Potential role for pentoxifylline as an anti-inflammatory drug for patients with acute coronary syndrome

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Received October 26, 2021; Accepted November 25, 2021

DOI: 10.3892/etm.2022.11305

Abstract. The link between inflammation and acute coronary syndrome (ACS) remains to be sufficiently elucidated. It has been previously suggested that there is an inflammatory process associated with ACS. Pentoxifylline, a methylxanthine derivate, is known to delay the progression of atherosclerosis and reduce the risk of vascular events, especially by modulating the systemic inflammatory response. The present study is a single-blind, randomized, prospective study of pentoxifylline 400 mg three times a day (TID) added to standard therapy vs. standard therapy plus placebo in ACS patients with non-ST elevation myocardial infarction (NSTEMI). Patients with ACS were randomized to receive standard therapy plus placebo in one arm (group A; aspirin, clopidogrel or ticagrelor, statin) and in the other arm (group B) pentoxifylline 400 mg TID was added to standard therapy. The primary outcome was the rate of major adverse cardiovascular events (MACEs) at 1 year. A total of 500 patients underwent randomization (with 250 assigned to group A and 250 to group B) and were followed-up for a median of 20 months. The mean age of the patients was 62.3±10.3 years, 80.4% were male, 20.8% had diabetes, 49.4% had hypertension, and 42% were currently smoking. The statistical analysis was performed for 209 patients in group A and 210 patients in group B (after dropouts due to study drug discontinuation). A primary endpoint occurred in 12.38% (n=26) of patients in group B, as compared with 15.78% (n=33) of those in group A [relative risk (RR), 0.78; 95% confidence interval (CI), 0.486-0.1.263; P=0.40], including cardiovascular death (RR, 0.93; 95% CI, 0.48-1.80, P=0.84), non-fatal myocardial infarction (RR, 1.1; 95% CI, 0.39-3.39, P=0.78), stroke (RR, 0.99; 95% CI, 0.14-6.99, P=0.99) and coronary revascularization (RR, 0.12; 95% CI, 0.015-0.985, P=0.048). Thus, adding pentoxifylline to standard treatment in patients with ACS did not improve MACE at 1 year but had some benefit on the need for coronary revascularization.

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Key words: acute coronary syndrome, pentoxifylline, inflammation, primary outcome, major adverse cardiovascular events

Introduction

The link between inflammation and acute coronary syndrome (ACS) remains to be sufficiently elucidated. It has been previously suggested that there is an inflammatory process associated with ACS. Activation of the local inflammatory process leads to damage of the endothelium. This mechanism leads to the dysfunction of the endothelium, altering its antithrombotic properties (1).

In the past, plaque rupture was considered the only pathophysiological process behind ACS (2). In the past few years, numerous mechanisms have been found to be involved in the pathogenesis of ACS. In an excellent review, Crea and Libby (3) suggested plaque erosion in addition to plaque rupture as a mechanism for ACS. This process can be with or without inflammation. The presence of inflammation associated with plaque rupture or erosion may have clinical implications. Considering this, it is mandatory that inflammation become a target for therapy Increased concentrations of highly sensitive C-reactive protein (hs-CRP) and the release of cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-8 in unstable angina and myocardial infarction (MI) (4,5), have been identified in patients with ACS. In addition, high levels of IL-6 have been described in patients with unstable angina and these patients had a worse outcome (6).

Previous findings have shown that high levels of hs-CRP are an independent risk factor for coronary syndromes. High levels of hs-CRP highlight the inflammatory process associated with the progression of atherosclerosis albeit not necessarily with ACS (7). Patients with levels of hs-CRP >2 mg/l were associated with more major adverse cardiovascular events (MACEs), as reported by a cohort study in Switzerland (8). High levels of hs-CRP have been reported up to three months in >50% of patients with ACS despite optimal medical treatment (9). The revascularization procedures [percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)] that

patients with ACS undergo may cause myocardial injury and can add to the inflammation process (10).

Pentoxifylline was used in the treatment of patients with intermittent claudication due to its blood rheology properties (11). Some clinical trials utilizing pentoxifylline suggest that this drug may potentially delay the progression of atherosclerosis and reduce the risk of vascular events, especially by modulating the systemic inflammatory response (12). The molecular biology underlying these various effects is not well known. In a previously published meta-analysis, the results showed that pentoxifylline did not change the levels of blood pressure (BP) or plasma IL-6 concentration, although it decreased circulating TNF-α and hs-CRP concentrations (13).

Adding pentoxifylline to dual antiplatelet therapy-DAPT (aspirin + clopidogrel) is not associated with increased platelet inhibitory effects in patients with coronary artery disease receiving DAPT, thus no increase in bleeding complications were identified (14).

