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Combined therapeutic approach in acute coronary syndrome patients under environmentally unfriendly working conditions

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Abstract

Background: The purpose of this study was to assess the effectiveness of the combined use of high doses of heparin, propranolol and monopril with percutaneous coronary intervention (PCI) on eco-endotoxicosis, systolic blood pressure, diastolic blood pressure, heart rate (HR), cardiodynamics and on the clinical course in acute myocardial infarction (AMI) among patients working in environmentally unfriendly conditions.

Material and methods: The study was conducted on 42 patients, aged 30 to 70 years (56.7 ± 1.20 years) with acute coronary syndrome (ACS), who were assessed for the anterior Q wave MI and ST segment elevation MI. Of 42 patients, 21 were treated with monopril, propranolol with heparin and PCI (group 1); and 21 patients underwent only PCI (group 2). The degree of eco-endotoxicosis in blood was studied in both groups, whereas the echocardiography and Doppler echocardiography were used to determine the end-systolic volume (ESV), end-diastolic volume (EDV), left ventricular ejection fraction (LV EF), local LV contractile dysfunction, local contractile dysfunction index (LCDI), restenosis via a repeated coronary angiography, echographic study of ST segment elevation and of repeated anginal pain.

Results: Patients treated with monopril with propranolol and heparin with PCI exhibited a stabilization of central hemodynamic indices, by a decrease in ESV, EDV, LCDI, and the degree of eco-endotoxicosis, as well as an improvement of LV systolic function by an increased EF. However, one patient from this group had an acute heart failure (AHF) on the 3rd day, whereas one patient experienced a MI relapse. The group of patients who underwent only PCI, revealed 3 cases of MI recurrence, 3 cases of restenosis, 2 cases of AHF and 2 patients died.

Conclusions: The combined use of drug and PCI therapy in acute coronary syndrome might lead to positive prognostic outcomes, rather than a separate PCI approach.

Key words: ecology, acute coronary syndrome, hemodynamics, percutaneous coronary intervention.

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Introduction

According to present WHO data, the high incidence rate of diseases is mainly due to the increasing rate of environmental stress: air, soil, water pollution, etc. [1-3]. The impact of anthropological and emergency factors (SO_2, H_2SO_4, NO, CO, CO_2, electromagnetic radiation, etc.) on the human body leads to chronic toxicity and eco-endotoxicosis [2-4]. Eco-endotoxicosis might increase the risks for coronary heart disease (CHD) and myocardial hypoxia, as well as reduce tissue resistance, aggravate blood and lymph rheology, and interferes with microcirculation. All these factors might result in extensive myocardial damage [1, 4], followed by heart failure (HF), abnormal heart rate (HR) and sudden coronary death in myocardial infarction (MI) [1, 3]. Therefore, new methods are currently being in search to reduce the level of average peptide molecular weight (PMW), as well as prevent or reduce the occurrence of various complications in early stages of MI [2, 3, 7, 12, 13]. Thrombolytic therapy and angioplasty (percutaneous coronary intervention – PCI) of the impaired coronary vessel have recently been used to reduce complications in the early MI stages [1, 5]. Therefore, there is a great demand in searching for new methods to prevent and decrease the occurrence of various complications in early MI [5–9]. Thrombolytic therapy and angioplasty (percutaneous coronary intervention – PCI) of the impaired coronary vessel have recently been used to reduce complications in the early MI [5, 7, 8]. However, there are evidences that every third patient develops a recurrent myocardial infarction on already the first day after the thrombolytic therapy has been carried out [5, 9, 10], followed by infarction-related coronary artery restenosis [5, 10, 11]. Moreover, the mechanical reperfusion in early myocardial infarction might increase the incidence of adverse outcomes [1, 11]. Thus, the effectiveness and safety of a combined therapeutic approach are still being discussed among specialists and there is no consensus upon this issue [5, 7, 10, 12]. At the same time, the combined use of

thrombolytics, anticoagulants, β-blockers, angiotensin converting-enzyme inhibitors (ACE inhibitors) and PCI, which play a significant role in eco-endotoxicosis among patients with acute myocardial infarction, working in ecologically unfriendly conditions is still neither fully understood nor sufficient attention is paid [1, 4, 8]. Based on the latest specialized literature data, this study was conducted on the effectiveness of a combined use of high doses of heparin, propranolol , monopril and PCI on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), cardiodynamics and the clinical course of acute MI associated with eco-endotoxicosis, among patients exposed to ecologically unfriendly working conditions.

