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Antioxidant effects of combined vitamins C and E in acute myocardial infarction. The randomized, double-blind, placebo controlled, multicenter pilot Myocardial Infarction and VITamins (MIVIT) trial

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Aims. There is a large body of evidence that reactive oxygen species (ROS) produced during myocardial ischemia and reperfusion play a crucial role in myocardial damage and endothelial dysfunction. The MIVIT pilot trial was designed to test the effects of antioxidant vitamins C and E on the clinical outcome of patients with AMI.

Methods and results. In this randomized, double-blind, multicenter trial, 800 patients (mean age 62) with AMI were randomly allocated to receive, on top of routine medication, one of two treatments: vitamin C (1000 mg/12 h infusion) followed by 1200 mg/24 h orally and vitamin E (600 mg/24 h) or matching placebo for 30 days.

Primary end point (composite of in-hospital cardiac mortality, non-fatal new myocardial infarction, VT/VF/asystole, shock/pulmonary edema) occurred less frequently in patients treated with antioxidants (55 [14%] vs 75 [19%], OR 0.82 [95% CI, 0.68-1.00], p=0.048).

Conclusions. This randomized pilot trial shows that supplementation with antioxidant vitamins is safe and seems to positively influence the clinical outcome of patients with AMI. A larger study is warranted to provide further evidence of this promising and inexpensive regimen.

Key words: MYOCARDIAL INFARCTION – FREE RADICALS – ANTIOXIDANT VITAMINS – PROGNOSIS

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INTRODUCTION

There is a large body of evidence that reactive oxygen species (ROS) generated during acute myocardial ischemia and reperfusion deteriorate the function of myocardial membranes and contribute to myocardial damage (1,2). Ascorbic acid and alpha-tocopherol are the most important physiologic scavengers of ROS (3,4). We have previously shown that supplementation with vitamins C and E decreases oxygen-free radical production by isolated leukocytes in healthy subjects (5) and in patients with acute myocardial infarction (AMI) (6) and also prevents deterioration of electric function of the heart as seen on signal-averaged ECG in patients with AMI (7). Experimental studies have documented that supplementation with these vitamins decreases heart injury in the setting of myocardial ischemia (8,9). However, there are only two small studies on the effects of antioxidant vitamins C and E on the clinical outcome of patients with AMI which gave some hints in favor of this regimen (10,11).

We designed a randomized, double blind, multicenter MIVIT (**M**yocardial **I**nfarction and **VIT**amins) trial in which vitamins C and E were supplemented in high doses in patients with AMI. The aim of this trial was to elucidate effect of this regimen on the clinical course of AMI.

METHODS

Study organization

The MIVIT trial was prospective, multicenter, double-blind, randomized and placebo controlled in design. The trial was organized as one arm of a larger study which other arm investigated the effects of L-arginine in AMI with ST-segment elevation (STEMI) on clinical outcome. The results of the L-arginine trial will be the subject of a separate publication.

The study was conducted at 37 Polish community hospitals (see Appendix). Randomization was performed by the coordinating center at the Postgraduate Medical School, Grochowski Hospital in Warsaw. Enrollment into the trial began on March 1, 2000 and ended on May 31, 2002.

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The names of co-investigators of the Myocardial Infarction and VITamins (MIVIT) Study Group are listed in the Appendix

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The results of this study were presented at the Scientific Sessions of the American Heart Assotiation, Orlando, 2003 and at the Congress of European Society of Cardiology, Munich 2004

Patient selection and eligibility

Patients of either gender, age≥21 years with AMI were enrolled into the study within 24 h from the onset of symptoms. AMI was documented by the presence of ECG changes (ST-segment elevation of 1 mm or more from baseline in at least two limb leads or 2 mm in at least two precordial leads or new LBBB), chest pain lasting more than 20 minutes and/or creatine kinase-MB elevation (more than twice the upper normal limit).

Patients were excluded if they suffered from cardiogenic shock, hypotension (systolic blood pressure less than 100 mmHg for at least 30 minutes), pulmonary edema, loss or limited consciousness, renal insufficiency (creatinine >2 mg/dl) and major systemic illnesses that might influence the prognosis.

At the time of this study, the community hospitals participating in the trial were without on-site angiographic facilities. Therefore, patients who required interventional treatment (i.e. primary angioplasty) were not eligible for enrollment but were transferred to tertiary centres.

