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CLINICAL RESEARCH

COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response

COLIN : intérêt d'un traitement par colchicine dans l'infarctus du myocarde avec réponse inflammatoire

Mariama Akodad[a,1], Benoît Lattuca[a,1], Nicolas Nagot[b], Vera Georgescu[b], Mathilde Buisson[b], Jean-Paul Cristol[c,d], Florence Leclercq[a], Jean-Christophe Macia[a], Richard Gervasoni[a], Thien-Tri Cung[a], Stéphane Cade[a], Frédéric Cransac[a], Jessica Labour[a], Anne-Marie Dupuy[c], François Roubille[a,d,*]

[a] *UFR de médecine, cardiology department, hôpital Arnaud-de-Villeneuve, université Montpellier 1, CHU de Montpellier, 371, avenue du Doyen-Gaston-Giraud, 34295 Montpellier cedex 05, France*
[b] *UFR de médecine, medical information department, université Montpellier 1, CHU de Montpellier, 34295 Montpellier, France*
[c] *UFR de médecine, department of biochemistry, université Montpellier 1, CHU de Montpellier, 34295 Montpellier, France*
[d] *PhyMedExp, Inserm U1046, CNRS UMR 9214, university of Montpellier, 34295 Montpellier, France*

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KEYWORDS
Colchicine;
Cardiovascular disease;

Summary
Background. — Inflammation is involved during acute myocardial infarction, and could be an interesting target to prevent ischaemia-reperfusion injuries. Colchicine, known for its pleiotropic anti-inflammatory effects, could decrease systemic inflammation in this context.

Abbreviations: AMI, Acute myocardial infarction; CRP, C-reactive protein; hs-cTnT, High-sensitivity cardiac troponin T; LAD, Left anterior descending; MRI, Magnetic resonance imaging; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in myocardial infarction.

* Corresponding author. UFR de médecine, cardiology department, hôpital Arnaud-de-Villeneuve, université Montpellier 1, CHU de Montpellier, 371, avenue du Doyen-Gaston-Giraud, 34295 Montpellier cedex 05, France.
E-mail address: francois.roubille@gmail.com (F. Roubille).

[1] Both B.L. and A.M. contributed equally to this work.

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Heart failure;
Acute coronary syndrome;
Myocardial infarction

Aims. — To evaluate the impact of colchicine on inflammation in patients admitted for ST-segment elevation myocardial infarction (STEMI).
Methods. — All patients admitted for STEMI with one of the main coronary arteries occluded, and successfully treated with percutaneous coronary intervention, were included consecutively. Patients were randomized to receive either 1 mg colchicine once daily for 1 month plus optimal medical treatment or optimal medical treatment only. C-reactive protein (CRP) was assessed at admission and daily until hospital discharge. The primary endpoint was CRP peak value during the index hospitalization.
Results. — Forty-four patients were included: 23 were treated with colchicine; 21 received conventional treatment only. At baseline, both groups were well balanced regarding age, sex, risk factors, thrombolysis in myocardial infarction flow and reperfusion delay. The culprit artery was more often the left anterior descending artery in the colchicine group ($P = 0.07$), reflecting a more severe group. There was no significant difference in mean CRP peak value between the colchicine and control groups (29.03 mg/L vs 21.86 mg/L, respectively; $P = 0.36$), even after adjustment for type of culprit artery (26.99 vs 24.99 mg/L, respectively; $P = 0.79$).
Conclusion. — In our study, the effect of colchicine on inflammation in the context of STEMI could not be demonstrated. Further larger studies may clarify the impact of colchicine in acute myocardial infarction.
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MOTS CLÉS
Colchicine ;
Pathologies cardiovasculaires ;
Insuffisance cardiaque ;
Syndrome coronarien aigu ;
Infarctus du myocarde

