 ± 9	47 ± 11	0.48
LDL cholesterol, mg/dL	92 ± 16	103 ± 24	0.33
Glucose, mg/dL	125 ± 28	114 ± 15	0.24
HbA1c, %	6.6 ± 0.7	6.1 ± 0.7	0.25
eGFR, mL/min/1.73 m^2	64 ± 15	66 ± 11	0.76
WBC count, WBC/mm^3	5655 ± 805	8406 ± 506	<0.001
hs-CRP, mg/dL	0.06 ± 0.04	0.12 ± 0.07	0.054
Hypertension, n (%)	16 (84.2)	9 (100.0)	0.11
Diabetes mellitus, n (%)	8 (42.1)	2 (22.2)	0.29
Current smoker, n (%)	6 (31.6)	2 (22.2)	0.60
Former smoker, n (%)	19 (100.0)	8 (88.9)	0.13
History of acute myocardial infarction, n (%)	12 (63.2)	4 (44.4)	0.35
History of percutaneous coronary intervention, n (%)	14 (73.7)	6 (66.7)	0.70
History of coronary artery bypass grafting, n (%)	1 (5.3)	0 (0.0)	0.37
History of stroke, n (%)	1 (5.3)	0 (0.0)	0.37
Calcium-channel blockers, n (%)	9 (47.4)	7 (77.8)	0.12
Statins, n (%)	14 (73.7)	9 (100.0)	0.04
Nitrates, n (%)	3 (15.8)	3 (33.3)	0.30

WBC indicates white blood cell; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein. Results are presented as means ± SD for continuous variables and percentages for categorical variables.

mellitus, and 27 (96.4%) had a history of smoking. All participants completed the trial.

3.2. Effects of colchicine on endothelial function and inflammation

FMD after administration of colchicine was not significantly different from that after administration of the placebo [median (interquartile range): 3.1% (1.5–5.3%) vs. 3.3% (1.9–5.2%), P = 0.384]. The serum concentration of hs-CRP was significantly decreased after administration of colchicine compared with that after administration of the placebo [median (interquartile range): 0.04 (0.02–0.08) mg/dL vs. 0.07 (0.04–0.11) mg/dL, P = 0.003]. We divided the patients into two groups according to the cutoff value of WBC count for predicting improvement in FMD after administration of colchicine (Table 2). The receiver-operator characteristic curve analysis revealed that WBC counts predicts patients with improved FMD after administration of colchicine with an area under the curve of 0.71 (Supplementary Fig. S1). The optimal cutoff value of WBC counts was 7500 WBC/mm^3. FMD was significantly improved in patients with WBC counts of ≥7500 WBC/mm^3 after administration of colchicine compared with that after administration of the placebo [median (interquartile range): 3.3% (2.1–6.6%) vs. 2.0% (1.4–3.8%), P = 0.043, n = 9; Fig. 2A]. The serum concentration of hs-CRP was significantly decreased after administration of colchicine compared with that after administration of the placebo in patients with WBC counts of ≥7500 WBC/mm^3 [median (interquartile range): 0.05 (0.03–0.08) mg/dL vs. 0.11 (0.07–0.16) mg/dL, P = 0.016; Fig. 2B).

3.3. Correlations between changes in FMD and changes in hs-CRP

Changes in FMD after administration of colchicine did not correlate with changes in hs-CRP ($\rho = -0.18$, P = 0.366). In patients with WBC counts of ≥7500 WBC/mm^3, changes in FMD after administration of colchicine did not correlate with changes in hs-CRP ($\rho = 0.50$, P = 0.207).

3.4. Adverse effects

There were no serious adverse events in the study patients during the study period.

4. Discussion

This study is the first double-blind, randomized, placebo-controlled, crossover-within-subject trial to evaluate the short-term effects of low-dose colchicine on endothelial function measured by FMD in patients with CAD. Treatment with low-dose colchicine inhibited inflammation represented by hs-CRP but did not improve endothelial function. Colchicine, however, significantly improved endothelial function in patients with WBC counts of ≥7500 WBC/mm^3. These results suggest, albeit hypothesis-generating, that low-dose colchicine might improve endothelial function through its anti-inflammatory effect in CAD patients with leukocyte activation.

As previously demonstrated, statins or other cardiovascular drugs such as renin angiotensin system inhibitors also show anti-inflammatory effects and improve endothelial function to some extent [26,27]. However, colchicine additively improved endothelial function possibly through its anti-inflammatory effect in our patients with high WBC counts who all were receiving statins. Colchicine might efficiently act as an anti-inflammatory drug and subsequently have favorable effects on endothelial function when inhibition of inflammation is insufficient with statins. This speculation is consistent with the results of study by Congwu et al. an experiment using a rat model of dyslipidemia that showed colchicine combined with atorvastatin more efficiently improved endothelial function and reduced inflammation than did either drug alone [21]. More than 90% of CAD patients were receiving high-

