Ineffectiveness of Colchicine for the Prevention of Restenosis After Coronary Angioplasty

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Colchicine, an antimitogenic agent, has shown promise in preventing restenosis after coronary angioplasty in experimental animal models. A prospective trial was conducted involving 197 patients randomized in a 2:1 fashion to treatment with oral colchicine, 0.6 mg twice daily (130 patients), or placebo (67 patients) for 6 months after elective coronary angioplasty. Treatment in all patients began between 12 h before angioplasty and 24 h after angioplasty. Compliance monitoring revealed that 96% of all prescribed pills were ingested. Demographic characteristics were similar in colchicine- and placebo-treated groups. A mean of 2.7 lesions/patient were dilated. Side effects resulted in a 6.9% dropout rate in the colchicine-treated patients.

Complete quantitative angiographic follow-up was obtained in 145 patients (74%) with 393 dilated lesions. Quantitative angiographic measurements were obtained in two orthogonal views at baseline before angioplasty and immediately and at 6 months after angioplasty. The quantitative mean lumen diameter stenosis before angioplasty was 67% both in the 152 lesions in the placebo-treated group and in the 241 lesions in the colchicine-treated group; this value was reduced to 24% immediately after angioplasty in the lesions in both treatment groups.

At the 6-month angiogram, lesions had restenosed to 47% lumen diameter narrowing in the placebo-treated group compared with 46% in the colchicine-treated group (p = NS). Forty-one percent of colchicine-treated patients developed restenosis in at least one lesion compared with 45% of the placebo-treated group (p = NS). In conclusion, colchicine was ineffective for preventing restenosis after coronary angioplasty.

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All currently available methods for percutaneous coronary revascularization (including balloon dilation, atherectomy, laser photoablation and intraluminal stenting) cause significant endovascular trauma. The subsequent reparative response involves myointimal proliferation that results in a significant renarrowing or restenosis in 30% to 40% of lesions by 6 months after angioplasty [1]. The stimuli for the smooth muscle cell proliferation involve mechanical and rheologic factors in addition to heterogeneous growth factors emanating from inflammatory cells and elements of the coagulation system [2,3]. The majority of restenosis trials performed to date have attempted to modify a single component of this complex redundant system. The failure of any single pharmacologic agent to consistently reduce the restenosis rate after coronary angioplasty is somewhat predictable in this context.

This exuberant, maladaptive smooth muscle cell prolifer-

ation has prompted some investigators to liken restenosis to a neoplastic process [4,5]. The term "malignant restenosis" has been used [6] to describe a syndrome characterized by rapid, refractory recurrences after repeated attempts at percutaneous coronary revascularization. When viewed from this perspective, the use of antimitogenic or antineoplastic agents is one of the most promising avenues of exploration in the search for a solution to the complex problem of restenosis.

Colchicine is an antimitogenic agent that binds to tubulin, disrupting spindle formation and resulting in the metaphase arrest of cell division. Colchicine has been shown to inhibit chemotaxis [7,8], collagen formation [9], muscle cell proliferation and platelet aggregation [10,11]. In experimental animal models, this agent has prevented or reduced the formation of atherosclerotic plaques [12,13]. Colchicine has also been effective in preventing myointimal proliferation after balloon arterial injury of the iliac artery in an atherosclerotic rabbit model [14] and has been reported to be effective in reducing fibroblastic proliferation in a patient with incipient hepatic cirrhosis [15]. Colchicine has not been used previously in a clinical trial for the prevention of restenosis after coronary angioplasty.

Methods

Study design. The study was designed as a double-blind randomized trial. The patients were randomized in a 2:1 fashion to treatment with oral colchicine, 0.6 mg twice daily, or placebo, one tablet twice daily. The 2:1 randomization scheme was used to maximize the number of patients treated with active drug and to encourage patient enrollment while preserving the statistical advantages of a randomized design. Treatment started within 24 h of angioplasty. Twenty-four percent of patients received one dose of colchicine or placebo before angioplasty; the remaining 76% of patients received their first dose within the 1st 24 h after angioplasty. Treatment was continued for 6 months or until the study end point (angiographic follow-up) was achieved.