Résumé
Contexte. — L'inflammation, impliquée au cours de l'infarctus du myocarde, pourrait représenter une cible thérapeutique intéressante et limiter les lésions d'ischémie-reperfusion. La colchicine, aux effets anti-inflammatoires pléiotropes, pourrait diminuer l'inflammation systémique au cours de l'infarctus du myocarde.
Objectif. — Évaluer l'impact de la colchicine sur l'inflammation systémique, dans l'infarctus du myocarde avec sus-décalage du segment ST.
Méthodes. — Tous les patients admis pour infarctus du myocarde avec occlusion de l'une des trois artères principales traités avec succès par angioplastie primaire étaient inclus de manière consécutive. Ils étaient randomisés pour recevoir 1 mg de colchicine par jour pendant 1 mois, en sus du traitement médical optimal, ou le traitement médical optimal seul. La C-réactive protéine était dosée à l'admission et quotidiennement jusqu'à la sortie. Le critère de jugement principal était le pic de CRP au cours de l'hospitalisation.
Résultats. — Quarante-quatre patients ont été inclus, 23 ont reçu la colchicine et 21 le traitement conventionnel seul. Les caractéristiques de base étaient comparables entre les 2 groupes concernant l'âge, le sexe, les facteurs de risque cardiovasculaires, le flux TIMI et le délai de reperfusion. L'artère interventriculaire antérieure était le plus souvent l'artère coupable dans le groupe colchicine ($p = 0,07$) reflétant un groupe plus sévère. Il n'y avait aucune différence significative entre les 2 groupes concernant la valeur du pic de CRP (29,03 mg/L dans le groupe colchicine vs 21,86 mg/L dans le groupe témoin ; $p = 0,36$), même après ajustement sur le type d'artère coupable (26,99 vs 24,99 mg/L ; $p = 0,79$).
Conclusion. — Aucun effet de la colchicine sur l'inflammation systémique dans l'infarctus du myocarde n'a pu être démontré. Des études complémentaires de plus grande envergure apparaissent nécessaires pour clarifier l'impact de la colchicine dans l'infarctus du myocarde.
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Background

After an acute myocardial infarction (AMI), inflammation is deeply involved in the pathophysiology of ischaemia-reperfusion lesions, as well as in the remodelling phenomenon [1]. In patients admitted for AMI, systemic biological inflammation is usually observed, and is reflected in a biological peak of C-reactive protein (CRP) around day 3 [2]; this peak is recognized as a prognostic marker, with a well-known correlation with infarct size [3]. During ischaemia, inflammatory factors and cytotoxic substances are released by inflammatory cells in myocardial tissue, leading to the systemic response (and CRP production). During reperfusion, oxygenated blood worsens the injury via the release of

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free oxygen radicals, and aggravates the inflammatory reactions. Endothelial permeability is then increased, leading to myocardial cell injury, apoptosis and necrosis, with myocardial destruction.

Many biological, immunomodulatory and antioxidative strategies have been proposed for cardioprotection [4,5]. However, no anti-inflammatory drugs have been shown to be clinically efficient, and none is presently used, except the pleiotropic effect of statins [6]. New biotherapies (especially targeting the interleukin-1 pathway) are currently under development in this clinical setting.

Colchicine has been used for centuries for the treatment and prevention of gouty attacks and rheumatic complaints, and is one of the oldest drugs still currently available [7]. Colchicine may exert pleiotropic anti-inflammatory effects, especially through the inhibition of neutrophil migration [8], and may also have direct anti-inflammatory effects [9], by inhibiting key inflammatory signalling networks, known as the inflammasome and proinflammatory cytokines [10]. Furthermore, colchicine has been shown to exert antiatherosclerotic actions [11], and was proposed to reduce inflammation in patients with stable coronary disease [12].

Recently, colchicine has been shown to decrease infarct size, with a reduction in the concentration of creatine kinase muscle-brain (CK-MB) fraction and infarct size on cardiac magnetic resonance imaging (MRI) in patients with AMI [13].

Taking all these considerations together, CRP could be considered as an acceptable surrogate endpoint representing the involvement of inflammation in post-AMI outcome. Our aim was to evaluate the impact of colchicine on inflammation, on the basis of CRP peak, in patients admitted for AMI.

Methods

This interventional, open-label, controlled, prospective study was conducted in the university hospital of Montpellier, France. All participants provided written informed consent, and the protocol was performed according to the principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Montpellier. The study was registered in the clinical trials database (NCT02363725).

