VICTOR BABEȘ UNIVERSITY OF MEDICINE AND PHARMACY TIMIȘOARA FACULTY OF MEDICINE DEPARTMENT VI – CARDIOLOGY

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PhD THESIS

THE ROLE OF PENTOXIFYLLINE AS AN ANTI-INFLAMMATORY DRUG IN THE TREATMENT OF PATIENTS WITH ACUTE CORONARY SYNDROME

ABSTRACT

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I. **Brie, D. M.**, Mornos, C., Brie, D. A., Luca, C. T. (2023). Pentoxifylline and inflammation markers in patients with acute coronary syndrome. Farmacia, 71(2), 384-391. (IF=1.55)

II. **Brie, D. M.**, Mornos, C., Brie, D. A., Luca, C. T., Petrescu, L., & Boruga, M. (2022). Potential role for pentoxifylline as an anti-inflammatory drug for patients with acute coronary syndrome. *Experimental and Therapeutic Medicine*, *23*(6), 1-6. (IF=2.751)

III. **Brie, D.**, Sahebkar, A., Penson, P. E., Dinca, M., Ursoniu, S., Serban, M. C., Banach, M. (2016). Effects of pentoxifylline on inflammatory markers and blood pressure: a systematic review and meta-analysis of randomized controlled trials. Journal of hypertension, 34(12), 2318-2329. (IF=4.776)

I.Introduction

Coronary heart disease, especially atherosclerotic coronary heart disease, is Romania's leading cause of death. Atherosclerosis is a process that begins in childhood whose mechanisms are not fully understood, affecting younger people and more women than in the past. The role of inflammation is increasingly well-defined and has become a mandatory therapeutic target (1).

In our study, we aimed to administer pentoxifylline in addition to standard medication in patients with acute coronary syndrome (ACS). The main objectives of the research were: 1. Establishing the role of pentoxifylline as an anti-inflammatory medication in patients with acute coronary syndrome, 2. Checking the tolerance of pentoxifylline administration in these patients, 3. The effects of pentoxifylline administration on inflammatory markers (highly sensitive C-reactive protein (PCR), tumor necrosis factor-alpha (TNF α), interleukin 6 (IL-6), 4. Effects of pentoxifylline administration on major cardiovascular events, 5. Establishing a correlation between the influence on the level of inflammatory markers and major cardiovascular events, 6. Establishing future lines of research

Key words: acute coronary syndrome, pentoxifylline, inflammatory markers, major cardiovascular events

II. General Part

II. 1. Inflammation and atherosclerosis

The process of atherosclerosis is initiated by endothelium activation by various cardiovascular risk factors that trigger a cascade of events (2). An important pathogenic factor is represented by inflammation, but this was not recognized until the early 1990s. The deposition of atheroma plaques in the coronary arteries is based on a chronic inflammatory process that differs from

the mechanism that destabilizes the atheroma plaques leading to ACS (rupture, fissure, or erosion in the plaque with subsequent thrombosis) (3). Moreover, ACS patients are often treated by Percutaneous Coronary Intervention (PCI), which causes mild myocardial injury as an additional source of inflammation (4). Three potential sources of inflammation have been described in ACS patients leading to increased blood and inflammatory markers (high sensitive C-reactive protein (hs CRP), interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFα)) in addition to increased classical myocardial injury biomarkers. (5). Given the development of this concept and the emphasis on the importance of inflammation in the formation and progression of atheroma plaques, especially the role of inflammation in their destabilization (which correlates directly with mortality from coronary artery disease), it has become obvious that inflammation should be a new therapeutic target in patients with coronary artery disease, but especially in those with ACS (6).

This has motivated us to choose our research topic, considering the fight against mortality from cardiovascular disease a topic of utmost importance in the present.

II. 2. Inflammatory markers in patients with acute coronary syndromes

High levels of inflammatory markers such as hs-CRP, serum amyloid A, IL-6, IL-1 and TNFα have been found in patients with ACS, and they correlate with higher in-hospital and short-term mortality (7, 8). These inflammatory markers correlate with atheroma plaque destabilization, the degree of myocardial necrosis and coronary reperfusion lesion.

II. 3. Inflammation as a therapeutic target in patients with acute coronary syndrome

Inflammation is involved in the various stages of coronary atherosclerosis, from atheroma plaque formation and progression to their destabilization and the development of ACS. Uncontrolled inflammation causes vulnerable atherosclerotic plaques to rupture or erode with subsequent plaque thrombosis. Several inflamed atheromatous plaques may co-exist in a patient with ACS and contribute to future events, with a recurrence rate after myocardial infarction of 10-12% in the first year and 18-20% at three years (9). Until recently, after the encouragement of lifestyle change, non-pharmacological interventions to control atherosclerosis were limited to lowering blood pressure and blood cholesterol levels. Recently, more and more researchers have included inflammation as a therapeutic target in patients with coronary atherosclerosis, especially those with ACS (10). Pathophysiologic acute coronary syndromes are divided into ACS with plaque rupture and systemic inflammation, ACS plaque rupture without systemic inflammation (or with low systemic inflammation), ACS with plaque erosion, and ACS with epicardial arteries without angiographically significant.