Patients were scheduled for routine follow-up office visits at 3 and 6 months, at which time baseline laboratory studies were repeated. Laboratory work included a hematology profile; liver function tests, and measurements of serum creatinine, blood urea nitrogen, total cholesterol, triglycerides and high-(HDL) and low-(LDL) density lipoprotein levels. An exercise thallium stress test was performed at 3 months. Coronary arteriography was performed before angioplasty, immediately after angioplasty and at 6-month follow-up or earlier if the patient had recurrent angina or a markedly abnormal thallium stress test.

Selection of patients. Eligibility criteria for entry into the trial were 1) successful elective coronary angioplasty; 2) single or multivessel angioplasty; 3) bypass graft angioplasty; 4) angioplasty of previously undilated (new) and restenosed lesions; 5) angioplasty performed for silent ischemia and stable or unstable angina pectoris. Exclusion criteria were 1) direct angioplasty for acute myocardial infarction; 2) unsuccessful coronary angioplasty; 3) premenopausal women; 4) baseline leukopenia; 5) active peptic ulcer disease; 6) active diarrhea; 7) creatinine ≥ 2.5 mg/dl at baseline; 8) known colchicine intolerance. Successful angioplasty was defined as the reduction of the dilated lesion to $\leq 50\%$ lumen diameter stenosis without documented acute reocclusion during the hospital stay. The research protocol was approved by the Institutional Review Board for Human Research at St. Luke's Hospital, Kansas City, Missouri. Informed consent was obtained from all patients before study enrollment.

Coronary angiographic measurements. The primary end point of the trial was angiographic restenosis. Angiographic measurements were made in a semiquantitative fashion by using an electronic caliper that was accurate to 0.01 mm. Lesion measurements, expressed as the minimal relative lumen diameter stenosis, were obtained by measuring each dilated lesion and adjacent angiographically normal segment three times in each of two orthogonal views. The relative lumen diameter stenosis was defined as the difference between the mean lumen diameter measurements of the normal segment and the dilated lesion divided by the mean lumen diameter of the normal segment. The measurements were

Table 1. Demographic Characteristics of Patients Treated With Colchicine or Placebo

	Colchicine (n = 130; 66%)	Placebo (n = 67; 34%)
Men	111 (85%)	58 (87%)
Mean age (yr)	59	62
Prior coronary bypass surgery	34 (26%)	17 (25%)
LVEF $\leq 40\%$	9 (7%)	5 (8%)
Class IV angina	52 (40%)	26 (39%)
Diabetes	16 (12%)	8 (12%)
Cholesterol (mg/dl)	213	208
Lesions dilated/pt	2.7	2.9

There were no significant differences between groups. Unless otherwise indicated all values indicate number of patients. Class IV = Canadian Cardiovascular Society functional class IV; LVEF = left ventricular ejection fraction; pt = patient.

taken on each lesion before angioplasty, immediately after angioplasty and at the 6-month follow-up study.

Statistical analysis. The study protocol called for analysis of the angiographic data by two separate statistical methods. In one model, restenosis was evaluated as a continuous variable. In this noncategoric model, the stenosis measurements in each of the two groups were compared before angioplasty, immediately after angioplasty and at the time of the 6-month angiographic follow-up. The second method used the more traditional approach of analyzing restenosis as a dichotomous function. In this model, restenosis was defined as a return to $\geq 70\%$ lumen diameter stenosis at the time of the follow-up study *and* a loss of $\geq 50\%$ of the initial gain with angioplasty. When this definition was used, restenosis was evaluated categorically as a binary outcome for the presence or absence of restenosis.

Data were analyzed with chi-square analysis and a Student t test where appropriate. Statistical significance was defined as $p \leq 0.05$.

Results

Demographic data (Table 1). With the 2:1 randomization scheme, 130 patients (66% of the total group of 197 patients) were randomized to colchicine treatment and 67 patients (34%) to placebo treatment. The groups were very closely matched with respect to all major demographic characteristics. In the colchicine group, 2.7 lesions/patient were dilated; in the placebo group, 2.9.