Of the 2456 patients with STEMI admitted to the CCU in the participating hospitals 800 were enrolled into MIVIT trial. The reasons for exclusion of 1656 patients from randomization are presented in Table I.

Study treatment

The patients were randomized to receive either vitamin C and E or placebo on top of routine therapy. The intervention group was given vitamin C (Pliva Kraków) 1000 mg in 500ml 0.9% NaCl for 12 h infusion, vitamin C (GZF Polfa) 400 mg orally and vitamin E (GSK Poland) 200 mg b.i.d. each for 30 days. The placebo group received a solution containing placebo identical with vitamin C in 500 ml 0.9% NaCl for 12 h infusion and capsules of placebo identical with vitamins C and E b.i.d. for 30 day oral treatment.

Follow-up and variables recorded

Clinical data, complications and drug therapy were recorded for the period of hospitalization. Laboratory data were obtained at entry into the study and routinely during hospitalization.

Table I. Reasons for patient exclusion before randomization

Patients fulfilling the entry criteria (total)	*2456*
Patients excluded from the trial	*1656*
Reasons for exclusion:	
Lack of patient consent	379
Unconsciousness	143
Shock	168
Hypotension	159
Malignant disease/alcohol abuse	231
Patient referred to other hospitals for primary angioplasty	182
Participants randomized to L-Arginine trial	394
Patients included in the MIVIT trial	*800*

Compliance

Plasma levels of ascorbic acid and alpha-tocopherol were measured at the beginning of treatment and repeated on day 5 or 6 in 40 randomly selected patients from each subgroup . Plasma ascorbic acid was determined by the method of *Ross* (12). Plasma alpha-tocopherol was measured by the method of *Kaplan* et al. (13).

Clinical outcome

The primary end-point was the composite of in-hospital major clinical events: cardiac mortality, presence of VT/VF or asystole, new MI, shock or pulmonary edema.

Prespecified subgroups to be analyzed were the following: gender, age (≤70 or >70 years), anterior myocardial infarction, fibrinolytic therapy, time from onset of symptoms to begining of study medication (≤12 or >12 hours), history of myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia and smoking.

Ethics

All patients gave their informed consent. The Research Ethics Committee of the Postgraduate Medical School in Warsaw approved the study protocol.

An independent Data and Safety Monitoring Committee reviewed clinical events.

Statistical analysis

All comparisons were performed on an intention-to-treat basis. Descriptive statistics were generated for baseline characteristics. Comparisons between treated groups were performed using χ^2 test for differences in the proportions of categorical variables and Student's t test for continous variables. All tests were two-sided and considered significant at $p<0.05$.

Multivariate logistic regression for binary response or proportional hazard regression for time to event adjusted for age, gender, infarct location, use of thrombolytic treatment, time from onset of symptoms to begining of study medication, history of myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia and smoking habit were done. In order to investigate whether certain prognostic factors influenced the results, a homogeneity test of odds ratios based on the logit approach and the Mantel-Haenszel test were performed. Calculations were made using Stata Statistical Software: Release 7.0, College Station, TX, Stata Corporation.

RESULTS

Of the 800 patients who were randomly assigned, 402 received vitamins C and E and 398 placebo.

There were no differences in baseline characteristics between the vitamin and placebo groups (Table II i III).

Effect of vitamins C and E on the clinical outcome

In a multivariate regression analysis, we observed significant reduction in the incidence of composite outcome events in the vitamin group compared to placebo (55 [14%] vs 75 [19%], OR 0.82 [95% CI, 0.68-1.00], p=0.048). There

Table II. Baseline patient characteristics [mean±SD or n (%)] of study participants

	Vitamin Group n=402	Placebo Group n=398
Demographic data		
Male sex n (%)	276 (69)	276 (69)
Age, y	62±12	62±11
>70 y n (%)	119 (30)	109 (27)
At admission:		
Blood Pressure, mmHg		
Systolic	134±24	135±22
Diastolic	81±13	83±13
Heart Rate, beats/min	78±14	78±15
Killip Class n (%)		
I	343 (85)	324 (81)
II	54 (14)	68 (17)
III	4 (1)	6 (2)
Time from onset of pain to beginning of study therapy, h	6,7±3,1	6,1±3,3
Time from onset of pain to beginning of fibrinolytic therapy, h	2,8±1,8	2,7±1,8
Duration of hospitalisation, days	13,4±2	13,4±3
Location of MI n (%)		
Anterior	152 (38)	173 (43)