II. 4. Antioxidant and anti-inflammatory effects of pentoxifylline

Numerous studies have shown the anti-inflammatory and antioxidant potential of pentoxifylline administration. The anti-inflammatory effect on neutrophils, macrophages and monocytes is due to its active metabolites (11, 12). The antioxidant properties are attributed to neutrophil inhibition, as activated neutrophils are known to generate superoxide via the NADPH oxidase pathway (13). Small trials have shown the potential beneficial role of pentoxifylline administration in stabilizing atheroma plaques by slowing their progression. This

may be due to the anti-inflammatory properties of this drug, manifested mainly by reduced plasma levels of proinflammatory cytokines such as TNFα , IL-1, and reductions in hs CRP levels (14-16). In a meta-analysis that we published, we showed that pentoxifylline administration reduced plasma TNFα and hs CRP concentrations without influencing plasma IL-6 concentrations. Additionally, pentoxifylline administration did not influence systolic and diastolic BP and was generally well tolerated in all included studies (17).

Given the obvious role of inflammation in all stages of the atherosclerotic process and the proven anti-inflammatory properties of pentoxifylline administration, we set out to see the role of admission of this drug in patients with ACS (unstable angina, NSTEMI).

III. EXPERIMENTAL PART

III. 1. Method

Five hundred patients referred to the Institute of Cardiovascular Diseases Timisoara (IBCV Timisoara) with acute coronary syndrome were included in our study. They were randomized into two groups (A and B). The recruitment period of patients was from December 2018 to May 2020. Patients in group A received, in addition to the standard medication, placebo, while in group B pentoxifylline, administered 400mg TID, was added for 6 months. Standard medication consisted of dual antiplatelet therapy (aspirin with a P2Y12-inhibitor - clopidogrel or ticagrelor), statin (atorvastatin, 80mg) in all patients, and angiotensin converting enzyme inhibitor (ACE inhibitor) or beta blocker where it was suitable. Prior to study enrollment, all patients signed an informed consent. The study was approved by the ethics committee of IBCV

Timisoara (8461/04.12.2018). After signing the informed consent and ethical approval was obtained, the study was conducted in concordance with the Declaration of Helsinki (18).

III. 1. 1. Inclusion criteria:1. Prolonged retrosternal pain in the last 24 hours or in the last week prior to enrollment, with a constrictive character, irradiating at the neck base, in the mandible, or on the left upper limb, lasting more than 20 minutes, with no change or partial remission on nitroglycerin administration**,** 2. Evolutive or newly discovered resting electrocardiogram changes - ST-segment elevation, negative T waves**,** 3. High titers of high-sensitivity cardiac troponin I (hs-cTnI)

III. 1. 2. Exclusion criteria

Patients presenting the following were excluded from the study:

a) Presence of malignant processes
b) Stroke in the last 3 months
c) Pregnancy
d) Severe liver failure
e) Chronic kidney disease stage IV or V (GFR below 60 mL/min/1.73 m^2)
f) Heart failure with reduced ejection fraction (left ventricular ejection fraction LVEF < 40%)
g) Contraindications to treatment with pentoxifylline
h) Patients with ST-segment elevation myocardial infarction
i) Chronic anticoagulant treatment
j) Type 1 diabetes mellitus
k) Chronic total occlusion of one coronary vessel

All patients who met inclusion criteria at admission, in addition to the usual laboratory tests (including highly sensitive T-tropinin, CK, CK-MB, LDH) were sampled for inflammatory markers - highly sensitive C protein (hs CRP),

tumor necrosis factor (TNFα) and interleukin 6 (IL-6). Sample collection on admission was called T0. Inflammatory markers were also measured at 48 hours after the acute event, termed T1 and 15 days, termed T2. After admission, all patients enrolled in the study underwent coronary angiography. The angiographic exploration was performed at 2 hours after admission, within 24 hours or up to 72 hours after admission, according to the severity criteria recommended by the European guidelines for the management of non-ST-segment elevation acute coronary syndromes (ESC Acute Coronary Syndrome in Patients Presenting without Persistent ST-Segment Elevation) (19). After coronary angiography, PCI or CABG was performed in patients requiring myocardial revascularization according to the 2018 European ESC/EACTS Guidelines (20). Patients were clinically and paraclinical evaluated at discharge and then at 15 days, one month, six months, and one year.

