https://doi.org/10.31925/farmacia.2023.2.19 **ORIGINAL ARTICLE**

PENTOXIFYLLINE AND INFLAMMATION MARKERS IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Abstract

In 500 consecutive patients with acute coronary syndrome, we added pentoxifylline 400 mg TID to standard therapy (group B) *vs*. placebo (group A). Blood was harvested for inflammatory markers (hsCRP, IL-6, TNF alpha) after admission, named T0, and at 48 h and 15 days after the acute event, called T1 and T2. We find that at 48 h (T1) was an attenuation of rise in hsCRP and TNF alpha level in group B compared with group A. Patients who received pentoxifylline (group B) attenuated the increase of hsCRP from baseline (1.25 ± 1.2 mg/L) to 48 hours (5.3 ± 1.6 mg/L), but not in group A patients who received a placebo (baseline 1.35 ± 1.2 mg/L and 48 hours 8.9 ± 2.2 mg/L, $p < 0.001$). The results were the same regarding TNF alpha level (administration of pentoxifylline reduced level in group B at 48 hours (at admission 33.4 ± 14.2 pg/L and 23 ± 19.3 pg/L at 48 hours), but not in group A ($p < 0.001$). However, the IL-6 level was not modified by the administration of pentoxifylline (group A, T0- 7.3 ± 5.1 pg/L and T1 24.4 ± 8.6 pg/L; group B, T0- 7.2 ± 4.8 pg/L and T1- 24.4 ± 8.6 pg/L, p = NS). At 15 days (T2) administration of pentoxifylline in group B normalized earlier the hsCRP and TNF alpha levels compared with group A (hsCRP - group A, T2- 4.4 ± 2.5 mg/L *vs*. group B, T2- 1.2 ± 1 mg/L, $p < 0.001$; TNF alpha- group A, T2-10.2 ± 7.3 pg/L *vs*. group B, T2-6.2 ± 3.4 pg/L, $p < 0.001$). This do not apply to IL-6 level at T2 (IL-6- group A, T2-12.5 ± 6.5 pg/L *vs*. group B, T2-11.3 ± 7.2 pg/L, p = NS). No correlation was found between the reduced level of inflammatory marker (hsCRP and TNF alpha) by adding pentoxifylline 400 mg TID to standard therapy.

Rezumat

La 500 de pacienți diagnosticați cu sindrom coronarian acut alături de terapia standard li s-a administrat 400 mg de pentoxifilina de trei ori pe zi (grupul B) *vs*. placebo (grupul A0. Tuturor pacienților incluși s-au recoltat sânge pentru măsurarea markerilor inflamatorii la internare, numit T0, la 48 ore și la 15 zile după evenimentul acut, numite T1 si T2. Rezultatele au arătat că la 48 de ore (T1) a existat o atenuare in creșterea nivelului PRC înalt sensibile și TNF alpha în grupul B comparativ cu grupul A. La pacienți care au primit pentoxifilină (grupul B) s-a constatat atenuarea creșteri PRC înalt de la nivelul inițial (1,25 ± 1,2 mg/L) la 48 ore (5,3 ± 1,6 mg/L), dar nu și la pacienți din grupul A care au primit placebo (inițial 1,35 ± 1,2 mg/L și la 48 ore 8,9 ± 2,2 mg/L, $p < 0,001$). Rezultatele au fost similare pentru nivelul TNF alpha (administrarea de pentoxifilină reduce nivelul în grupul B la 48 de ore (la internare 33,4 ± 14,2 pg/L și 23 ± 19,3 pg/L la 48 ore), dar nu în grupul A ($p < 0,001$). Oricum, nivelul de IL-6 nu a fost modificat de administrarea de pentoxifilină (grupul A, T0- 7.3 ± 5.1 pg/L și T1 24.4 ± 8.6 pg/L; grupul B, T0- 7,2 ± 4,8 pg/L și T1- 24,4 ± 8,6 pg/L, p = NS). La cinsprăzece zile (T2) administrarea de pentoxifilina în grupul B a dus la normalizarea mai rapidă a nivelului PRC înalt sensibile și TNF alpha comparativ cu grupul A (hsCRP - grupul A, T2- 4,4 ± 2,5 mg/L *vs*. grupul B, T2- 1,2 ± 1 mg/L, $p < 0,001$; TNF alpha- grupul A, T2-10,2 ± 7,3 pg/L *vs*. grupul B, T2-6,2 ± 3,4 pg/L, $p < 0,001$). Acest lucru nu este valabil în cazul nivelului de IL-6 la T2 (IL-6- grupul A, T2-12,5 ± 6,5 pg/L *vs*. grupul B, T2-11,3 ± 7,2 pg/L, p = NS). Nu a fost găsită nici o corelație directă între reducerea nivelului markerilor inflamatorii (PRC înalt sensibilă și TNF alpha) și evenimentele cardiovasculare majore (MACE) prin adăugare pentoxifilinei la tratamentul standard.