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Patients and methods

Ethics approval and informed consent. The patients were recruited from the Cardiovascular Disease Institute, Timisoara, Romania. Prior to commencement of the study, all patients included in our study granted written informed consent. Approval for the study (no. 8461/04.12.2018) was obtained from the Ethics Committee of the Cardiovascular Disease Institute (Timisoara, Romania).

Inclusion and exclusion criteria. Inclusion criteria were represented by prolonged chest pain 24 h or within the past week prior to enrollment, ECG changes (ST depression or negative T waves) with positive high-sensitive troponin levels. Exclusion criteria were the presence of malignancy, pregnancy, stroke within the previous 3 months, renal or hepatic diseases, severe heart failure with left ventricular ejection fraction of <35%, as well as contraindications to pentoxifylline treatment and chronic anticoagulation therapy. ST elevation myocardial infarction (STEMI) patients were also excluded from randomization because they were subjects in another study.

Patient data. Patients were included in the present study over the period December 2018 to May 2020; the last trial control was in June 2021. A total of 500 patients were included in the present study and randomized equally into groups A and B. The mean age was 62.3±10.3 years. Of the 500 patients, 80.4% were male, 20.8% had diabetes, 49.4% had hypertension, and 42% were currently smoking.

Patients were randomized to receive standard therapy, i.e., aspirin, clopidogrel or ticagrelor, and statin plus placebo in one arm (group A). In the other arm (group B), pentoxifylline 400 mg TID was added to the standard therapy. Coronary angiography was performed in all the patients enrolled in the study, 0-72 h after admission, according to the European Society of Cardiology (ESC) guidelines recommendations (15). All the patients who needed revascularization (interventional or surgical) were treated according to ESC recommendations (16). The patients were followed up at 1, 3 and 6 months after inclusion in the study. Levels of IL-6, TNF α, hs CRP were assessed at baseline (T0), 48 h (T1) and 15 days (T2).

Study end points. As a primary outcome, the MACEs [defined as a composite of ACS (recurrent angina, MI), ischemic-driven revascularization, death from any cause or stroke] at 1 year were assessed. An additional secondary composite endpoint was to determine the way pentoxifylline treatment affected stent restenosis in patients with PCI revascularization on admission and the levels of hs-CRP and IL-6, and TNF-α.

Statistical analysis. The statistical analysis was performed using CsS/Statistics 3.1 software (StatSoft Corp.) and EPI INFO 6.04. The Student's t-test and log rank test were used to make comparisons and determine differences between the two groups. Relative risk (RR) and 95% confidence interval (95% CI) were also obtained. In the primary outcome, a linear regression model, and a Wald test were used to reject the null hypothesis. Data are reported as RRs with 95% CI. $P<0.05$ was considered to indicate statistical significance.

Results

Patient data. A total of 500 patients were screened and divided into two groups (with 250 being assigned to group A and 250 to group B). Patients were followed up for a median of 20 months after being included in the study. The mean age of the participants was 62.3±10.3 years, 80.4% were male, 20.8% had diabetes, 49.4% had hypertension, and 42% were current smokers. In addition, following admission, 59.4% had hs-CRP ≥2 mg/l and all 500 patients had abnormal troponin at baseline. The revascularization procedures were introduced: 87.4% patients underwent PCI and the remaining patients were treated with medication or underwent CABG according to the ESC guidelines.

Patient characteristics at baseline. The trial medication was discontinued in 16.4% of patients in group A (n=41) and in 16% of patients in group B (n=40). They were considered dropouts and were excluded from the final analysis. In group A, 209 patients remained and in group B, 210 patients remained. Patient characteristics at baseline are presented in Table I. There was no major side effect reported in the two groups. Patients in group B (n=5, 1%) complained of abdominal discomfort and nausea, headache (n=3, 0.6%) but did not

Table I. Baseline characteristics.

Characteristics	Group A: Standard therapy and placebo (n=209)	Group B: Pentoxifylline added to standard therapy (n=210)
Age (years)	61.8±10.2	62.3±10.7
Male sex [no. (%)]	167 (79.9%)	168 (80%)
Body mass index, kg/m^2	29±4.8	28.8±5.2
Current smoking [no. (%)]	83 (39.7%)	84 (40%)
Diabetes [no. (%)]	40 (19.13%)	42 (20%)
Hypertension [no. (%)]	105 (50.2%)	102 (48.5%)
History of PCI [no. (%)]	30 (14.42%)	32 (15.23%)
History of CABG [no. (%)]	10 (4.78%)	10 (4.76%)
hs-CRP ≥2 mg/l [no. (%)]	126 (60.28%)	128 (60.95%)
Patients who underwent PCI [no. (%)]	184 (88%)	183 (87.14%)

CABG, coronary artery by-pass grafting; hs-CRP, highly sensitive C-reactive protein; PCI, percutaneous coronary intervention.