Population

All patients admitted consecutively to our institution between December 2014 and May 2015 for ST-elevation myocardial infarction (STEMI), with occlusion of one of the main coronary arteries (thrombolysis in myocardial infarction [TIMI] grade 0 or 1 flow), and successfully treated with primary percutaneous coronary intervention (PCI), were considered for inclusion in the study (Fig. 1). The diagnosis of AMI was based on typical chest pain lasting for > 30 minutes and < 12 hours. Emergency PCI was performed because of signs of ongoing ischaemia (persistent pain or/and ST-segment elevation). The culprit lesion was defined as the occluded artery consistent with the electric territory.

The main exclusion criteria were cardiogenic shock, severe chronic kidney failure (clearance < 30 mL/kg/min), colchicine intolerance or contraindication.

Medical treatment

All patients received the recommended medical treatment, including aspirin, a $P2Y_{12}$ inhibitor and unfractionated heparin. Before the primary PCI procedure, all patients received, following the emergency protocol: 250—500 mg of aspirin intravenously, 4000—5000 IU of heparin intravenously and a loading dose of clopidogrel (600 mg) or prasugrel (60 mg) or ticagrelor (180 mg). Additional treatment with glycoprotein IIb/IIIa inhibitors or intracoronary treatments, such as vasodilators, were left to the discretion of the interventional cardiologist. All patients were monitored initially in the intensive care unit, and were then transferred to the conventional cardiology ward; they were treated with optimal medical treatment, including angiotensin-converting enzyme inhibitors, beta-blockers, dual antiplatelet therapy, including aspirin with clopidogrel or prasugrel or ticagrelor, and lipid-lowering drugs (atorvastatin 80 mg or rosuvastatin 20 mg), following the current guidelines [14].

Procedure characteristics

The first coronary angiography injection determined coronary perfusion according to the TIMI criteria [15,16]. Primary PCI was performed in accordance with guidelines [14], and the number and types of stents were left to the discretion of the interventional cardiologist. PCI success was determined by a TIMI grade 3 flow at the end of the procedure, which has been linked with morbidity and mortality after pharmacological and mechanical reperfusion in clinical trials of STEMI [15—18].

Treatment allocation

Eligible patients were automatically randomized with a 1:1 ratio to either colchicine and optimal medical treatment or optimal medical treatment alone. Randomization was centralized, available online, performed by minimization and stratified on age and sex. The study drug (oral colchicine, 1 mg once daily) was administered on the first day of the AMI and for 1 month, without a loading dose.

Blood sampling

Venous blood samples were collected at admission and then daily until hospital discharge. Biochemistry variables were performed on a cobas® 8000 analyser using reagents from Roche Diagnostics (Meylan, France) with the c701© module and the e602© module for immunoassay. Evaluations of high-sensitivity CRP by the immunoturbidimetric method, of creatinine by the enzymatic method, and of creatine kinase according to the International Federation of Clinical Chemistry-approved method (creatine kinase-N-acetylcysteine kinetic measurement; 37 °C) were carried out at inclusion and every day until the end of hospitalization. The high-sensitivity cardiac troponin T (hs-cTnT) assay was performed on the cobas® 8000/e602 analyser. The lowest concentration measurable at the 10% assay imprecision (CV) level is 13 ng/L, and the 99th percentile among healthy individuals is 14 ng/L (confidence interval: 12.7—24.9) [19], according to the manufacturer. The estimated glomerular filtration rate was