Adverse effects (Table 2). Adverse drug effects occurred more frequently in colchicine- than in placebo-treated patients. Twenty-eight percent of colchicine-treated patients developed diarrhea that was often refractory and resulted in discontinuation of the drug in nine patients (7% dropout rate). Death occurred during the follow-up period in one colchicine-treated patient and in two placebo-treated patients (p = NS).

Angiographic follow-up. Complete angiographic follow-up was obtained in 145 of the 197 patients, yielding an

Table 2. Adverse Drug Effects in 197 Patients Treated With
Colchicine or Placebo

|	Colchicine (n = 130)	Placebo (n = 67)
Diarrhea	36 (28%)	3 (5%)*
Nausea/vomiting	5 (4%)	4 (6%)
Rash	2 (1.5%)	1 (1.5%)
Dyspepsia		1 (1.5%)
Death	1 (0.8%)	2 (3%)
Dropout rate	9 (6.9%)	1 (1.5%)†

*p = 0.0001. †p = 0.15; other differences are not significant. Unless
otherwise indicated, all values indicate number of patients.

angiographic follow-up rate of 74%. Follow-up coronary
angiography was performed a mean of 5.5 months after
angioplasty. Angiographic follow-up was not obtained in 52
patients because of death in 3 patients, dropout due to
treatment side effects in 10 (9 receiving colchicine, 1 receiv-
ing placebo) and refusal to undergo elective follow-up cath-
eterization in the remaining 39. In the 184 patients eligible for
the 6-month cardiac catheterization (excluding patients who
died or were intolerant to study medication), the follow-up
rate was 79% (83% in placebo and 77% in colchicine groups,
p = NS). In the 145 patients with complete angiographic
follow-up, initial angiographic success was achieved in 393
(98%) of the 401 lesions dilated.

The restenosis rate was 22%/lesion in both the colchicine-
and placebo-treated groups. Forty-one percent of colchicine-
treated patients had restenosis in at least one lesion com-
pared with 45% of the placebo-treated group (p = NS). The
mean lumen diameter stenosis was essentially identical in
the two groups at baseline, immediately after angioplasty
and at 6-month follow-up (Fig. 1).

Thallium stress test data. A 3-month postangioplasty
exercise thallium-201 stress test was performed in 118 (63%)

Figure 1. The mean coronary lumen diameter stenoses of the
placebo- and colchicine-treated groups were almost identical before
angioplasty (Pre-PTCA), immediately after angioplasty (Post-
PTCA) and at 6-month angiographic follow-up (p = NS). PTCA =
percutaneous transluminal coronary angioplasty.
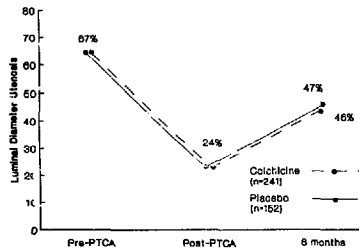
of patients. Scintigraphic evidence for recurrent ischemia in
the distribution of a dilated vessel was noted in 56 (58%) of
96 segments in the colchicine-treated patients and 27 (50%)
of 54 segments in the placebo-treated patients (p = NS).
Recurrent ischemia on thallium stress testing was noted in
at least one dilated vessel distribution in 66% of the 73
colchicine-treated patients and in 58% of the 45 placebo-
treated patients (p = NS).