Table IV. Independent predictors of in-hospital clinical outcome

Variable	OR	95% CI	p
Vitamin C+E	**0.82**	**0.68-1.00**	**0.048**
Age >70 years	1.98	1.33-2.95	0.001
History of MI	1.91	1.16-3.14	0.01
Anterior Myocardial Infarction	1.45	0.99-2.14	0.06
Time from onset of symptoms to the Beginning of study treatment >12 h	1.87	0.94-3.71	0.07

OR indicates odds ratio; CI – confidence interval

were two factors which independently unfavourably influenced in-hospital clinical outcome: age>70 years (p=0.001), and a history of previous MI (p=0.01). Anterior location of MI (p=0.06) and time from onset of symptoms to beginning of study medication more than 12 h (p=0.07) did not reach significance (Table IV).

Univariate analysis of the prespecified subgroups showed a consistent beneficial trend among patients receiving vitamins (Figure 1). However, given the small number of patients in each subgroup this may have been a chance finding.

Basal mean ascorbic acid and alpha-tocopherol levels did not differ between the controls and vitamin-supplemented group. After 5-6 days, a significant increase was seen in the intervention group only (Table V).

Table III. Baseline patient characteristics [mean±SD or n (%)] of study participants

	Vitamin Group n=402	Placebo Group n=398
Medical history n (%)		
Myocardial infarction	50 (12)	54 (14)
PTCA	3 (1)	3 (1)
CABG	2 (0.5)	4 (1)
Diabetes mellitus	59 (15)	63 (16)
Hypertension	176 (44)	193 (48)
Current smoker	262 (65)	255 (64)
Dyslipidemia (at admission): Cholesterol ≥240 mg/dL and/or LDL ≥130 mg/dL	186 (46)	174 (44)
In-hospital medication n (%)		
Aspirin	393 (98)	389 (98)
Thrombolytic therapy	344 (86)	340 (85)
Unfractioned heparin	91 (24)	94 (24)
Low molecular weight heparin	247 (61)	245 (62)
Oral anticoagulants	33 (8)	35 (9)
Platelet IIb/IIIa Inhibitor	7 (2)	10 (3)
Other antiplatelet agents (i.e. ticlopidine)	59 (15)	48 (12)
Intravenous nitrate	204 (51)	227 (57)
Oral nitrate	257 (64)	273 (69)
Intravenous beta-blocker	51 (13)	67 (17)
Oral beta-blocker	312 (78)	321 (81)
ACE-Inhibitor	259 (64)	279 (70)
Diuretic	113 (28)	132 (33)
Angiotensin II receptor blocker	4 (1)	7 (2)
Statin	220 (55)	211 (53)
Fibrate	7 (2)	10 (3)

Table V. Plasma concentrations (mean ± SD) of ascorbic acid and alpha-tocopherol before and after 5-6 days of treatment

	Ascorbic Acid (μmol/L)	Alpha-Tocopherol (μmol/L)
PLACEBO (n=20)		
Initial	18.6±15	21.5±10
After 5-6 days	15.9±10	17.7±3
	NS	NS
VITAMIN (n=20)		
Initial	25.1±12	21.8±6
After 5-6 days	101.5±35	37.3±12
	p<0.0001	p<0.004

DISCUSSION

We have found that antioxidant vitamins significantly improved the clinical course of AMI decreasing the incidence of in-hospital major clinical events. Although this small pilot study was not meant to elucidate the possible impact of this regimen on mortality and incidence of new acute coronary syndromes, a trend towards lowering these events became apparent.