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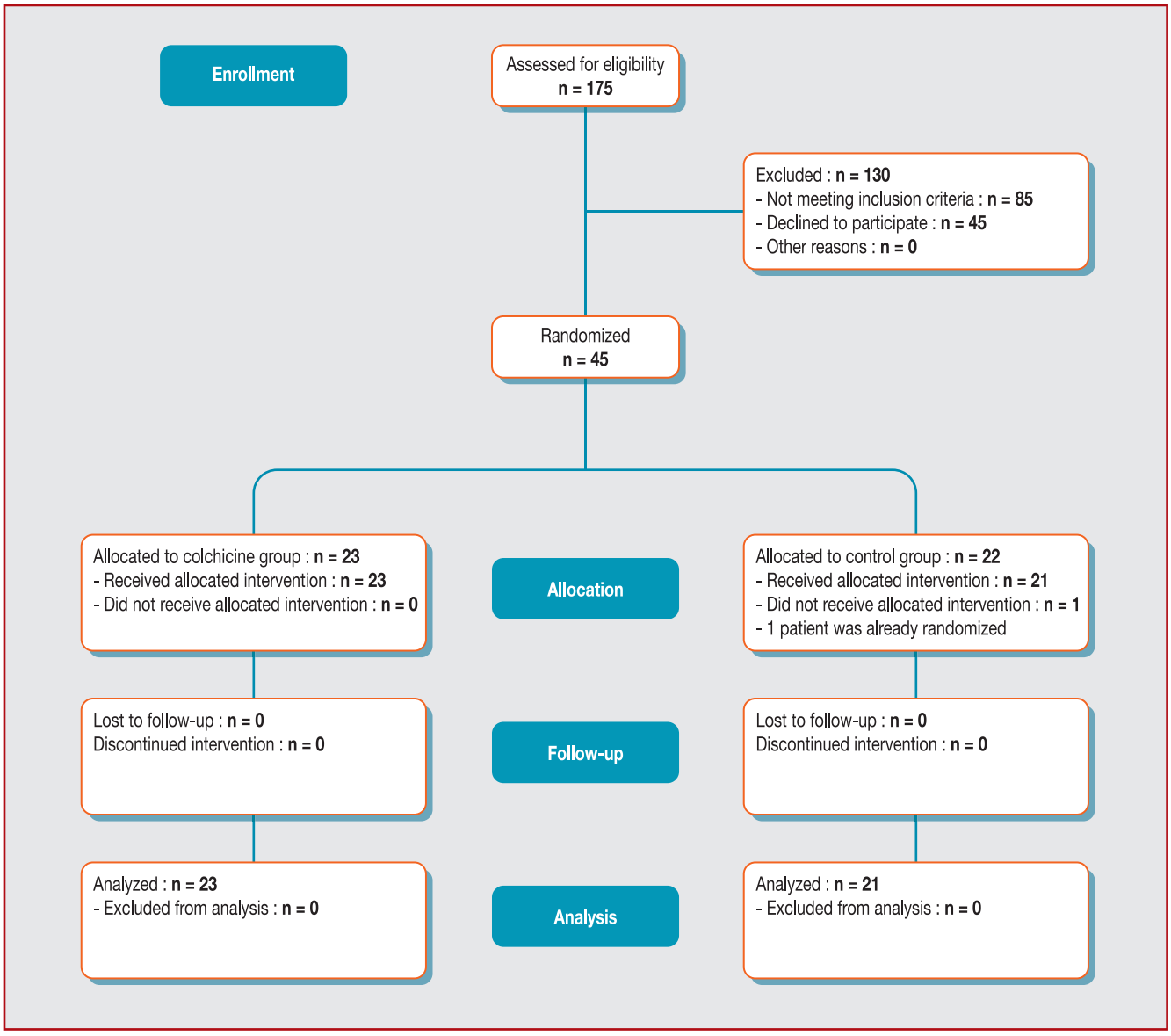

Figure 1. Flow diagram according to CONSORT 2010.

computed using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [20]. Procalcitonin was measured by a commercial chemiluminescence assay on a Kryptor® immunoanalyser (ThermoFisher, Agnières, France), following the manufacturer's instructions.

Primary and secondary endpoints

The primary endpoint was the CRP peak value during the index hospitalization. The secondary endpoints were troponin peak, tolerance of colchicine, hospitalization duration, major adverse cardiac events (death, resuscitated cardiac arrest, ventricular arrhythmias, stent thrombosis, myocardial infarction, urgent coronary revascularization and acute heart failure) at 1-month follow-up, cardiac remodelling on echocardiography (left ventricular end-systolic and end-diastolic volumes) and MRI data.