Discussion

Previous studies. In the current study, treatment with
oral colchicine that was started at the time of coronary
angioplasty had no effect on the subsequent rate of resteno-
sis after angioplasty. In another trial (16) using colchicine
preliminary results were also negative, although that trial
used clinical nonangiographic end points. Although colchi-
cine was demonstrated to be effective in reducing intimal
proliferation after balloon injury to a rabbit iliac artery (14),
the effect was apparent only with the highest dose of the
medication. In that study, Currier et al. (14) found a reduced
rate of restenosis in animals treated with high dose
(0.2 mg/kg per day) but not with low dose (0.02 mg/kg per
day) colchicine. In the standard 70-kg human, the high dose
regimen would translate to 14 mg/day of colchicine. High
dose colchicine has been used as an antineoplastic agent for
conditions such as leukemia (5) but was poorly tolerated
because of serious adverse effects, such as hemorrhagic
gastritis and bone marrow suppression. Although the colchi-
cine regimen in the current trial (1.2 mg/day) was considered
to be relatively low dose, 7% of treated patients were unable
to complete the study owing to severe gastrointestinal ad-
verse effects (generally diarrhea). The incidence of signifi-
cant diarrhea (28%) in the treated group in the current trial
suggests that the systemic antimitogenic effects were ade-
quate to interfere with gastrointestinal mucosal cell turn-
over. Furthermore, this same regimen (colchicine,
1.2 mg/day) was reported to be effective in reducing peripor-
tal fibrosis in the setting of incipient hepatic cirrhosis (15).

Limitations. The lack of consistent pretreatment in the
current study is a potential limitation of the trial. However,
the antimitogenic effects of colchicine are clinically apparent
within hours of its use. Postmortem human studies (17) have
shown that the migration of smooth muscle cells from the
media to the intima occurs within the 1st 2 to 3 days after
angioplasty. The actual proliferation of these cells begins
shortly thereafter (11 to 30 days after angioplasty). Thus,
antimitotic therapy with colchicine started at the time of the
procedure should be adequate for the inhibition of subse-
quent myointimal proliferation.

Other neoplastic agents. Other neoplastic agents have
been used in experimental animal angioplasty models. The
hyperplastic smooth muscle cells responsible for the re-
stenotic process are of mesenchymal cell origin (18). The
chemotherapeutic agents generally used for tumors arising
from mesenchymal cells include methotrexate, vincristine,

cyclophosphamide and anthracycline antibiotic agents. Accordingly, the antineoplastic agents investigated so far in animals have generally been from this group of drugs. Combination therapy with vincristine and actinomycin D has been evaluated in a rabbit aortic model (19). Short-term therapy resulted in less smooth muscle cell hyperplasia 3 days after endothelial denudation in the rabbits treated with antineoplastic agents. The intermediate and long-term effects of this therapy were not observed in this study. The effectiveness of local methotrexate therapy on intimal proliferation after balloon arterial injury was evaluated by Muller et al. (20). After initial balloon arterial injury to the porcine carotid artery, methotrexate was intramurally administered through a Wolinsky coronary infusion balloon catheter (21). In this model, the local infusion of methotrexate did not abolish or even attenuate intimal proliferation. The use of systemic antineoplastic agents for restenosis was also addressed by Murphy et al. (22). In their trial utilizing a porcine coronary restenosis model, the use of oral or intramuscular methotrexate or azathioprine did not inhibit intimal proliferation and restenosis.

Clinical implications. The relatively low restenosis rate per lesion (22%) and per patient (43%) resulted from the use of a "conservative" definition of restenosis (as called for by the study protocol). The rate of restenosis per vessel by scintigraphic criteria on thallium-201 stress testing was significantly higher (55%). This finding suggests that some lesions had become hemodynamically significant again, although they had not returned to the baseline 70% lumen diameter stenosis, and had lost at least 50% of the initial gain with angioplasty. Additionally, many patients had more than one lesion dilated in a single vessel or vascular territory. Thus, they had an increased likelihood that recurrent ischemia would be detected in this distribution by tomographic thallium imaging, reflecting the additive risk of restenosis when multiple lesions are dilated (23).

Conclusions. The use of colchicine, although theoretically promising, proved ineffective in preventing restenosis after coronary angioplasty in the current study. Although the use of antineoplastic and antimitogenic agents in this application merits further consideration, therapy with higher doses and more potent agents will be limited to some degree by frequent, serious and even life-threatening adverse effects inherent in such regimens. Delivery systems to allow for local application of these agents may obviate some of these limitations.

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