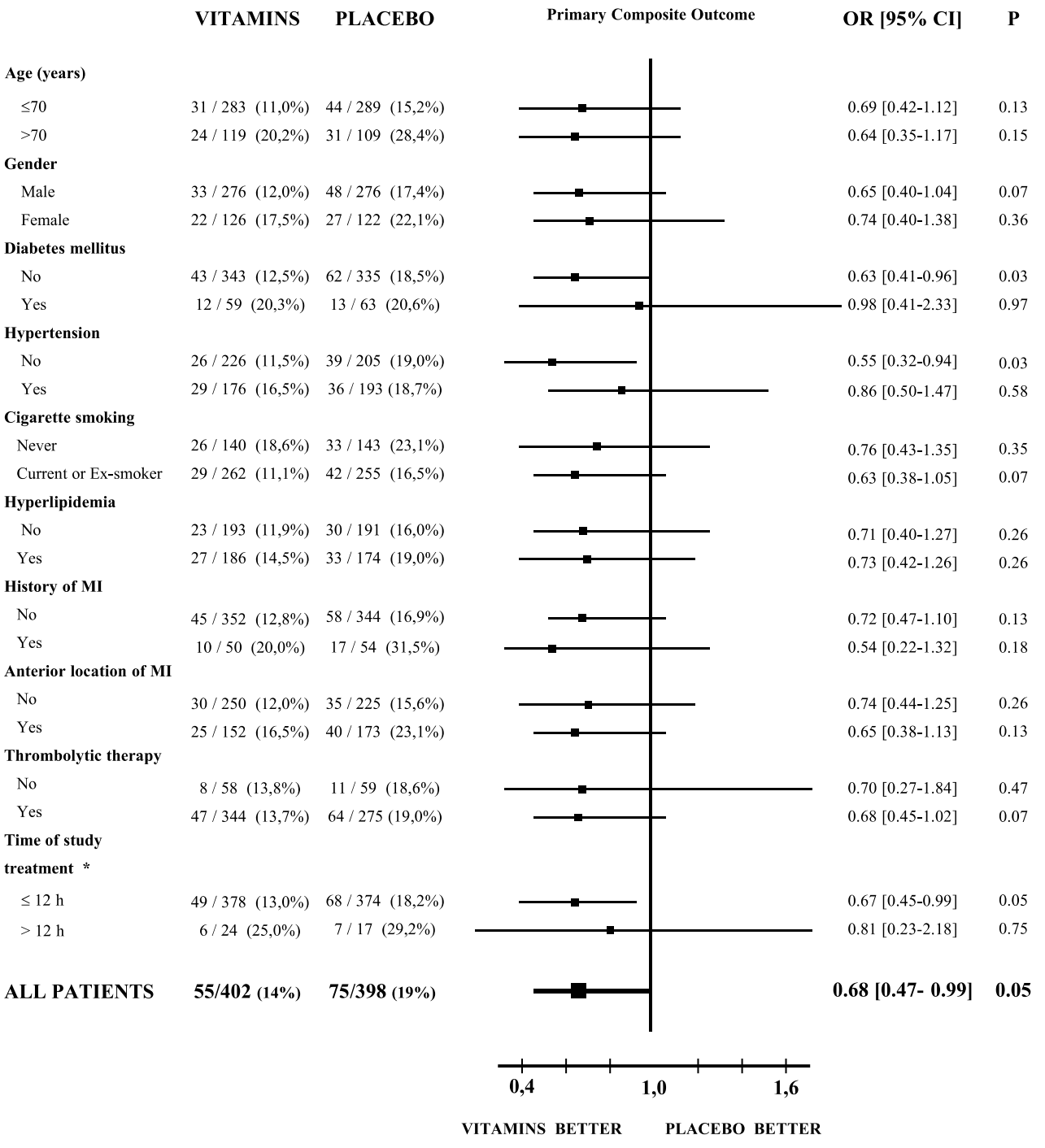

Figure 1. Overall effects of vitamins on in-hospital clinical outcome in prespecified subgroups. Univariate analysis. Point estimates of odds ratio (OR) given with 95% confidence interval (CI).
** Time from onset of symptoms to the beginning of study treatment*

To date, only two small studies concern this subject. *Singh* et al. (10) in 125 patients showed that administration of antioxidant vitamins A,C,E and beta-carotene within a few hours after the onset of AMI was associated with a significant decline in total cardiac end points defined as a combination of cardiac mortality and non-fatal MI and in myocardial necrosis measured biochemically and echocardiographically.

In the second open label trial, *Laskowski* et al. (11) reported that intravenous vitamin C and mannitol in addition to fibrinolytc therapy given to 42 patients, decreased the number of complications including shock, pulmonary edema and severe arrhythmias, during the first and subsequent days of AMI. However, both cited studies have limitations demanding cautious interpretation of the results. First, the number of patients was small. Furthermore, in the study by

Singh et al., the combination of vitamins included vitamin A with as yet unconfirmed antioxidant properties and it can be potentially toxic when used in high doses. In the study of *Laskowski* et al., the combined use of mannitol and vitamin C makes interpretation of the vitamin efficacy difficult.