Statistical analyses

The initial hypothesis was a reduction in median CRP concentration of at least 15%. A 0.72-standard deviation associated with the ''group-effect'' was estimated based on a preliminary study conducted in the unit. To obtain an estimation of this ''group-effect'' with ± 10% precision for a 5% alpha and allowing for 10% of patients being lost to follow-up, it was necessary to include 44 patients.

The preliminary descriptive analysis included either means ± standard deviations or medians and first and third quartiles for continuous variables (depending on the normality of the data, checked with the Shapiro-Wilk test), and frequencies for categorical variables. Continuous variables were compared between the two study groups using Student's *t* test if the data were normal or the Wilcoxon-Mann-Whitney test otherwise. Categorical variables were

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compared using the χ^2 test or Fisher's exact test when χ^2 validity conditions were not met.

The evolution of the biological variables (CRP, creatinine phosphokinase, procalcitonin) was compared between the two study groups using the maximum value for each patient and the area under curve. As the type of culprit artery differed between groups at baseline, the analysis of the primary endpoint (CRP peak value) was adjusted for this variable with a two-factor analysis of variance, considering the effect of group (colchicine or control) and type of culprit artery (left anterior descending [LAD] or others). For each biological variable (CRP, creatinine phosphokinase, procalcitonin), a graphical representation of the evolution of the mean and standard error from days 1 to 5 since inclusion was produced for the two study groups. As the time span between two successive measurements varied for each patient, cubic smoothing splines were fitted to the data to obtain predictions every 24 hours since inclusion, from 1 to 5 days (using a smoothing parameter of 0.35 for all variables). Statistical analyses were carried out with SAS 9 (SAS Institute, Cary, NC, USA) for descriptive statistics and analysis of variance (PROC GLM), and with R version 3.0.2 (package stats, function ''smooth.spline''; package pracma, function ''trapz'') for calculating area under the curve.

Results

Study population

Forty-four patients were included in this study: 23 were treated with colchicine in combination with conventional treatment; 21 received conventional treatment only.

Baseline and procedural patient characteristics on admission are presented in Table 1, and were well balanced between the two study groups. The reperfusion delay was similar between the two groups: 4.8 hours in the colchicine group and 4.7 hours in the control group. Importantly, the area at risk (and then, logically, the infarct size, because the area at risk is one of the main determinants of infarct size) was different, suggesting that the two study groups were not adequately balanced. Indeed, the culprit artery was more often LAD in the colchicine group (strong trend, $P = 0.07$), reflecting a more severe group.

Table 1 Baseline characteristics of the study population.

Characteristics	Colchicine group ($n = 23$)	Control group ($n = 21$)	*P*
Men	19 (82.5)	16 (76.2)	0.9
Age (years)	60.1 ± 13.1	59.7 ± 11.4	1
Hypertension	9 (39.1)	10 (47.6)	0.5
Diabetes mellitus	3 (13.0)	3 (14.3)	1
Smoker	17 (73.9)	14 (66.7)	0.7
Dyslipidaemia	8 (34.8)	8 (38.1)	1
History of CABG	0 (0)	1 (4.8)	0.5
History of PCI	1 (4.3)	1 (4.8)	1
Chronic kidney failure	0 (0)	0 (0)	1
LVEF			
< 30%	2 (9.1)	0 (0)	0.5
30—50%	7 (31.8)	5 (25.0)	
> 50%	13 (59.1)	17 (75.0)	
Antiplatelet therapy			
Clopidogrel	7 (30.5)	9 (42.9)	0.12
Prasugrel	15 (65.2)	8 (38.1)	
Ticagrelor	1 (4.3)	4 (19.0)	
Culprit artery			
LAD	14 (60.9)	7 (33.3)	0.07
Circumflex	3 (13.0)	2 (9.6)	
RCA	6 (26.1)	12 (57.1)	
TIMI flow			
0	16 (69.6)	15 (71.4)	1
1	7 (30.4)	6 (28.6)	
2	0 (0)	0 (0)	
3	0 (0)	0 (0)	

Results are expressed as mean ± standard deviation (normal distributions) or number (%). CABG: coronary artery bypass graft; LAD: left anterior descending; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIMI: thrombolysis in myocardial infarction.