Material and methods

The study was conducted on 42 patients aged 30 to 70 years (56.7 ± 1.20 years), presenting with acute coronary syndrome (ACS): the anterior Q-wave myocardial infarction and ST-segment elevation acute myocardial infarction were assessed. The study included 35 (83.3%) men and 7 (33.3%) women. The patients were randomly divided into 2 groups of 21 subjects each. The 1st group was administered propraponol, heparin and monopril combined with PCI, whereas the 2nd group underwent PCI only. All patients worked in environmentally unfriendly conditions and were in contact with anthropological-emergency factors (SH_2, SO_2, H_2SO_4, NO, CO, CO_2), electromagnetic radiation, etc. (tab. 1).

Both groups were assessed for the clinical course of the disease including SBP, DBP, heart rate, the early restenosis, recurrent myocardial infarction, acute heart failure (ACF) and mortality rate during the follow-up period. Additionally, ACF was determined according to the Killip classification over the last 7 days. The echocardiographic study of heart hemodynamics was carried out via SSD-2 (Aloka. Co., Ltd. Tokyo, Japan). The end-systolic volume (ESV), end-diastolic volume(EDV), local contractile dysfunction index (LCDI), left ventricular ejection fraction (LV EF), restenosis via a repeated coronary angiography, echocardiographic assessment of ST segment elevation and of recurrent anginal chest pains were determined. Monopril was administered over the first 3 days, 2.5 mg once daily in the morning, then 5 mg / day over 10 days and 10 mg /day on the following days of MI. 5 mg of 0.1% propranolol were injected intravenously within 5 minutes, followed by a 0.02 mg / kg / min IV dosage, 20-25 drops/minute, 4 times/day. Afterwards, the patients were given a dose of 80 to 120 mg /day per oral. The 1st group of patients used heparin: 20.000 units were first administered intravenously, concomitantly with the therapeutic dose of 10.000 units subcutaneously, followed by a 6-hour administration interval on the 1st day, then 10.000 IU on the 2nd-3rd days – every 8 hours, 10.000 IU on the 4^{th}-5^{th} days – every 12 hours, 10.000 IU on the 6th day – once a day, followed by warfarin anticoagulant, 1 tablet – 2 times/ day and a daily dose of 300 mg aspirin. The patients from the 2nd group underwent PCI and were administered 300 mg of aspirin per day.

The obtained data was statistically processed by using the "Statistics 6.0" software program. The M values, their standard errors (m) and a 95% confidence interval were estimated. The study applied both the non-parametric Mann-Whitney U test criterion and the Fisher's exact test criterion. The difference was considered statistically significant with $P < 0.05$.

Results

The analysis of environmental endotoxicosis-related SBP, DBP, and heart rate hemodynamic parameters, which were expressed by a higher level of PMW both in the group of patients treated with heparin, monopril and propranolol and PCI, as well as in PCI-treated subjects at the time of their hospital admission, showed no statistically significant difference ($p > 0.05$). The groups included those patients

Table 1

Characteristics of patients working in environmentally unfriendly conditions

Environmentally stressful Conditions (n=42)	Monopril + propranolol + heparin (n=21)		PCI (n=21)	
	Number of patients	Work experience (years)	Number of patients	Work experience (years)
1. Machine engineering	4	10.20±2.35	4	10.31±3.10
2. Oil and gas processing industry	6	10.40±6.30	5	10.20±2.20
3. Chemical plant	4	10.56±4.60	3	10.49±3.0
4. Motor vehicle repair workshops	5	10.40±2.30	6	10.23±2.10
5. "Electroterm" plant	2	10.05±1.40	3	10.50±2.10
Total	21	10.31±3.30	21	10.23±2.60
Admission period	1-5 h		1-5 h	

who suffered mainly of hyper- and eukinetic hemodynamic variants (tab. 2.)