So far, the interest of researchers has been almost entirely focused on the effects of antioxidant vitamins in the setting of chronic coronary heart disease (CHD) or in the population with high risk for cardiovascular events. In several large epidemiological and observational studies, the intake of vitamins C and E was inversely associated with the incidence of CHD, and in the cross-population comparisons, plasma vitamin levels were inversely associated with CHD (14).

The results of large, prospective, randomized clinical trials are equivocal: CHAOS (15) showed the positive effect of vitamins on the frequency of coronary events. Harvard IVUS (16) in heart transplant recipients and ASAP (17) in hypercholesterolemic patients also presented the benefits of such treatment. However, recently published trials HOPE (18) and HPS (19) showed no benefit of this approach.

It may be expected that if the main virtue of antioxidant vitamins is their free radical scavenging property, they should be most effective in the acute phase of MI associated with an outburst of free radicals production. This might be the reason that our study showed positive effects of this regimen despite the small group of patients.

There is a number of potential mechanisms whereby an intake of antioxidant vitamins could be related to a less severe clinical course of AMI.

Essential clinical interventions aimed at restoring coronary flow in the ischemic region carry the risk of causing reperfusion injury. Current evidence to support the benefits of antioxidant vitamins in ischemia / reperfusion injury is limited and comes only from experimental studies (8,9). Clinically important components of reperfusion injury, namely reperfusion arrhythmias, the „no reflow'' phenomenon and myocardial stunning can all be experimentally attenuated by free radical scavengers (2). For methodological reasons it is difficult to assess these effects in the setting of AMI in a human subject. Therefore, the concept that vitamins C and E can positively influence some components of reperfusion injury in the clinical setting of AMI still remains unproven but is a logical hypothesis.

In patients with coronary artery disease, endothelial vasodilator dysfunction is reversed by vitamin C (20) as well as by vitamin E (21) administration. The concept is that increased NO inactivation by ROS contributes to impaired endothelium-mediated vasomotion. Vitamins C and E can save endothelial NO due to direct inactivation of free radicals (4,21). Because of the rapid reaction between superoxide and NO radicals, relatively high concentrations of ascorbate are required to prevent effectively this reaction in vivo. There is also experimental evidence that vitamin C facilitates NO generation by preventing inactivation of tetrahydrobiopterin – an important co-factor in NO production by endothelial NO synthase (22).

ROS also stimulate platelets, key players in the thrombotic processes (24). Vitamin E supplementation reduces platelet aggregation and adhesion ex vivo (25) and inhibits thrombin formation (26). Vitamin E also potentates the release of arachidonic acid and prostacyclin from endothelial cells (3), but its full antioxidant effect is reached only in the presence of vitamin C (23).

The elimination of free radical excess and the reduced rate of their formation may protect membranes of myocytes from arrhythmogenic activity. *Mehta* et al. (27) have shown that administration of a free radical scaveger reduces arrhythmias accompanying reperfusion of the myocardium during thrombolytic therapy. Our earlier experience indicates that treatment with vitamins C and E reduces leukocyte free radical generation in patients with MI (6) and also reduces the number of late potentials (7), predictors of complex ventricular tachyarrhythmias.

Vitamins C and E act synergistically. Antioxidant activity of alpha-tocoperol is due to oxidation of the molecule to toxic tocopherol radical but is reconverted to alpha-tocopherol by vitamin C (23). As shown in healthy volunteers, administration of ascorbic acid raised not only its serum level but also that of alpha-tocopherol (28). Because of the synergism between vitamin C and E in the human body, it is hypothesized that the best effects are attained by combined supplementation.

Furthermore, as shown recently, the inconsistent results of previous vitamin studies may have been related to insufficient plasma concentrations of vitamin C. Ascorbic acid scavenges superoxides in concentrations of 1 to 10 mmol/L or higher (29). Long-term oral administration typically raises ascorbic acid concentrations to only 0.1 mmol/L (30). In contrast, parenteral administration of the same dose produces plasma ascorbate concentrations up to 10-fold higher (4). In our study, vitamin C was given intravenously during the first hours of AMI and this might be another reason that our study showed positive effects.

The vitamin regimen in our trial was within the range considered to be safe and effective (4,14). The MIVIT trial, like other previous studies (6,7,16,17,19), has shown that antioxidant vitamins C and E are safe and well tolerated.