Keywords: acute coronary syndrome, pentoxifylline, inflammation markers, MACE

Introduction

Pentoxifylline is a methylxanthine derivative that influences blood rheology by lowering plasma fibrinogen, promoting local fibrinolysis, reducing neutrophil activation and enhancing erythrocyte distensibility [1].

Pentoxifylline seems to have systemic anti-inflammatory effects delaying the progression of atherosclerosis and reducing the risk of cardiovascular events, as shown

in several clinical trials [2]. The molecular biology underlying these various effects has yet to be well known. A meta-analysis published some years ago found that pentoxifylline did not alter blood pressure (BP) or plasma interleukin (IL) 6 concentration. However, it significantly reduced circulating TNF alpha and high sensitive C reactive protein (hs CRP) concentrations [3].

The link between inflammation and acute coronary syndromes (ACS) is complex and needs to be fully understood. Inflammation can lead to cytokine release, activating the endothelium and attenuating its natural antiadhesive and anticoagulant properties [4].

Inflammation is a critical pathway in the pathogenesis of atherosclerosis. The histopathological analysis of coronary arteries from patients who died following an acute coronary syndrome revealed the presence of inflammatory infiltrate in ruptured atheroma plaques (lymphocytes, foam cells, macrophages) [5].

In excellent reviews, Filippo Crea and Peter Libby [6] propose to split coronary artery thrombosis due to plaque rupture into cases with or without signs of concomitant inflammation. This distinction may have substantial therapeutic implications as direct anti-inflammatory interventions for atherosclerosis emerge.

Investigating the expression of inflammatory markers is one of the research areas of interest today. Increased concentrations of hsCRP have been reported in unstable angina and acute myocardial infarction. Aldo, TNF alpha, IL-1, IL-6 and IL-8 levels are raised in unstable angina [7, 8]. Some clinical trials report that hsCRP levels (> 3.0 mg/L) could be associated with complications in patients with ACS [9]. The principal cytokines driving the hepatic production of these acute-phase reactants are IL-1 and IL-6. Concentrations of IL-6 correlate well with the level of hsCRP and are both with high levels in ACS and associated with an adverse prognosis [10].

Although, the evidence supports hsCRP as an independent risk factor for ischemic heart disease, the mechanism is unknown. High sensitive CRP levels could be a marker of ongoing inflammation in the atherosclerotic plaque responsible for plaque progression or complication. In ACS, we find persistent instability for weeks to months after the initial presentation, which correlates with high levels of hsCRP [11].

In a contemporary multicenter prospective cohort study in Switzerland, the risk of major adverse cardiovascular events (MACE) was higher in patients with hsCRP levels between 2 and 5 mg/L or higher compared with hsCRP below two mg/L [12]. It is reported that in up to 50% of patients with ACS serum hsCRP concentrations remain increased at the time of discharge and three months follow-up [13].

Patients with ACS need, in most cases, interventional revascularization or surgery. Both procedures cause different levels of iatrogenic myocardial injury that can be another source of inflammation [14]. Pentoxifylline treatment is not associated with increased platelet inhibitory effects and adding to standard dual anti-platelet therapy-DAPT (aspirin + clopidogrel) does not increase bleeding complications [15].

In our study, we tried to find what happened with the inflammatory marker (hsC reactive, TNF alpha, IL-6 level) when adding pentoxifylline 400 mg TID to standard therapy *vs*. placebo and standard treatment in 500 consecutive patients with ACS (unstable angina, non-ST elevation myocardial infarction).