A significantly low level of PMW was recorded in patients from the 1st group, over 12 hours, viz. from 0.58 ± 0.03 to 0.29 ± 0.01 units (p <0.001). A reduction in blood pressure was also registered, ranging between 138.0 ± 2.3 / 86.7 ± 1.3- to 123.0 ± 2.3 / 78.7 ± 1.7 mm Hg and which dropped up to 118.0 ± 1.8 / 75.9 ± 3.2 mm Hg until the end of the study (p> 0.001). Three patients from this group exhibited high level of PMW, though the blood pressure showed a decreasing tendency (up to 100/60 mm Hg). After the treatment, the level of PMW rapidly decreased (0.24 ± 0.11 unit), whereas blood pressure increased up to 115/65 mm Hg. PCI contributed to a slight decrease in PMW and blood pressure. The level of PMW decreased from 0.59 ± 0.6 to 0.56 ± 0.04 units, within 24 hours (p> 0.05), whereas blood pressure revealed 124.8 ± 3.4 / 74.00 ± 2.40 mm Hg, and 118.0 ± 1.7 / 75.1 ± 1.6 mm Hg on the 7th day (p <0.001). Changes of central hemodynamics and PMW during the treatment have been presented in table 2 (p> 0.05).

A significant decrease in heart rate among the 1st group patients was recorded over 24 hours, viz. from 100.0 ± 1.2 to 75.20 ± 1.40 beats/ minute, thus being of 74.10 ± 1.9 beats / minute at the end of the study. No heart rate decrease was registered in the 2nd group over 24 hours. However, it reduced up to 75.30 ± 2.1 beats/ minute within 72 hours.

The changes in the left ventricular (LV) function indices during the study are presented in table 2. The 1st group revealed a progressively decreasing EDV that was statistically significant difference in both the index before the treatment for MI (p <0.001), and the study results obtained in the 2nd group (p <0.01). Patients treated with just PCI also showed a decrease in EDV. 84% of patients from the 1st group and 75% of patients from the 2nd group showed a reduced LV EDV. 16% of patients of the 1st group and 25% of the 2nd group exhibited no decrease in both EDV index and its dynamics.

LV ESV in both the 1st group and the 2nd group decreased by 43.3% and 32.9% of patients, respectively, with a significant difference of p <0.01.

Indicators of the LV systolic function revealed no difference between groups (p <0.005). By the end of the 1st day and on the 7th day of the follow-up period, patients from the 1st group showed an increased EF (45.40 ± 2.5% and 61.91 ± 1.12%, respectively), which differed from the indicators of the 2nd group (45.90 ± 2.10% and 54.31 ± 1.11%). A decrease in the LV contractile function was recorded in 2 patients (9.5%) of the 1st group and in 10 patients (38.1%) of the 2nd group.

The values of LV LCDI were also different. Following a significant decrease in both the volume of myocardial deterioration and the severity degree of myocardial asynergy in patients from the 1st group, LV LCDI also exhibited lower values (1.88 ± 0.10- before treatment, and 0.81 ± 0.21 at the end of therapy). The indicators of LV LCDI from the 2nd group decreased from 1.78 ± 0.13 to 0.90 ± 0.12. (p> 0.001). Thus, a significant decrease in LV LCDI was registered in 97% of patients from the 1st group, and 57% of patients from the 2nd group .