Primary endpoint

The CRP peak occurred on the second day after the AMI in the control group in 8 (38.1%) patients, and on the first day after the AMI in the colchicine group in 11 (47.8%) patients (Fig. 2). In the univariate analysis, the mean ± standard deviation value of the CRP peak was not significantly different between the two study groups: 29.03 ± 25.56 mg/L in the colchicine group vs 21.86 ± 25.39 mg/L in the control group ($P = 0.36$; Fig. 3). This was also true for the area under the curve of CRP ($P = 0.4$; Fig. 4). After adjustment for the culprit artery (LAD or others) using a two-factor analysis of variance, the effect of group (colchicine or control) remained non-significant ($P = 0.79$). The mean values of peak CRP, adjusted for the type of culprit artery, were 26.99 mg/L in the colchicine group and 24.99 mg/L in the control group.

Biological endpoints

Inflammation assessed by procalcitonin peak did not differ between the two study groups: 0.48 mg/dL in the colchicine group ($n = 22$) vs 0.11 in the control group ($n = 21$) ($P = 0.38$). The leukocyte peak was 13.1 g/L in the colchicine group vs 11.5 g/L in the control group ($P = 0.16$). There was no significant difference in the values of the hs-cTnT peak (6,476.774 ng/L in the colchicine group vs 4,635.581 ng/L in the control group; $P = 0.14$) or the creatine kinase peak (2984.9 IU/L vs 1706.3 IU/L, respectively; $P = 0.10$). The area under the curve of creatinine phosphokinase was not statistically different between the two study groups ($P = 0.2$; Fig. 5).

Echocardiographic data

There was no significant difference between the two study groups regarding left ventricular ejection fraction, left

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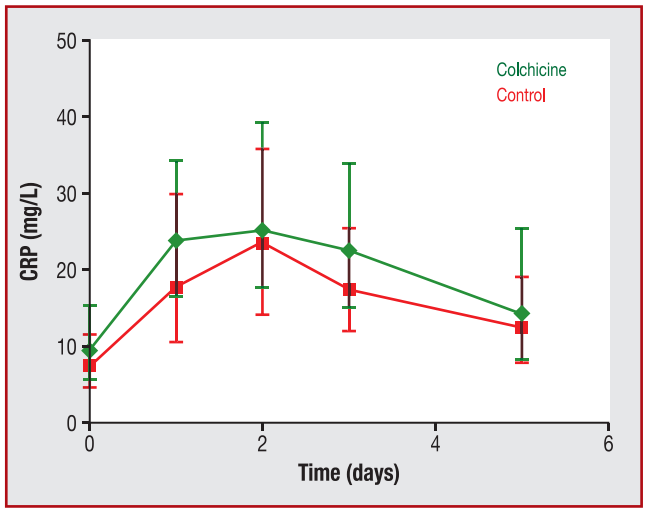

Figure 2. Time to peak and kinetics of C-reactive protein (CRP) during hospitalization in the two study groups.

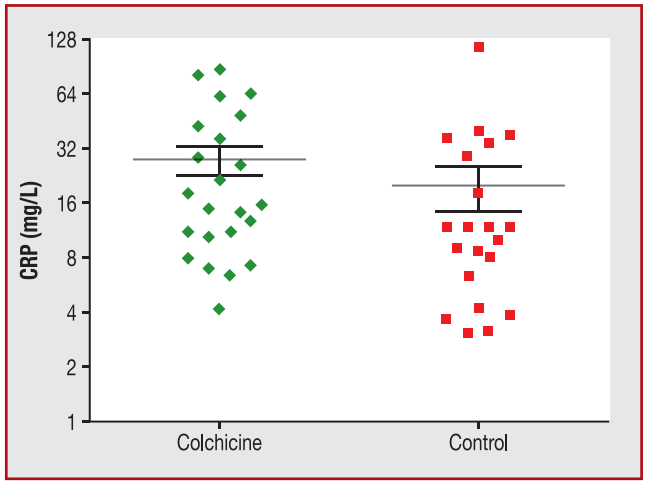

Figure 3. Peak level of C-reactive protein (CRP) in the two study groups.

ventricular strain values and left ventricular systolic and diastolic diameters.