Table II. Primary clinical endpoints.

Components of primary end points	Group A (n=209)	Group B (n=210)	Relative Risk (RR) (95% CI)	P-value
Death	17 (8.13%)	16 (7.61%)	0.93 (0.48-1.80)	P=0.84
Non-fatal MI	6 (2.87%)	7 (3.33%)	1.1 (0.39-3.39)	P=0.78
Stroke	2 (0.95%)	2 (0.95%)	0.99 (0.14-6.99)	P=0.99
Coronary revascularization	8 (3.82%)	1 (0.47%)	0.12 (0.015-0.985)	P=0.048

MI, myocardial infarction.

discontinue the medication. Symptoms disappeared before discharge.

Another important aspect in the present study was the evolution of inflammatory markers. CRP, TNF-α and IL-6 levels at baseline were examined at 24 h and at 1 month. The secondary outcome for this study was the effect of adding pentoxifylline [400 mg TID to standard therapy on inflammatory markers (hs-CRP, TNF-α, and IL-6 level)] and the correlation between that level of inflammatory marker and the rate of MACEs at 1 year.

At admission, the median IL-6 level was 7.3±5.1 pg/l in group A vs. 7.2±4.8 pg/l in group B [P=NS (not significant)], median hs-CRP level was 1.35±1.2 mg/l in group A vs. 1.25±1.2 mg/l in group B (P=NS) and the median TNF-α level was 34.5±14.8 pg/l in group A vs. 33.4±14.2 pg/l in group B (P=NS). It was found that at 48 h (T1) there was an attenuation of rise in the hs-CRP and TNF-α levels in group B after administration of pentoxifylline compared with group A that received a placebo. Administration of pentoxifylline in group B attenuated the increase in hs-CRP from baseline (1.25±1.2 mg/l) to 48 h (5.3±1.6 mg/l) when compared with group A (baseline, 1.35±1.2 mg/l and 48 h, 8.9±2.2 mg/l, P<0.001). Regarding the TNF-α level, administration of pentoxifylline reduced the level in group B at 48 h (at admission 33.4±14.2 pg/l and 23±19.3 pg/l at 48 h), but not in group A (at admission 34.5±14.8 pg/l, P=NS and 43.3±18.5 pg/l at T1, P<0.001). This finding did not apply to the IL-6 level which was not affected by administration of pentoxifylline (group A at T0, 7.3±5.1 pg/l and at T1, 24.4±8.6 pg/l; group B at T0, 7.2±4.8 pg/l and at T1, 24.4±8.6 pg/l, P=NS). In addition, at 15 days (T2), it was noted that administration of pentoxifylline in group B normalized earlier the hs-CRP and TNF-α level compared with group A (hs-CRP: group A at T2, 4.4±2.5 mg/l vs. group B at T2, 1.2±1.0 mg/l, P<0.001; TNF-α: group A at T2, 10.2±7.3 pg/l vs. group B at T2, 6.2±3.4 pg/l, P<0.001). This did not apply to the IL-6 level at T2 (IL-6: group A at T2, 12.5±6.5 pg/l vs. group B at T2, 11.3±7.2 pg/l, P=NS).

Primary endpoint. MACEs were present in 12.38% (n=26) in group B, and in 15.78% (n=33) in group A (RR, 0.78; 95% CI, 0.486-0.1.263; P=0.40). RR for the components of the primary endpoint, including death (RR, 0.93; 95% CI, 0.48-1.80, P=0.84), non-fatal MI (RR, 1.1; 95% CI, 0.39-3.39, P=0.78), stroke (RR, 0.99; 95% CI, 0.14-6.99, P=0.99), and the need for coronary revascularization (RR, 0.12; 95% CI, 0.015-0.985, P=0.048) are presented in Table II.

Discussion

Adding pentoxifylline 400 mg three times a day (TID) to standard therapy in ACS patients may improve clinical outcome, reducing proinflammatory and increasing the

anti-inflammatory response. Treating inflammation in ACS is a fact to be considered when selecting medication. (11,17).

CABG is associated with a high inflammatory state. Administration of pentoxifylline before surgery was found to decrease the intensive care unit stay, ventilation time by reducing TNF-α and IL-6 levels, without influenced the troponin level (11,18,19).

In the present study, administration of pentoxifylline in patients with high inflammatory state (ACS) reduced the level of hs-CRP, TNF-α but not IL-6.

In a study by Altman *et al* (20), meloxicam, an anti-inflammatory drug, was added to heparin and aspirin in the treatment of patients with ACS without ST elevation. The study supports our hypothesis of the potential benefits of anti-inflammatory treatment (meloxicam in this case), and that inhibition of inflammation may decrease short-term events, mainly the occurrence of angina pectoris and revascularization in ACS patients without ST-segment elevation.