Table 2

The dynamic patterns of central hemodynamic, LV systolic function and APM indices (M ± m)

Indices	Monopril + propranolol + heparin + PCI (n = 21)					PCI(n=21)					P_1 P_2
	Time elapsed since the start of treatment										
	Before treatment	12 h	24 h	72 h	7 day	Before treatment	12 h	24 h	72 h	7 day	
SBP mm Hg	138,0±2,3 P>0,05	123,0±2,3	126,0±1,6	125,2±1,6	118,0±1,8	140,4±2,2 P>0,05	122,2±2,1	124,8±3,4	125,5±2,2	118,0±1,7	<0,001 >0,05
DBP mm Hg	86,7±1,3 P>0,05	78,7±1,7	73,7±1,6	75,1±3,3	75,9±3,3	84,9±1,2 P>0,05	65,0±1,0	74,00±2,4	72,4±1,3	75,1±1,6	=0,05 >0,05
PMW, IU	0,58±0,03 p>0,05	0,29±0,01	0,30±0,06	0,28±0,02	0,26±0,05	0,59±0,06 P>005	0,56±0,04	0,54±0,03	0,49±0,03	0,46±0,02	<0,001 <0,01
HR beats/min	100,0±2,4 P>0, 05	88,6±2,80	75,20±1,40	76,72±2,1	74,10±1,90	98,6±3,10 P>0,05	96,50±2,2	96,19±2,00	75,32±2,10	75,30±2,10	<0,01 >0,05
ESV, ml	90,20±2,90 P>0,05	70,23±2,31	65,90±2,42	53,2±2,61	51,5±2,60	89,33±2,6 P> 0,05	78,5±2,31	75,20±2,42	68,20±2,1	65,10±2,4	<0,001 <0,01
EDV, ml	165,10±2,90 P>0,05	150,11±2,29	143,71±2,15	135,82±2,17	134,76±2,1	164,18±2,00 P>0,05	159,82±2,16	155,92±2,12	151,82±2,16	148,92±2,11	<0,001 <0,01
EF, %	45,40±2,5 P>0,05	53,20±0,10	54,8,±1,41	60,81±1,17	61,91±1,12	44,80±2,30 P>0,05	45,73±1,61	48,82±1,53	52,71±1,47	54,31±1,11	<0,001 <0,01
LCDI	1,88± 0,10 P>0,05	1,48± 0,23	1,35± 0,30	0,81± 0,17	0,81± 0,21	1,78± 0,13 P>0,05	1,73 ±0,17	1,52±0,15	0,87 ±0,12	0,90 ±0,13	< 0,01

Note: P – initial statistically significant difference; P_1- statistically significant difference between initial and final results; P_2 – statistically significant difference of the final study results between the two groups.

There were no significant differences in the clinical condition of patients on the 1st day. Acute heart failure was found in 2 patients from the 2nd group. One patient from the 1st group developed AHF on the 7th day. No restenosis, MI recurrence, and mortality cases were registered.

The group of patients, undergoing only PCI (the 2nd group) included 2 (9.5%) cases of recurrent MI; 4 patients developed restenosis, according to the repeated coronary angiography data; and 2 (9.5%) patients died. One patient died in the first 12 hours of PCI, the other one over 72 hours after the restenosis onset.

Therefore, the combined drug therapy and PCI used for revascularization of the coronary arteries contributed to reduction of PMW, ESV, EDV, LV LCDI, as well as an increase in LVEF, leading to a stabilization of hemodynamic patients without a critical decrease in their blood pressure during the MI follow-up. The combined therapeutic approach prevented the development of coronary artery restenosis, MI recurrence and mortality.

Discussion

Recently, the impact of environmental endotoxicosis has been highlighted regarding the hypoxia in peri-infarction area, myocardial metabolic impairment, and volume of myocardial deterioration, which leads to a change in LV systolic and diastolic function, as well as to the development of various complications, which are proportional to the degree of environmental endotoxicosis and volume of myocardial involvement [1, 5- 7].