Materials and Methods

Study design

All patients included in our study were addressed to Cardiovascular Disease Institute in Timișoara, Romania, with ACS. The participating institutions granted the ethical study approval, and after that, all patients included signed written informed consent. All participants in this study were granted ethical approval, sign informed consent, and the study was conducted in accordance with the Declaration of Helsinki [16]. Inclusion criteria represented prolonged chest pain 24 hours or within the past week before registration, ECG changes (ST depression or harmful T waves) with positive high-sensitive troponin levels. Exclusion criteria were malignancy, stroke within the previous three months, pregnancy, renal or hepatic diseases, severe heart failure, left ventricular ejection fraction of less than 35%, contraindications to pentoxifylline treatment, and chronic anticoagulation therapy. In our study, we do not include patients with acute ST-elevation myocardial.

Patients were divided into two groups- standard therapy plus placebo in one arm - group A and in the other arm (group B) - pentoxifylline 400 mg TID was added. At the time of randomization, all patients received standard therapy consisting of beta-blockers, angiotensin-converting enzyme inhibitors, dual anti-platelet therapy, and statins. We performed coronary angiography in all patients enrolled in the study, 0 to 72 hours after admission, and they were treated using the European ACS guidelines recommendations [17, 18]. After acute events, patients were evaluated at 15 days, one month, three months, and every six months during follow-up.

In all patients, CRP, TNF alpha, and IL-6 levels were obtained at admission (T0), 48 h (T1), and at 15 days (T2).

Peripheral venous blood under aseptic conditions was withdrawn from patients. Blood was harvested for inflammatory markers (hsCRP, IL-6, TNF alpha) after admission, named T0, as well as at 48 h and at 15 days after the ischaemic event, called T1 and T2. The collected samples will be frozen and maintained at -80°C until they are sent to the central laboratories, which will produce high-sensitivity CRP, interleukins 6, and tumoral necrosis factor-alpha (TNF-alpha). The

serum's C-reactive protein (CRP) concentrations were determined using the Latex Immunoturbidimetry method on the Cobas 6000 analyser (Roche Diagnostics, Indianapolis, USA). The average value was considered when hsCRP level < 0.15 mg/L. Serum levels of TNF alpha were measured using the Chemiluminescent immunoassay (CLIA) method on the Cobas 8000 analyser (Roche Diagnostics, Indianapolis, USA). The average value was considered when TNF alpha level < 8.1 pg/L. Serum levels of IL-6 were measured using an Electrochemiluminescence immunoassay (ECLIA method) on the Cobas 8000 analyser (Roche Diagnostics, Indianapolis, USA). The average value was considered when IL-6 level < 7 pg/L.

Study End Points

The primary outcome of this study was the influence of adding pentoxifylline 400 mg TID to standard therapy on an inflammatory marker (hsCRP, TNF alfa, IL-6 level) and the correlation between that level of inflammatory markers and rate of major adverse cardiovascular events (MACE) at one year. MACE is a composite of acute coronary syndrome (recurrent angina, MI), ischemic-driven revascularization, and death from any cause of stroke. The result regarding the rate of MACE at one year was reported elsewhere.

Statistical analysis

Measurement data are reported as means ± SDs, and the count data are expressed as percentages. We used the Student's *t*-test or analysis of variance for the measurement data; the $\chi 2$ test was used to compare the count data. Wilcoxon's two-sample test was used to the calculated p-value for separate group data. Spearman's rank-order correlation analysis was used to evaluate correlations. Cytokine associations with events were analysed with univariate analysis (logistic Regression). Variables significantly associated with events at univariate analysis were then entered into multivariate analysis to identify potential independent associations. For the association between increased cytokines value and clinical affairs, we use the ANOVA test. A p-value < 0.05 was statistically significant. All data were analysed using the SPSS 13.0 software.

Results and Discussion

Trial enrolment began in December 2017 and was completed in May 2020; the last trial visit was in June 2021. A total of 500 patients consecutive underwent evaluation. The trial medication has been discontinued in 16.4% of patients in group A (n = 41) and 16% in group B (n = 40). After excluding patients with discontinue medication we included 209 patients in group A and 210 patients in group B. No significant side effect was reported in the two groups. Patients in group B (n = 5, 1%) complained of headache, abdominal discomfort, and nausea (n = 3, 0.6%), but these symptoms did not lead to medication dropout. Symptoms disappeared before discharge. The mean age of the participants was 62.3 ± 10.3 years; 80% were male, 20% had diabetes, 50.6% had hypertension, and 39.8% were currently smoking. We presented the baseline characteristics of both groups in Table I.