The outcome of patients with ACS might be improved by administration of anti-inflammatory drugs that lower the levels of IL-1 and IL-6 as previously shown (21-23). In the MRC-ILA Heart study administration, anakinra (an IL-1 receptor antagonist) reduced the level of hs-CRP without affecting troponin but with a high rate of MACEs at 3-month follow-up (24).

Kleveland *et al* (25) used tocilizumab to block the IL-6 receptors as an anti-inflammatory drug in patients with non-ST elevation myocardial infarction (NSTEMI). They concluded that tocilizumab attenuated the inflammatory response (reduced hs-CRP levels) and the level of myocardial injury after PCI (troponin level was low in the tocilizumab group) but did not reduce cardiovascular outcomes.

In another study, the use of colchicine treatment for five days in STEMI patients did not improve the outcome of the patients (26). In the COMPlement inhibition in MI treated with thrombolytics (COMPLY) study, the role of a novel C5 complement monoclonal antibody fragment pexelizumab was investigated. The administration of pexelizumab did not reduce infarct size or improve clinical outcome (27). Identical results as those obtained in the COMPlement inhibition were obtained in the MI treated with angioplasty (COMMA) trial (28,29).

A meta-analysis aiming to assess the risk/benefit profile of pexelizumab (bolus + infusion) vs. a placebo in addition to current medication in the management of patients with STEMI or undergoing coronary artery bypass showed no benefit, but concluded that it may reduce the risk of death in patients revascularized by coronary artery bypass grafting (30).

Administration of varespladib (a non-specific pan sPLA2 inhibitor) had favorable effects on atherosclerotic plaques, as shown in the Vista-16 study (31). The Colchicine Cardiovascular Outcomes Trial (COLCOT) used colchicine as an anti-inflammatory drug in patients with ACS. They found a lower incidence of MACE in the colchicine arm due to a reduced need for coronary revascularization and lower stroke number (32,33).

There are few studies of pentoxifylline in ACS. In a group of STEMI patients, the authors administered 1,200 mg pentoxifylline before thrombolytic but no benefit regarding MACEs and biomarker levels was observed (34). Previous findings have shown that pentoxifylline may exert an anti-inflammatory effect and administration in ACS could be beneficial (17).

To the best of our knowledge, the present study is the first that uses pentoxifylline in patients with ACS (NSTEMI) with primary endpoint represented by MACEs and secondary endpoints being the level of inflammatory markers.

The results showed that there were no differences between groups regarding MACEs as the primary endpoint but adding pentoxifylline was associated with a lower need of coronary revascularization (RR, 0.12; 95% CI, 0.015-0.99, P=0.004). This result was probably determined by the low number of acute stent thrombosis events and restenosis in the pentoxifylline group. Adding pentoxifylline to standard therapy in ACS patients could influence the inflammatory marker level. In the present study, the addition of pentoxifylline to standard treatment in patients with ACS reduced the increase in hs-CRP and TNF-α levels and caused early normalization but did not influence the IL-6 level.

There are several limitations to the present study. This was a single-center experience study, not a multicenter trial. Secondly, it was not a double-blinded randomized trial. Thirdly, the number of patients included was small and this may have affected the overall results of the trial. Therefore, the power of an adequate sample size to demonstrate the benefit of pentoxifylline in ACS is lacking.

In conclusion, the addition of pentoxifylline to standard treatment in patients with ACS reduced the rise of hs-CRP and TNF levels and caused early normalization but did not influence the IL-6 level. This attenuation in inflammation did not improve MACEs at 1 year, although it may have some benefit on coronary revascularization. These results suggest a potential benefit of adding pentoxifylline to standard treatment in patients with non-STEMI ACS, but further clinical trials are needed in order to draw definitive conclusions.

Acknowledgements

Professional editing, linguistic and technical assistance performed by Irina Radu, Individual Service Provider (credentials: E0048/2014, Medicine-Pharmacy).

Funding

No funding was received.

Availability of data and materials

Corresponding author will provide all supplementary data and materials by request. The materials are not publicly available to limit the amount of publicly available personal information, as classified by the European Union General Data Protection Regulation.

Authors' contributions

DMB and LP contributed to the study conception and design. DMB, DAB, MB, CTL and CM were involved in the investigation of patients, collection of resources, and analysis and

interpretation of results. DMB and LP drafted and wrote the manuscript. All the authors have read and approved the final article. DMB and LP confirmed the authenticity of the raw data.

Ethics approval and consent to participate

Approval of the study (8461/04.12.2018) was provided by the Ethics committee of the Cardiovascular Disease Institute Timisoara (Romania). Written informed consent was obtained from patients prior to enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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