Currently, in order to determine the degree of environmental endotoxicosis and the overall toxicity degree within the body, the PMW is being studied. The average peptide molecule is a marker of ischemic toxin, which impairs microcirculation, has a toxic effect on cardiomyocytes, and enhances the ischemic zone spread [1, 2]. Additionally, ecoendotoxicosis leads to an increase of PMW within the body, which inhibits the biosynthesis of proteins and the activity of a number of enzymes; oxidation and phosphorylation are impaired, the synthesis of adenine and glucose metabolism are also inhibited. The treatment failure of ecoendotoxicosis-related myocardial infarction is mainly due to insufficient assessment of the severity degree of endotoxemia associated with large doses of xenobiotic intake and anthropological-emergency factors, as well as the catabolic products derived from the peri-infarction area [1].

Therefore, cardiologists are searching for new drugs and methods to prevent complications and improve prognosis of AMI, which remains an urgent problem worldwide [7, 8, 10]. Recently, thrombolytic therapy and angioplasty (PCI) of the infarct-related coronary artery have been used [3, 9-12]. However, arrhythmia and reperfusion syndrome might occur in patients following a thrombolytic drug treatment. After drug reperfusion, remodeling of residual stenosis of the infarct-related coronary artery continues over the following week [9, 10]. There are evidences that a standard PCI, performed immediately after a successful thrombolysis, might increase the frequency of complications, namely of AHF, restenosis, and recurrence of MI.

The combined drug and PCI treatment does not only restore the coronary blood flow but also helps to restore the local kinetics of myocardium segments in the peri-infarction area [9, 10], as well as to reduce the level of PMW [1, 4, 6]. The clinical data and our study results have revealed that the use of β-adrenergic antagonists, particularly of propranolol [1] and metoprolol succinate [7, 8] prior to PCI and coronary bypass surgery are considered essential for myocardial protection and thus, reducing the mortality rate in this category of patients [12]. However, due to the high BP and negative inotropic actions, they were applied in only 20-35% of patients with MI (1, 7, 8), which is contrary to specialized literature data [7, 8] and our experience. Thus, if reasonable contraindications are followed, the use of propranolol or metoprolol succinate does not result in negative outcomes [1, 7]. Moreover, propranolol, which improves lymphocirculation, also helps in removing the eco- and endotoxins out from the peri-infarction area, and in reducing the systolic and diastolic LV functions.

In recent years, much attention has been paid to the use of ACE inhibitors in AMI, aimed at preventing the post infarct left ventricular remodeling and AHF [1, 2, 6]. Monopril (fosinopril) is the latest representative of ACE inhibitors, which is widely used in treatment of hypertension and congestive heart failure.

Thus, based on the research data, we concluded that the combined use of propranolol with monopril, heparin and PCI can reduce eco-endotoxicosis, restore myocardial blood flow, and improve LV systolic function. It also might increase the values of SI, CI, EF in patients, stabilize their SBP, DBP and heart rate. It also shows a more favorable impact on the clinical course of the disease.

Conclusions

1. The group of patients working under environmentally unfriendly conditions, and who underwent treatment with heparin, propranolol and monopril along with PCI at early stages of AMI, showed a rapid decrease in PMW, central hemodynamic stabilization, reduced systolic and diastolic LV functions, which might lead to early LV remodeling.

2. The combined use of heparin, propranolol and monopril together with PCI in the early stages of AMI patients, working in environmentally stressful conditions, revealed a more favorable clinical course of the disease; whereas MI recurrence, infarction-related coronary artery restenosis and mortality cases were not recorded.

3. The group of patients, subjected to PCI only, exhibited a high incidence of AHF, MI recurrence, infarction-related coronary artery restenosis, and mortality cases.

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Authors' contributions
MA conceptualized the project and designed the research. TA interpreted the data and drafted the manuscrit. All authors revised and approved the final version of the manuscript.

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Ethics approval and consent to participate
The study was approved by the ethics committee of Azerbaijan Medical University and *Abdulaev* Institute of Cardiology, Baku, Azerbaijan. The consent was received from every patient.

Conflict of Interests
No competing interests were disclosed.