Table I

Baseline characteristics

Characteristics	Group A: Standard therapy and placebo (209 patients)	Group B: Pentoxifylline added to standard therapy 210 patients)
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%)
High-sensitivity C-reactive protein ≥ 2 mg/L, (%)	126 (60.28%)	128 (60.95%)
No. of patients who underwent PCI	184 (88%)	183 (87.14%)

PCI, percutaneous coronary intervention; CABG, coronary artery by-pass grafting

We measured the level of IL-6, TNF alpha, and hsCRP at baseline (T0), 48 h (T1) and 15 days (T2). At admission, 59.4% had high-sensitivity C-reactive protein ≥ two mg/L, and all patients had abnormal troponin at baseline. We performed PCI in 87.4% of patients, and the rest were treated with medication or CABG according to the guidelines.

The level of inflammatory markers studies (IL-6, hs CRP, TNF alpha) at admission (T0), 48h (T1), and 15 days (T0) are presented in Table II.

At admission 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), median hsCRP level was 1.35 ± 1.2 mg/L in group A *vs.* 1.25 ± 1.2 mg/L in group B (p = NS), and median TNF alpha level was 34.5 ± 14.8 pg/L in group A *vs.* 33.4 ± 14.2 pg/L in group B (p = NS). We find that at 48 h (T1) was an attenuation of rise in his CRP and TNF alpha level in group B after administration of pentoxifylline compared with group A who received a placebo. Administration of pentoxifylline in group B attenuated the increase of hsCRP from baseline

(1.25 ± 1.2 mg/L) to 48 hours (5.3 ± 1.6 mg/L) when compared with group A (baseline 1.35 ± 1.2 mg/L and 48 hours 8.9 ± 2.2 mg/L, p < 0.001). Regarding TNF alpha level administration of pentoxifylline reduced level in group B at 48 hours (at admission 33.4 ± 14.2 pg/L and 23 ± 19.3 pg/L at 48 hours), 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). The IL-6 level was not affected by the administration of pentoxifylline (group A, T0 7.3 ± 5.1 pg/L and T1 24.4 ± 8.6 pg/L; group B, T0 7.2 ± 4.8 pg/L and T1 24.4 ± 8.6 pg/L, p = NS). Also, at 15 days (T2), we find that by adding pentoxifylline to standard therapy (group B), the hsCRP and TNF alpha levels normalized earlier (hsCRP - group A, T2 4.4 ± 2.5 mg/L *vs*. group B, T2 1.2 ± 1 mg/L, p < 0.001; TNF alpha- group A, T2 10.2 ± 7.3 pg/L *vs*. group B, T2 6.2 ± 3.4 pg/L, p < 0.001). This do not apply to IL-6 level at T2 (IL-6- group A, T2 12.5 ± 6.5 pg/L *vs*. group B, T2 11.3 ± 7.2 pg/L, p = NS).

Table II

Level of inflammatory markers

Inflammatory marker	Time	Group A	Group B	p value
IL-6	T0	7.3 ± 5.1 pg/L	7.2 ± 4.8 pg/L	p = NS
	T1	24.4 ± 8.6 pg/L	23.9 ± 7.8 pg/L	p = NS
	T2	12.5 ± 6.5 pg/L	11.3 ± 7.2 pg/L	p = NS
hsCRP	T0	1.35 ± 1.2 mg/L	1.25 ± 1.2 mg/L	p = NS
	T1	8.9 ± 2.2 mg/L	5.3 ± 1.6 mg/L	p < 0.001
	T2	4.4 ± 2.5 mg/L	1.2 ± 1 mg/L	p < 0.001
TNF alpha	T0	34.5 ± 14.8 pg/L	33.4 ± 14.2 pg/L	p = NS
	T1	43.3 ± 18.5 pg/L	23 ± 19.3 pg/L	p < 0.001
	T2	10.2 ± 7.3 pg/L	6.2 ± 3.4 pg/L	p < 0.001

Data are expressed median ± SD; Normal value - IL-6 < 7 pg/L; hsCRP < 0.15 mg/L; TNF alpha < 8.1 pg/L, NS = not significant.