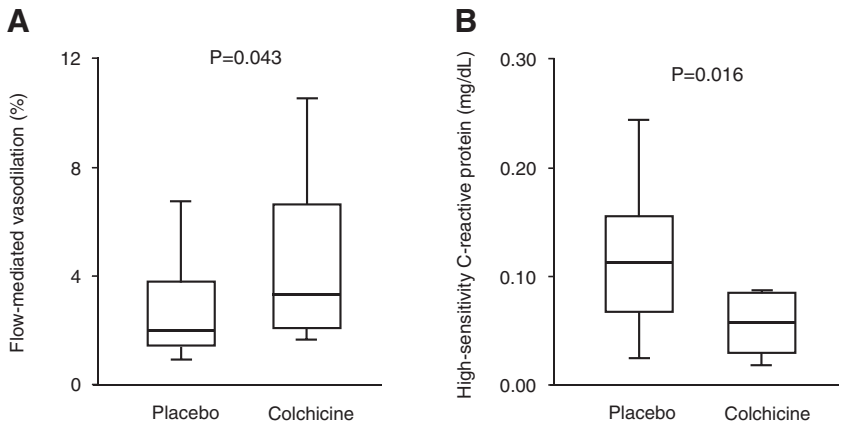

Fig. 2. The graphs show flow-mediated vasodilation (A) and high-sensitivity C-reactive protein (B) after administration of colchicine and placebo in patients with white blood cell counts ≥7500 WBC/mm^3.

dose statins in a previous clinical trial that showed significant risk reduction by low-dose colchicine [19].

Chronic inflammation has been shown to play a critical role in endothelial dysfunction by reducing the bioavailability of NO and in the development of atherosclerosis [1,2,13]. Recently, inflammation has been considered as one of the therapeutic targets for prevention of atherosclerotic cardiovascular diseases [14,15]. Indeed, the results of a recent successful trial with canakinumab strongly support the inflammation hypothesis [15]. Colchicine is also apparently one of the candidate anti-atherosclerotic drugs because of its pharmacological effects, i.e., inhibitory effects on leukocyte activation and production of interleukin 1β through inhibition of inflammasome activation, effects that are shared with canakinumab [28]. Indeed, a retrospective cohort study showed that the use of colchicine was associated with lower risk of cardiovascular events in gout patients, and a clinical trial with colchicine in a small number of patients showed reduction of cardiovascular event risk in CAD patients [19,20]. Epidemiological evidence also suggests that an elevated WBC count, which is one of the most common biomarkers for inflammation, is associated with unfavorable cardiovascular risk factors and a high incidence of cardiovascular events [29,30]. Therefore, our subgroup analysis in patients with high WBC counts is based on epidemiological and pharmacological evidence and, thus, may be justified for hypothesis generation. The next step might be a phase II clinical trial for evaluating the dose responsiveness of colchicine through its effects on inflammation and endothelial function in CAD patients with high WBC counts who are likely to benefit from treatment with colchicine.

We evaluated anti-inflammatory effects of colchicine by the measurement of hs-CRP, which is one of the most common markers of inflammation and is reportedly associated with risk of cardiovascular events [31]. In the present study, although we confirmed the results of previous studies showing that administration of colchicine decreased hs-CRP levels [18,32], there was no significant correlation between changes in FMD and hs-CRP. This is, however, not surprising and is interpretable. Levels of CRP may reflect inhibitory effect of colchicine on release of interleukin 1β from macrophages [33,34], but other anti-inflammatory pathways of colchicine such as inhibition of neutrophil activation and degranulation might contribute to the improvement of endothelial function [16,17]. CRP itself does not affect endothelial function in the first place. Lack of correlation might also be explained by relatively low levels of hs-CRP in our patients.

4.1. Perspectives

The development of cardiovascular drugs is more costly and requires a larger number of patients than does the development of drugs in other disease fields. However, more targeted development such as ours might allow lower cost and smaller trials. In fact, as mentioned above, we are conducting a randomized, double-blind, and placebo-controlled phase II trial to evaluate the dose-dependent effect of colchicine on endothelial function in patients with CAD who had WBC counts of ≥7500 WBC/mm^3 on the basis of present results (URL for Clinical Trial: https://upload.umin.ac.jp; Registration Number for Clinical Trial: UMIN000029170).

4.2. Study limitations

The present study has some limitations. First, the number of patients was relatively small. We should, however, point out that lack of statistically significant improvement of endothelial function in our primary analysis did not result from insufficient power. Indeed, our study had sufficient power to detect a significant intra-subject difference by a crossover design as suggested by the guideline for FMD [4]. Second, although we showed significant improvement of endothelial function after colchicine administration in CAD patients with leukocyte activation, this was exploratory analysis and the results must be considered hypothesis-generating. However, given the mechanism of action of colchicine and epidemiological evidence, our subgroup analysis seems clinically meaningful and the results appear to be plausible. Third, we only evaluated the short-term effect of colchicine on endothelial function. Long-term interventions are needed to determine whether short-term effects of colchicine are sustained over time. In terms of the safety issue, although this study showed no adverse events including diarrhea, which was commonly observed in other studies [35–37], we cannot rule out the possibility that long-term administration of low-dose colchicine has harmful effects. Finally, additional measurements including nitroglycerine-induced vasodilation and many more inflammatory mediators other than hs-CRP would have enabled more specific conclusions concerning the role of low-dose colchicine in vascular function to be drawn.

In conclusion, administration of low-dose colchicine did not improve endothelial function in patients with CAD, but exploratory analysis suggests that colchicine seems to improve endothelial function in patients with CAD and leukocyte activation. Further studies are needed to assess the long-term effects of colchicine on vascular function and cardiovascular events in CAD patients, particularly in CAD patients with high WBC counts.

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Conflict of interest

None.

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Clinical trial registration information

URL for Clinical Trial: https://upload.umin.ac.jp; Registration Number for Clinical Trial: UMIN000016185.

Role of each author

M.K., and Y.H., drafting the article and conception of this study; M.K., H.T., T.M., S.K., and A.M. acquisition of data; S.U., and Y.K. revising the article critically for important intellectual content. Y.H. and S.U. are the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.054.

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