MRI data

MRI data were available for 19 patients in the colchicine group and 17 patients in the control group. There was no significant difference between the two study groups in terms of left ventricular ejection fraction (56.5% in the colchicine group vs 50.6% in the control group; $P = 0.15$), end-systolic volumes, end-diastolic volumes, no-reflow and pericardial effusion. However, transmural infarctions were more frequent in the colchicine group than in the control group (16 patients [69.6%] vs 9 patients [42.9%]; $P = 0.04$).

Major adverse cardiac events at 1-month follow-up

During the index hospitalization, one patient (2.2%) in the control group presented an episode of acute heart failure, and one patient (2.2%) in the colchicine group presented a sustained ventricular tachycardia. There was no difference between the two study groups regarding the rate of major adverse cardiac events ($P = 1$).

At 1-month follow-up, no difference was found between the two study groups, with one recurrence of myocardial infarction in the control group and one acute heart failure in a patient treated with colchicine ($P = 1$). None of the patients died during hospitalization or at 1-month follow-up.

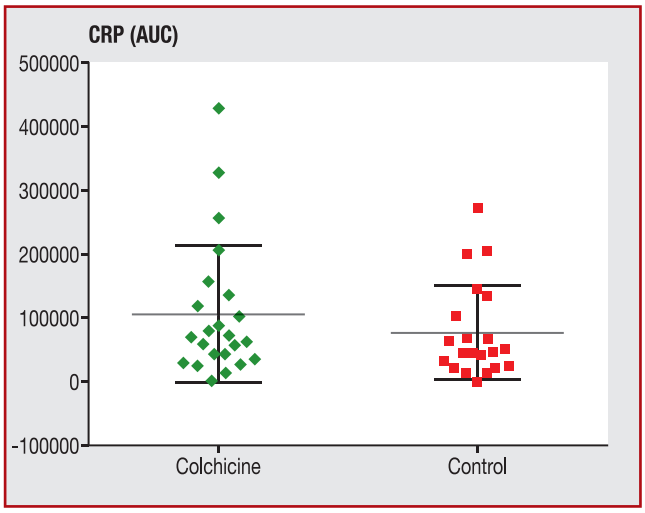

Figure 4. Area under the curve of C-reactive protein (CRP) in the two study groups.

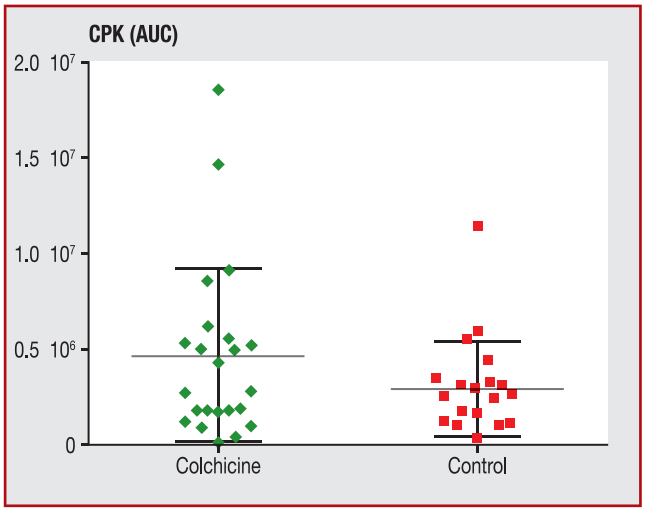

Figure 5. Area under the curve (AUC) of creatinine phosphokinase (CPK) in the two study groups.

Adverse effects

Ten patients presented digestive intolerance of colchicine (43.4%), with diarrhoea, nausea or vomiting, but discontinuation of treatment was necessary for only three patients (13.0%). No cases of hepatotoxicity or myelotoxicity occurred.