MACE event occurred in 12.38% (n = 26) in group B and 15.78% (n = 33) in group A (RR, 0.78; 95% confidence interval [CI], 0.486 to 0.1.263; p = 0.40), death (RR, 0.93; 95% CI, 0.48 to 1.80, p = 0.84), non-fatal myocardial infarction (RR, 1.1; 95% CI, 0.39 to 3.39, p = 0.78), stroke (RR, 0.99; 95% CI, 0.14 to 6.99, p = 0.99), and the need for coronary revascularization (RR, 0.12; 95% CI, 0.015 to 0.985, p = 0.048).

No correlation was found between the reduced level of inflammatory marker (hsCRP and TNF alpha) by adding pentoxifylline 400mg TID to standard therapy and MACE (Superman rho = 0,0015, p = 0.33), but was a correlation with reduced need of coronary revascularization in group B *vs*. group A.

In our study was no difference between groups regarding MACE as the primary end-point, but adding pentoxifylline was associated with a lower need for coronary revascularization (RR, 0.12; 95% CI, 0.015 to 0.99, p = 0.004). This result was because of a low number of acute stent thrombosis and restenosis in pentoxifylline group B and was correlated with a reduced level of inflammatory marker (Superman rho = 0.47, p < 0.0001).

In the past years, the role of inflammation in ACS has been well established. We now know the part of inflammatory markers in ACS, but we do not see the correlation between these elevated inflammatory markers (especially hsCRP, IL-6, TNF alpha) and clinical outcome. Administration of pentoxifylline 400 mg TID in ACS patients may improve clinical outcomes by reducing proinflammatory and increasing anti-inflammatory response [19, 20]. It also improved outcomes in patients with coronary artery disease who required CABG revascularization [1, 21, 22]. Treating inflammation in acute coronary syndrome is a fact to be considered when selecting a medication. In the study by Morrow *et al*. (TIMI 11A trial), CRP level elevated to ≥ 1.55 mg/dL was a more sensitive marker for increased mortality than was early troponin T level. They concluded that in patients with ACS (UA or NSTEMI), elevated CRP levels correlate with 14-day cardiovascular mortality [23]. We do not find such a correlation in our study. In patients with ACS, the elevation of acute-phase reactants (especially CRP, which may remain elevated for three months) could represent a marker of instability and recurrent angina episode [24]. According to several studies, CRP level is significantly higher in complex lesions, and this could probably be correlated with a new therapeutic target [25].

Past studies have shown that in patients receiving a conventional stent, hsCRP values > 2.5 mg/L at 30 days were associated with a greater incidence of late MACEs, particularly in-stent restenosis [26]. In our study, the administration of pentoxifylline was not correlated with reducing MACE despite the reduction in his CRP level. Still, it was associated with fewer restenosis and thrombosis in group B.

We know from a past study that elevated levels of IL-6 are associated with an increased risk of future MI in apparently healthy men [27]. In patients with coronary heart plasma, IL-6 levels are significantly increased and not influenced by other risk factors [28]. The levels of IL-6 and TNF-alpha are higher in patients with stable angina and correlate with worse prognosis [29].

Interleukin-6 (IL-6) is a local and circulating marker of coronary plaque inflammation and was increased in patients with STEMI [30], unstable angina[31, 32], and NSTEMI patients [33] than in those with stable angina [33]. IL-6 levels began to increase after troponin and CK release (range 8 - 20 with a maximal after 36h (range 24 - 48 h).

Plasma concentrations of IL-6 and hsCRP have been predictive, especially in patients with acute coronary syndrome. The different study found no correlation between the level of troponin and CK and the extent of the IL-6 increase, but maximal IL-6 levels correlated significantly with maximal CRP levels [32, 34, 35].

In another study, ACS patients showing elevated IL-6 levels (≥ 3.3 pg/mL) had an 8.6-fold increased hazard of dying from cardiovascular causes within six years as compared to patients with low IL-6 values (< 3.3 pg/mL) and suggested that circulating IL-6 levels are more accurate to predict long-term cardiovascular mortality than concentrations of hsCRP [36].

The inflammatory cytokine TNF alpha exerts deleterious cardiovascular effects. The level of TNF alpha is high in a patient with acute myocardial infarction [37, 38]. Still, the administration of Etanercept (a TNF alpha antagonist) showed no benefit in patients with acute myocardial infarction [39].

In a pilot study that included patients with acute coronary syndrome without elevation of the ST segment were administered, at the time of admission, 15 mg of meloxicam intravenously, followed by 15 mg a day *per os*, which was maintained for 30 days. The author reported that recurrent angina, myocardial infarction, and death were significantly less frequent ($p = 0.007$) in the group treated with meloxicam [40].