III. 2. Objective

The primary objective of our study was to see whether pentoxifylline added to ACS patients on standard therapy influences major cardiovascular events (MACE). By major cardiovascular events, we included mortality, recurrence of new ACS (unstable angina, NSTEMI or STEMI), the need for subsequent revascularization, and stroke. A secondary objective of the study was to see if pentoxifylline administration influences the level of inflammatory markers (hs CRP, IL-6, TNFα) and whether this influence correlates with major cardiovascular events at one year.

III. 3. Results

500 ACS patients referred to IBCV Timisoara were included in our study, with 250 in group A and 250 in group B. In group A in addition to standard therapy, patients received placebo, while those in group B received 400mg pentoxifylline TID. Standard therapy of ACS patients included dual antiplatelet

therapy (aspirin together with a P2Y12 inhibitor -clopidogrel or ticagrelor), statin (initially, most patients had taken atorvastatin, 80 mg), ACEI or beta blocker. As the study medication was discontinued by 41 of the patients in group A (16.4%) and 40 patients in group B (16%) for various reasons, these subjects were excluded from the final analysis. Thus, 209 patients in group A and 210 patients in group B were included for the final analysis. The mean age of the included patients was 62.3± 10.3 years, with 61.8± 10.2 years in group A and 62.3± 10.7 years in group B.

Of the 419 patients included in the study, 80.4% were male, 20.8% had type 2 diabetes mellitus, 49.4% were hypertensive with home treatment, and 42% smokers at admission. In our study a total of 254 patients (60.6%) had hs CRP levels > 2mg/L. The two groups were relatively homogeneous, with an average age of 61.8± 10.2 years in group A and 62.3± 10.7 in group B.

All 419 patients underwent coronary angiography. 367 patients (87.5%) were revascularized by PCI, and 40 patients (9.54%) by triple coronary artery bypass grafting. In group A, 184 patients (88%) were revascularized interventional, while 183 patients (87.14%) were in group B. In group A, 21 patients (5%) and 19 patients (4.53%) in group B were revascularized by triple coronary artery bypass grafting. Our study there is included 312 (74.5%) patients with NSTEMI (group A, 157 pts; group B, 155 pts) and other patients with unstable angina (107 pts, 25.5%). After angiography, 238 pts (56.8%) had coronary multivessel disease. Because of emergency settings in most patients included in our study (NSTEMI and unstable angina), a culprit-lesion PCI was performed. In multivessel coronary patients, the decision for subsequent revascularization, if is needed (surgical or interventional) was made within the Heart Team. In group A, 184 pts (88%) were revascularized with a stent, and in group B, 183 pts (87.14%). PCI was successful in 360 pts (98%) of subjects, with no fatal complication in the control or pentoxifylline group. Radial access was used in 312 pts (85%) and femoral artery in 44 pts (12%), with 11 pts (3%)

needing to switch from radial to femoral artery due to severe kinking. All patients in both groups (control and pentoxifylline) were completely revascularized. In patients with multivessel coronary disease (238 pts, 56.8%), completed revascularization was performed as a staged procedure (1–40 days from the acute event). We used drug-eluting stents in all PCI revascularized patients.

Administration of pentoxifylline 400mg TID was well tolerated, and no significant side effect was noted in groups A and B. Was recorded some complained in group B patients, like headache (5 pts, 1.1%) abdominal discomfort, and nausea (3, 0.6%), but these symptoms did not lead to medication dropout. The symptoms disappeared before discharge.

The first result on the inflammatory marker on T0 noted that there are no significant differences between group A and B 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 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 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).

We find that at 48 h (T1) due to the administration of pentoxifylline in group B was an attenuation of rise in his CRP and TNF α level. This attenuation was not observed in group A, which received a placebo. The IL-6 levels were not affected by the administration of pentoxifylline in group B.

At baseline, hs CRP is in group B was 1.25±1.2 mg/L, and the rises to 48 hours was attenuated (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 α 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).

The effect persists at 15 days (T2) after administration of pentoxifylline to standard therapy in group B. We find that hs CRP and TNF α levels normalized earlier (hs CRP - group A, T2- 4.4±2.5 mg/L vs. group B, T2- 1.2 ±1 mg/L, p<0.001; TNF α- group A, T2-10.2±7.3 pg/L vs. group B, T2-6.2±3.4 pg/L, p<0.001). This does 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).

Major cardiovascular events were present in 12.38% (n=26) in group B, and in 15.78% (n=33) in group A (RR, 0.78; 95% confidence interval [CI], 0.486 to 1.263; P=0.40). We have found that relative risk of death was (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 further coronary revascularization (RR, 0.12; 95% CI, 0.015 to 0.985, p=0.048).