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Discussion

In this study, 1 month of oral treatment with colchicine, administrated after reperfusion, did not reduce the CRP peak in STEMI patients. Moreover, other inflammatory variables, such as procalcitonin or leukocyte peaks, and myocardial variables, such as hs-cTnT peak, creatine kinase peak and left ventricular remodelling variables, were not modified by oral administration of colchicine after reperfusion. The two study groups were not, however, balanced with regard to area at risk, which is obviously a major bias. This could only be random, because of the small number of patients, and because the randomization process did not take into consideration the culprit lesion.

Despite the smaller population, these results differ strongly from those reported from the recent trial by Deftereos et al. [13]. Indeed, in this prospective randomized study involving 151 patients, with 77 treated with colchicine, the authors showed that administration of oral colchicine reduced the infarct size, with a reduction in creatine kinase area under the curve and a reduction in infarct size on cardiac MRI in patients admitted for STEMI. The treatment also reduced inflammatory variables after reperfusion, namely neutrophil count and CRP. However, the timing and methods of colchicine administration were different—colchicine was administrated orally, but directly, in the catheterization laboratory, and just before the reperfusion, with a 2-mg loading dose, and continued for 5 days. The study by Deftereos et al. was clearly designed to target ischaemia-reperfusion lesions and infarct size, based on the involvement of inflammation in the ischaemia-reperfusion lesions. This concept is currently under considerable debate after the negative result of the first large study in the field: the CIRCUS trial [21].

By contrast, our study aimed at addressing the ability of colchicine to reduce the inflammation that is triggered by the infarction and is involved in a vicious circle. Moreover, in our small study, the study groups were not well-balanced, despite it being a prospective, randomized trial in consecutive patients. Indeed, infarct territory and culprit artery were deeply different, with a higher rate of LAD in the colchicine group, with a larger infarct size and a higher rate of transmural infarction. On the other hand, our population was different, with 100% procedural success compared with only 70% with TIMI 3 flow after PCI in the study by Deftereos et al. [13], and with lower CRP peaks in our study. Finally, despite a similar experimental protocol in the context of STEMI, it seems difficult to compare these two studies because of the different populations and reperfusion results.

Colchicine exerts an anti-inflammatory effect, and may limit reperfusion injury [7,8,11—13]. The lack of effect of colchicine in our study could be explained by late administration in the intensive care unit after the reperfusion and without a loading dose. These results may indicate that the treatment should be given at the onset of reperfusion, as soon as possible, to optimize its action and to reduce reperfusion injuries associated with inflammation burden.

Study limitations

Many study limitations have to be discussed, despite the prospective, randomized design: the small number of patients included in a single-centre study; the low statistical power; and the imbalanced population, especially regarding clinical characteristics. The STEMI population was particularly heterogeneous, with a different infarct size according to the culprit artery. In the colchicine group, the LAD was involved in the majority of cases (60.9%), whereas in the control group, the right coronary artery was more often involved (57.1%). However, we showed that the CRP peak values were not significantly different, even after adjusting for the culprit artery, suggesting that the lack of effect may not be the result of a more important infarct size in the colchicine group. Moreover, the study population presented a small level of inflammation, in comparison with the population that is classically encountered in this context, with values of CRP peak < 30 mg/L in the two study groups, whereas we expected a peak at about 60 mg/L [3]. Thus, our population was probably not an appropriate target population to benefit from an anti-inflammatory therapy or to answer the study hypothesis. Another limitation of the study was the lack of a placebo in the control group, and therefore the open-label design. However, as the primary endpoint of this preliminary study was an objective biological criterion, we believe that the impact of such a design on the results may have been very low. Nevertheless, our results should be replicated in a study evaluating clinical endpoints with a placebo-controlled double-blind design.

Conclusion

By contrast with expensive approaches, colchicine is cheap and easy to obtain worldwide. Furthermore, this venerable drug appears to be a good candidate to offer cardioprotection in various clinical settings, especially in chronic heart failure and in acute coronary syndromes with or without ischaemia-reperfusion injuries. In our study, the effect of colchicine in the context of STEMI could not be demonstrated, with no improvement in inflammatory profiles or diminution of infarct size. Further larger studies with an appropriate population may be beneficial to clarify the impact of colchicine in STEMI patients.

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Disclosure of interest

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The other authors declare that they have no competing interest.

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