Another study suggested that the blockade of interleukin-1 (IL-1) and IL-6 as an anti-inflammatory treatment might improve the outcome of ACS. Randomized trials have shown that anakinra, an IL-1 receptor antagonist (IL-1Ra), attenuated hsCRP levels in patients with both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI). In the MRC-ILA Heart Study, 182 patients with NSTEMI were randomly assigned to anakinra or placebo, and the authors found that hsCRP level within the first seven days was significantly reduced by anakinra as compared to placebo. Anakinra did not reduce troponin T (TnT) release and was associated with a disturbing increase in major cardiovascular events at a 3-month follow-up [41].

In a study by Altman *et al*. [42], meloxicam was added to treat patients with ACS without ST elevation. The outcome of these patients improved regarding the occurrence of angina pectoris and the need for revascularization. The study supports our hypothesis of the potential benefits of anti-inflammatory treatment (meloxicam in this case) [43]. Administration of ED50 diclofenac-eugenol (DFC + EUG) in healthy rats has no effect on proinflammatory cytokines (IL-6, TNFα and MAPKs) except for the increased level of IL-1β [44].

Cleveland *et al*. [45] used tocilizumab, an anti-inflammatory drug indicated in treating adult patients with rheumatoid arthritis in NSTEMI patients. The cardiovascular outcome was not reduced even though tocilizumab attenuated the inflammatory response (reduced hsCRP levels) and troponin level after PCI. Also, in our study, adding pentoxifylline does not reduce MACE despite reducing hsCRP and TNF alpha levels.

Administration of pexelizumab (C5 complement inhibitor) did not reduce infarct size or improve clinical outcomes in COMPLY study conducted by Mahaffey *et al*. [46] and in the COMMA trial by Granger *et al*. [47, 48].

In traditional medicine, *Polygonum plebeium* is used to treat inflammation-related diseases. The anti-inflammatory effect of the aqueous methanolic extract of *Polygonum plebeium* was demonstrated in a recent study, but did not include patients with acute coronary syndrome [49].

An interesting study was The Colchicine Cardiovascular Outcomes Trial (COLT), which used colchicine added to standard treatment in patients with ACS. In the group arm treated with colchicine, the incidence of MACE was low because of a low number of strokes and a reduced need for coronary revascularization [50, 51].

There are few studies with pentoxifylline in ACS. Administration of 1,200 mg pentoxifylline before thrombolytic treatment in STEMI patients has no benefit regarding MACE. Also not change the cardiac injury and inflammation marker level [52]. We know that pentoxifylline may exert an anti-inflammatory effect, and some authors speculated that t could help treat patients with ACS. But no study was done before use to test that hypothesis [20].

We used our hypothesis that adding pentoxifylline in ACS patients could benefit the outcome and the level of inflammatory markers. Administration of pentoxifylline in group B over standard therapy in our study attenuated the inflammation by reducing the rise of hsCRP and TNF alpha level and caused early normalization but did not influence IL-6 level.

We found no correlation between the reduced level of inflammatory marker (hsCRP and TNF alpha) by adding pentoxifylline and MACE. But in the group treated with pentoxifylline was a lower need for coronary revascularization (RR, 0.12; 95% CI, 0.015 - 0.99, $p = 0.004$). This is likely done to reduce in-stent restenosis by lower inflammation and low in-stent thrombosis by improving blood rheology. Maybe a combination with a medication that lowers the IL-6 levels could improve the outcome.

We have some limitations to our study. First, it was not a multicenter experience, and we did not perform

double-blinded randomization. Secondly, the conclusion of our study may be influenced by the small number of participants. But inflammation has a significant role in ACS and, in the future, will become a target for therapy.

Conclusions

In conclusion, treating patients with ACS with pentoxifylline attenuated the inflammation. Reduced the rise of hsCRP and TNF levels and caused early normalization but did not influence IL-6 levels. This attenuation in inflammation does not improve MACE at one year. But we observe a reduction of stent-related complications (restenosis and thrombosis) with benefits in the future of coronary revascularization. These results suggest a potential use of pentoxifylline in treating patients with ACS, but further clinical trials are needed to draw definitive conclusions. A combination with other medications that also reduce IL-6 levels will be beneficial.

Conflict of interest

The authors declare no conflict of interest.

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