No correlation was found between the attenuation of increases and faster normalization of the level of inflammatory markers (hs CRP and TNF α) detected by the administration of pentoxifylline 400 mg TID and major cardiovascular events (Spearman-ρ=0.0015, p=0.33). Instead, a correlation was found between it and the need for subsequent coronary revascularization, which was lower in group B compared to group A (Spearman-ρ=0.47, p<0.0001). This result was due to a lower number of in-stent restenosis in group B (which received pentoxifylline in addition to standard medication) compared to group A (which received placebo in addition to standard medication). The results are published in Experimental and Therapeutic Medicine and Farmacia (21, 22).

III. 4. The contributions of the doctoral student.

We performed a meta-analysis and systematic review of the effect of pentoxifylline administration on inflammatory markers and blood pressure (17), and this was the first step in our research. This meta-analysis stated the anti inflammatory role of pentoxifylline administration by reducing the level of hs CRP and TNF α, but not IL-6, and no significative modification in blood pressure.

In our study, we try to find the role of adding pentoxifylline to standard therapy in patients with ACS. There are many studies that include pentoxifylline as a cardiovascular drug, but no studies were performed on this type of patient. Our study was the first to use pentoxifylline in patients with unstable angina or NSTEMI. We excluded the STEMI patients from these studies, but this could be the subject of the future research paper.

The scope of our study was to assess the impact of adding pentoxifylline first on inflammatory markers (in our case, hs CRP, TNF, and IL-6) and then on major cardiovascular events. We also tried to determine if there is a correlation between the level of inflammatory markers and major cardiovascular events.

Our results regarding inflammatory markers (hs CRP, TNF, and IL-6) were like what we published in a meta-analysis that consisted the basis of our study. This adds value to our results. We go further with the investigation and try to find that administration of pentoxifylline reduces the incidence of major cardiovascular events. The results showed that pentoxifylline administration does not influence the incidence of major cardiovascular events compared with placebo. Second, there is no correlation between the reduction in inflammatory markers and major cardiovascular events.

Our study is a monocenter single-blind randomized trial with a low number of patients recruited, so we can not generalize the result. It is evident from other randomized trials that targeting inflammation is important in patients with ACS if we want to improve outcomes. Therefore, we think that pentoxifylline, as an anti-inflammatory drug, is a good option. It is a not expensive drug and is well tolerated by patients with fewer side effects. The benefit of pentoxifylline

administration in patients with coronary artery disease can derive from improved red blood cell deformability, decreased red blood cell aggregation, and inhibit neutrophil adhesion and the production of some cytokines, such as TNF-α and IL-1.

It is obvious that further studies are required to establish that there is a future for pentoxifylline as an anti-inflammatory drug in patients with ACS.

III. 5. Limitations

We have some limitations in our study. First was a monocenter single-blind randomized trial. Second, the number of patients included in the study is low, which may affect the conclusion's generalization. This is a small study with limited funding. The inflammatory marker determination is made in an external laboratory, and we supported the cost. The duration of follow-up was short, with a median of 20 months.

IV. Conclusions

1. We have published a meta-analysis showing a significant anti-inflammatory effect of pentoxifylline treatment by reducing TNF-a and hs CRP levels in coronary artery disease, type 2 diabetes mellitus, idiopathic and ischemic cardiomyopathy, and chronic kidney disease. Pentoxifylline treatment was associated with anti-inflammatory effects when given alone or added to standard therapy.

2. Our study uses pentoxifylline added to standard therapy in patients with acute coronary syndrome without ST elevation. To the best of our knowledge, this is the first that uses pentoxifylline as an anti-inflammatory drug in patients with acute coronary syndrome.

3. Adding pentoxifylline to standard therapy reduced the rise of hs CRP and TNF α and determined early normalization of this inflammatory markers level in patients with acute coronary syndrome. Treatment with Pentoxifylline does not influence the level of IL-6.

4. Even though administration of pentoxifylline reduced the level of hs CRP and TNF α and cause rapid normalization, this do not correlate with a reduction in major cardiac events.

5. The two groups had no difference in major cardiovascular events regarding death, stroke, and non-fatal infarction. We find that in the group with active medication (pentoxifylline) was a lower incidence o target vessel failure due to the reduction of in-stent restenosis.

6. In group B, we found a correlation between the reduction of inflammatory markers (hs CRP, TNFα) and a lower incidence of target vessel failure.

7. Administration of pentoxifylline was very well tolerated with few side effects, making it an attractive anti-inflammatory treatment in patients with coronary artery disease compared to colchicine.

8. Because the administration of pentoxifylline does not reduce the level of IL-6, a combination with a drug that blocks IL-6 could be beneficial in patients with acute coronary syndrome regarding the reduction of major cardiac events.

9. We conducted a small study with promising results regarding pentoxifylline administration as an anti-inflammatory drug in patients with acute coronary syndrome.

10. Double-blind, randomized controlled trial is needed to establish the role of pentoxifylline as an anti-inflammatory drug in type of patients.

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