Limitations of the study

Results of the present study should be confirmed with a larger number of patients.

In our trial a pharmacological rather than invasive angioplastic technique therapy of reperfusion was used. However, the patomechanisms of oxidative stress in both of these approaches is similar.

A further limitation of the present study was the delay of vitamin C infusion in relation to the beginning of fibrinolytic therapy (mean 6,7 h vs 2,8 h from the onset of MI, respectively) which might have decreased the effectiveness of the study treatment.

CONCLUSIONS

This clinical trial shows that in a small group of patients with AMI, supplementation with antioxidant vitamins C and E is safe and positively influences clinical outcome. This encourages the initiation of a large study to confirm or refute the benefit of this inexpensive management in AMI.

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Appendix

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WPŁYW WITAMIN ANTYOKSYDACYJNYCH C+E na PRZEBIEG KLINICZNY OSTREGO ZAWAŁU SERCA.

Pilotowe, randomizowane, wieloośrodkowe, podwójnie ślepe, kontrolowane placebo badanie MIVIT

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(Kardiol. Pol. 2005, 62, 350)

STRESZCZENIE

Wstęp. Zawał serca stanowi nadal jeden z głównych problemów zdrowotnych współczesnego świata. Istnieją przekonywujące dane, zarówno doświadczalne, jak i kliniczne, że wolne rodniki powstające w przebiegu niedokrwienia i reperfuzji, zaburzają czynność śródbłonka naczyniowego, a także bezpośrednio uszkadzają myocardium. Dotychczasowe badania doświadczalne, a także biochemiczne wskazują na to, że podawanie witamin antyoksydacyjnych w ostrym zawale serca może być szczególnie uzasadnione, bo właśnie wtedy procesy oksydacyjne są wybitnie nasilone. Jak dotąd brakuje prac klinicznych na ten temat.

Cel badania. Celem niniejszego wieloośrodkowego, randomizowanego, podwójnie ślepego badania MIVIT jest ocena bezpieczeństwa oraz wpływu na przebieg kliniczny witamin antyoksydacyjnych C+E u chorych z ostrym zawałem serca.

Grupa badana i metodyka. Badaną grupę stanowiło 800 chorych z ostrym zawałem serca, do 24 godzin od początku objawów, którzy poza standardowym leczeniem, otrzymywali w sposób losowy, witaminy C oraz E lub placebo. Witaminę C podawano zarówno dożylnie (wlew 1000 mg przez 12 godzin), jak i doustnie (1200 mg/d przez kolejne 30 dni), zaś witaminę E jedynie doustnie (600 mg/d przez kolejne 30 dni).

Oceniano przebieg kliniczny choroby w obu podgrupach badanych w oparciu o główny punkt końcowy, określony jako wewnątrzszpitalne zgony sercowe, niezakończone zgonem VF/VT/asystolia, ciężka niewydolność serca – obrzęk płuc i wstrząs kardiogenny.

Wyniki. Stwierdzono, że u chorych leczonych witaminami C+E, w porównaniu do otrzymujących placebo, rzadziej dochodzi do powikłań klinicznych określanych jako główny punkt końcowy (55 [14%] vs 75 [19%], OR 0,82 [95% CI, 0,68-1,00], p=0,048).

Leczenie witaminami antyoksydacyjnymi C+E jest bezpieczne.

Objawy uboczne ewentualnie związane z tym leczeniem wystąpiły sporadycznie – podobnie jak w grupie placebo – i tylko w nielicznych przypadkach stały się powodem ich odstawienia.

Wnioski. Pilotowe, randomizowane, wieloośrodkowe, podwójnie ślepe, badanie MIVIT wskazuje na to, że intensywne leczenie witaminami antyoksydacyjnymi chorych ze świeżym zawałem serca jest bezpieczne i wpływa korzystnie na przebieg kliniczny.

Niniejsze badanie uzasadnia potrzebę i wykazuje celowość zainicjowania podobnej pracy na dużej populacji chorych, aby ostatecznie ustalić miejsce witamin C+E w leczeniu ostrego zawału serca.

Słowa kluczowe: zawał serca – stres oksydacyjny – witaminy antyoksydacyjne – rokowanie

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Dane uczestników badania MIVIT są wymienione w dodatku

Wyniki tej pracy były prezentowane na kongresach: American Heart Association w Orlando w 2003 roku oraz European Society of Cardiology w Monachium w 2004 roku.

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